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The Role of Open Diagnostic Peritoneal Lavage in the Evaluation of Peritoneal Cytology for Advanced Gastric Cancer: An Old Diagnostic Modality with New Usage

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Abstract

Background: Positive peritoneal cytology is a critical factor in prognosis. Peritoneal lavage is associated with long-term survival in patients with gastric cancer. Diagnostic peritoneal lavage (DPL) is a method for diagnosing visceral injury in trauma patients. This study aimed to investigate the usage of DPL in staging the work-up of patients with gastric cancer.

Method: In this prospective study, we enrolled gastric cancer patients referring to Cancer Institute; they underwent DPL and washing specimen was sent for cytology review. After DPL, all patients underwent staging laparoscopy (SL) via the same abdominal incision.

Results: DPL and SL were successful in all patients. There were six (11%) cases of peritoneal seeding discovered in SL; all of these patients had positive peritoneal cytology on DPL. Also, four patients showed positive cytology in the absence of positive SL. Thus, sensitivity, specificity, negative predictive value, positive predictive value, and accuracy of DPL were 100 % (95% CI: 54.1-100), 91.6 % (95%: 79.2-97.5), 100 % (95%CI: 85.3-100), and 60 % (95%CI: 37-79.3). The accuracy of DPL in determining the peritoneal dissemination of gastric cancer was 92.31% (95% CI: 81.5-97.9).

Conclusion: DPL had an excellent ability to find peritoneal dissemination in a gastric cancer patient, which is of great value in the setting of low-resource countries.

Keywords: Gastric cancer, Diagnostic peritoneal lavage, Staging laparoscopy, Peritoneal cytology

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Introduction

Although the prevalence rate of gastric cancer is steadily decreasing globally, it is still the third most frequent cause of cancer death.[1, 2] The prognosis of this disease is low in most areas of the world, with just around 10%of the afflicted population surviving for five years. The reason for such horrible prognosis is that the disease is diagnosed at a late (metastasis) stage of development.[3, 4] Appropriate treatment of gastric cancer is achieved through the exact staging of cancer.[5]

The National Comprehensive Cancer Network (NCCN) guidelines have recommended staging laparoscopy (SL) with cytological evaluation for T1b or higher gastric cancer.[6] However, the availability and feasibility of this procedure have been questioned.[7] Groh et al. reported that only 13% of their study population underwent SL prior to treatment and SL use increased annually to 22.2%.[8] Moreover, SL is performed on a day other than the planned gastrectomy, exposing patients to the possible complications of general anesthesia and surgery.

The current American Joint Committee on Cancer (AJCC) tumor, node, and metastasis staging system uses peritoneal cytology as an important prognostic factor and recommends systemic chemotherapy as if it is positive.[9] The peritoneal cytology was reported positive in 4 to 41% of gastric cancer series.[10] Also, the more aggressive the tumor became, the higher the chances of positive peritoneal cytology would be (T1/ T2, 0%; T3/T4, 10%; M+, 59%);[11] furthermore, the disease was classified as a stage IV disease.[12] The impact of positive cytology on survival was compared to other variables such as serosal or lymph node involvement and it was shown to be an indicator of poor prognosis.[13] Positive peritoneal cytology is a critical factor in prognosis. Peritoneal lavage is associated with long-term survival in patients with gastric cancer.[14, 15] Although the rate of positive peritoneal cytology is unknown, some studies have reported it between 6.5 and 31%. This rate can be correlated with phases T and N. In 1965, Root et al. introduced a diagnostic peritoneal lavage (DPL (as a tool for assessing the likelihood of peritoneal penetration and damage to abdominal viscera in trauma cases.[16] Mezhir et al. were the first to apply DPL (previously used as an indicator of peritoneal penetration and injury to the abdominal viscera in trauma patients) to obtain peritoneal specimen as part of the staging for patients with locally advanced gastric cancer.[15] Therefore, in this study, the idea of using DPL originated from the fact that there was a long waiting list of patients for SL, which delay in receiving appropriate treatment. Moreover, the technical requirements for performing SL are not widely available in our country and this procedure involves a high cost during hospitalization. We also utilized SL as a current standard of peritoneal evaluation and compared the cytology reports of DPL to laparoscopic findings. We intended to use DPL as part of the staging work-up of patients with gastric cancer.

Materials and Methods

This prospective study included patients referring to Cancer Institute, Tehran University of Medical Sciences, Tehran, Iran, from March 2018 to March 2019. All participants signed a written informed consent. The gastric adenocarcinoma of all the subjects was pathologically confirmed through needle biopsy of the gastric lesion via endoscopic ultrasonography evaluation. Also, the computed tomography scan of the chest, abdomen, and pelvis was performed. All the gastric cancer patients enrolled in the study were planned to undergo SL. Exclusion criteria were radiological evidence of metastatic disease or any synchronous abdominal cavity malignancies. The institutional review board and the Ethics Committee of Tehran University of Medical Sciences approved the study design (IR.TUMS.IKHC.REC.1397.088). To check the null hypothesis that the sensitivity was at least 80%, we expanded the number of patients until at least ten patients with positive lavage were found. Gastric cancer patients with a slightly lower occurrence of positive lavage

Table1. Tumor characteristics of the study population

Variable		Number(Percent)
Gender	Male	36 (67)
	Female	18 (33)
Tumor location	Cardia	31 (57)
	Fundus	3 (6)
	Body	13 (24)
	Antrum	7 (13)
EUS Stage		
	T3N0	3(6)
	T3N1	15 (28)
	T3N2	11 (20)
	T3N3	1 (2)
	T4N1	5 (9)
	T4N2	11 (20)
	T4N3	8 (15)
CTS stage		
	T2N2	1 (2)
	T3N0	6 (11)
	T3N1	17 (31)
	T3N2	8 (15)
	T4N1	3 (6)
	T4N2	15(28)
	T4N3	4 (7)

EUS: Endoscopic ultra-sonography, CTS: Computed tomography scan

cytology have been chosen as an inclusion criterion for this study.

Under general anesthesia and in a supine position, DPL and SL were performed by one of the three attending surgical oncologists. DPL was done first using a midline vertical 10 mm abdominal incision above the umbilicus. After entering the abdominal cavity, 1000cc of warmed normal saline was infused through the abdominal cavity by a 16 French nelaton urethral catheter. The patients' position was then changed from right lateral decubitus to left lateral decubitus to ensure fluid distribution in the whole abdomen. Afterwards, the infused fluid was completely withdrawn and sent for cytology. The urethral catheter was dismissed, and a 10 mm optic laparoscopic port was inserted via the same midline incision. All four quadrants of the abdomen and pelvis were inspected during laparoscopy; biopsy was taken from any suspicious lesion through the insertion of another 5 mm port. All specimens underwent cytological evaluation by two independent pathologists. The presence of any malignant cells, regardless of the number, confirmed positive cytology. Atypical and suspicious cytology were respectively characterized as negative and positive. In the event of discordant reports between two pathologists, specimens were sent to the third pathologist who was blinded to the previous results. The laparoscopic evaluation was considered positive, if the adjacent organ involvement, omental involvement, or peritoneal seeding were detected and confirmed by the pathological report.

We used the Statistical Package of Social Science software (SPSS version 22; SPSS, Inc., Chicago, IL) to determine the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of DPL in the assessment of peritoneal cytology compared to laparoscopic peritoneal lavage.

Results

We recruited a total number of 54 patients with a mean age of 67 ± 1.2 years (44-86) and a male to female ratio of 36:18. The tumor was located in the cardia, fundus, body, and antrum

in 31 (57%), 3 (6%), 13 (24%), and 7 (13%) of cases, respectively. Table 1 depicts the tumor characteristics. All the procedures were successfully carried out, and there was no postoperative complication.

Among the 10 cases of positive cytology in DPL, only six had gross metastatic disease (four cases in the form of peritoneal seeding and two cases in the form of omental involvement) during laparoscopy. Seven out of the 10 cases of positive cytology on DPL had T4 primary tumors and three had T3. There was a 100% concordance with DPL and laparoscopic findings. The sensitivity, specificity, NPV, PPV and DPL were 100% (95% CI: 54.1-100), 91.6% (95%: 79.2-97.5), 100% (95%CI: 85.3-100), and 60% (95%CI: 37-79.3), respectively. The accuracy of DPL in detecting the peritoneal dissemination of gastric cancer was 92.31% (95% CI: 81.5-97.9).

In two (6 %) out of 31 T3 patients and four (18 %) out of 22 T4 patients, SL adjusted the treatment plan by seeking intra-abdominal seeding. Furthermore, DPL washing changed previous treatment plan to palliative chemotherapy in three T3 cases (3/31, 9%) and seven T4 cases (7/22, 31%).

Discussion

Based on the results, DPL was reasonably accurate in terms of finding a positive cytology case compared to laparoscopic findings. All cases who were positive based on laparoscopic result had positive cytology on DPL. DPL can be easily performed even under local anesthesia and mild sedation; thus, it provides an excellent staging modality. This finding is important given the significance of positive cytology, currently considered as stage IV disease. This means that when DPL is positive in a candidate for gastrectomy of any extent and D1 or D2 lymphadenectomy, the treatment plan must immediately change to systemic chemotherapy or even palliative treatments.

Pak et al.[17] used almost the same technique to provide percutaneous peritoneal lavage. They employed a 9-French peritoneal catheter over the guidewire utilizing the Seldinger technique following the insertion of a Veress in the left upper quadrant of the patients' abdomen. They reported a sensitivity, specificity, NPV, and PPV of 87%, 100%, 96.5%, and 100%, respectively. They also had six cases of a technical failure associated with percutaneous lavage due to either failure in the entrance to the abdominal cavity via Veres's needling or acquisition of adequate specimens. Of these cases, two had positive cytology in laparoscopy washing and grossly disseminated metastatic disease in the abdominal cavity. A similar study was performed by Mezhir et al.[15] They successfully obtained percutaneous peritoneal lavage specimen in 22 out of 27 gastric cancer cases; the sensitivity and specificity were 92.3 % and 100 %, respectively. In their study, a similar technique for open DPL was employed by the authors. To collect the specimens, they used an 8-French Silastic catheter with extra side holes through infra umbilical incision. One patient had insufficient cells for analysis on DPL, but the specimen from laparoscopy washing was positive. In DPL cytology, there was one false negative that showed no evidence of gross M1 disease.

Previous studies emphasized the role of positive peritoneal cytology on the survival of gastric cancer patients, hence the necessity of a timely treatment; the current study showed that open DPL was able to spare patients from non-therapeutic laparotomy when M1 disease was discovered. Due to the high costs of SL, this modality is of great value, especially in low-resource settings. It can also facilitate the outpatient staging work-up of gastric patients and reduce the hospital stay and the subsequent costs.

The main limitation of this approach is the inability to detect peritoneal, liver, mesenterium, Douglas pouch, and omental surface in the abdominal cavity. Furthermore, based on the previous studies, the false negative and false positive results of open DPL might limit its clinical accuracy. Immunocytochemistry studies revealed 5 to 15% improvement in detection rates. Potent molecular markers of various target genes such as transcripts of CEA, CK-20, MMP-7, and heparanase may be utilized in open DPL settings

for enhanced accuracy.[18, 19]

Our study had several limitations. Primarily, the study population was small and definitive conclusions can only be drawn after performing studies with larger populations. Also, the DPL was performed under general anesthesia in the operating room, while it seems to be clinically executable in an outpatient setting under local anesthesia, which can be evaluated in another study.

In conclusion, open DPL is of great importance for an early detection of intra-abdominal disseminated metastatic disease in patients with advanced gastric cancer. The use of molecular markers in reverse transcriptase-poly chain reaction method, while assessing peritoneal cytology may enhance the sensitivity and specificity of cytology reports.

Conflicts of Interest

None declared.

References

1. Crew KD, Neugut AI. Epidemiology of gastric cancer. *World J Gastroenterol.* 2006;12(3):354-62. doi:10.3748/wjg.v12.i3.354.
2. Roder DM. The epidemiology of gastric cancer. *Gastric Cancer.* 2002;5 Suppl 1:5-11. doi:10.1007/s10120-002-0203-6.
3. Axon A. Symptoms and diagnosis of gastric cancer at early curable stage. *Best Pract Res Clin Gastroenterol.* 2006;20(4):697-708. doi:10.1016/j.bpg.2006.03.015.
4. Bernal C, Aguayo F, Villarroel C, Vargas M, Díaz I, Ossandon FJ, et al. Reprimo as a potential biomarker for early detection in gastric cancer. *Clin Cancer Res.* 2008;14(19):6264-9. doi:10.1158/1078-0432.CCR-07-4522.
5. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2014 (ver. 4). *Gastric Cancer.* 2017;20(1):1-19. doi:10.1007/s10120-016-0622-4.
6. Shiozaki H, Elimova E, Slack RS, Chen HC, Staerkel GA, Sneige N, et al. Prognosis of gastric adenocarcinoma patients with various burdens of peritoneal metastases. *J Surg Oncol.* 2016;113(1):29-35. doi:10.1002/jso.24087.
7. Allen CJ, Newhook TE, Vreeland TJ, Das P, Minsky BD, Blum M, et al. Yield of peritoneal cytology in staging patients with gastric and gastroesophageal cancer. *J Surg Oncol.* 2019;120(8):1350-7. doi:10.1002/ jso.25729.
8. Groh EM, Gupta S, Brown ZJ, Enewold L, Gamble LA, Hernandez JM, et al. Staging laparoscopy is underutilized in the management of gastric adenocarcinoma. *Ann Surg Oncol.* 2020;27(5):1473-9. doi:10.1245/s10434-019-08077-1.
9. Virgilio E, Giarnieri E, Giovagnoli MR, Montagnini M, Proietti A, D'Urso R, et al. Gastric cancer cells in peritoneal lavage fluid: a systematic review comparing cytological with molecular detection for diagnosis of peritoneal metastases and prediction of peritoneal recurrences. *Anticancer Res.* 2018;38(3):1255-62. doi:10.21873/anticanres.12347.
10. Badgwell B, Cormier JN, Krishnan S, Yao J, Staerkel GA, Lupo PJ, et al. Does neoadjuvant treatment for gastric cancer patients with positive peritoneal cytology at staging laparoscopy improve survival? *Ann Surg Oncol.* 2008;15(10):2684-91. doi:10.1245/s10434-008-0055-3.
11. Jamel S, Markar SR, Malietzis G, Acharya A, Athanasiou T, Hanna GB. Prognostic significance of peritoneal lavage cytology in staging gastric cancer: systematic review and meta-analysis. *Gastric Cancer.* 2018;21(1):10-8. doi:10.1007/s10120-017-0749-y.
12. Fujitani K, Yang HK, Kurokawa Y, Park DJ, Tsujinaka T, Park BJ, et al. Randomized controlled trial comparing gastrectomy plus chemotherapy with chemotherapy alone in advanced gastric cancer with a single non-curable factor: Japan Clinical Oncology Group Study JCOG 0705 and Korea Gastric Cancer Association Study KGCA01. *Jpn J Clin Oncol.* 2008;38(7):504-6. doi: 10.1093/jjco/hyn058.
13. Lee SD, Ryu KW, Eom BW, Lee JH, Kook MC, Kim YW. Prognostic significance of peritoneal washing cytology in patients with gastric cancer. *Br J Surg.* 2012;99(3):397-403. doi: 10.1002/bjs.7812.
14. Bentrem D, Wilton A, Mazumdar M, Brennan M, Coit D. The value of peritoneal cytology as a preoperative predictor in patients with gastric carcinoma undergoing a curative resection. *Ann Surg Oncol.* 2005;12(5):347-53. doi: 10.1245/ASO.2005.03.065.
15. Mezhir JJ, Posner MC, Roggin KK. Prospective clinical trial of diagnostic peritoneal lavage to detect positive peritoneal cytology in patients with gastric cancer. *J Surg Oncol.* 2013;107(8):794-8. doi: 10.1002/jso. 23328.
16. Root HD, Hauser CW, McKinley CR, LaFave JW, Mendiola RP. Diagnostic peritoneal lavage. *Surgery.* 1965;57(5):633-7. doi: 10.5555/uri:pii:0039606065900310.
17. Pak LM, Coit DG, Eaton AA, Allen PJ, D'Angelica MI, DeMatteo RP, et al. Percutaneous peritoneal lavage for the rapid staging of gastric and pancreatic cancer. *Ann Surg Oncol.* 2017;24(5):1174-9. doi:10.1245/s10434-016-5757-3.

18. Takata A, Kurokawa Y, Fujiwara Y, Nakamura Y, Takahashi T, Yamasaki M, et al. Prognostic value of CEA and CK20 mRNA in the peritoneal lavage fluid of patients undergoing curative surgery for gastric cancer. *World J Surg*. 2014;38(5):1107-11. doi: 10.1007/s00268-013-2385-y.
19. Nakabayashi K, Uraoka T, Shibuya M, Matsuura N, Tsujimoto M. Rapid detection of CEA mRNA in peritoneal washes using One-Step Nucleic acid Amplification (OSNA) for gastric cancer patients. *Clin Chim Acta*. 2015;439:137-42. doi:10.1016/j.cca.2014.10.014.