Annals of Clinical and Medical Case Reports

Research Article ISSN: 2639-8109 | Volume 8

Effect of Preoperative Chemotherapy and Postoperative Adjuvant Chemotherapy for Gastric Cancer with Positive Peritoneal Lavage Cytology (CY1): A Retrospective Study

Wen-Zhe Kang, Jian-Ping Xiong, Yang Li, Peng Jin, Xin-Xin Shao, Hai-Tao Hu and Yan-Tao Tian*

Department of Pancreatic and Gastric Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China

***Corresponding author:**

Yan-Tao Tian, MD, Professor, Surgeon, Department of Pancreatic and Gastric Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, No. 17 Panjiayuan Nanli, Chaoyang District, Beijing 100021, China,
E-mail: tianyantao@cicams.ac.cn

Received: 19 Nov 2021
Accepted: 02 Dec 2021
Published: 08 Dec 2021
J Short Name: ACMCR

Keywords:

Gastric cancer; Preoperative chemotherapy; Adjuvant chemotherapy; Peritoneal lavage cytology

Citation:

Yan-Tao Tian, Effect of Preoperative Chemotherapy and Postoperative Adjuvant Chemotherapy for Gastric Cancer with Positive Peritoneal Lavage Cytology (CY1): A Retrospective Study. Ann Clin Med Case Rep. 2021; V8(1): 1-9

1. Abstract

Background: Peritoneal metastasis is one of the most common forms of metastases for gastric cancer [1]. The 15th edition of the Japanese Classification of Gastric cancer defines patients with positive peritoneal lavage cytology (CY1) as stage IV gastric cancer [2-3]. Treatment options are inconclusive for patients whose peritoneal metastases are limited to CY1[4].

1.2. Methods: This study includes 120 patients with gastric cancer who attended the Cancer Hospital of Chinese Academy of Medical Sciences from 2013 to 2018. All patients have no clear distant metastases except for positive cytology by peritoneal lavage. 26 patients received preoperative chemotherapy and 84 patients received postoperative chemotherapy. All patients are retrospectively followed to check the overall survival time and recurrence-free survival time, and at the same time univariate and multivariate analyses are performed using Cox proportional risk models to predict the factors affecting the prognosis.

1.3. Results: Preoperative chemotherapy does not improve OS value (median OS 19.00 vs. 19.87 months, p =0.620) and RFS (median RFS 16.00 vs. 15.00 months, p =0.843) of patients. However, postoperative chemotherapy improved the OS value (median OS 23.00 vs. 14.00 months, p =0.001) and RFS (median OS 19.50 vs. 10.00 months, p =0.02) of patients. Multivariate analyses that adjuvant chemotherapy, vascular invasion and pN3b disease are significant independent risk factors for OS and RFS.

1.4. Conclusions: Patients with positive peritoneal lavage cytology after preoperative chemotherapy may not benefit from preoperative chemotherapy. However, adjuvant chemotherapy is necessary. Adjuvant chemotherapy, vascular invasion and pN3b disease are significant independent risk factors for OS and RFS.

2. Introduction

Stomach cancer is one of the most prevalent malignant tumors in the digestive system [5]. Peritoneal metastasis is one of the most common forms of gastric cancer metastasis [1], which seriously affects the prognosis of gastric cancer patients. Japanese guidelines for the treatment of gastric cancer recommend routine peritoneal lavage cytology to further clarify tumor stage and seek for guide treatment [2 - 5]. One study reported that even in cT1-2 and cN0 gastric cancer, the positive rate of lavage cytology is as high as 10.9%, and it suggested that preoperative laparoscopic exploration with lavage cytology is necessary and applicable beyond to progressive gastric cancer [6]. The 15th edition of the Japanese Classification of Gastric Cancer defines peritoneal lavage positive cytology (CY1) as a stage IV disease, which could severely

affect patient prognosis [7-8]. Laparoscopic laparoscopic lavage (LPL) for cytology is an effective and not a such expensive mean of preoperative evaluation and deserves wider dissemination [9]. The treatment of stage IV gastric cancer is based on systemic chemotherapy. However, for patients with positive peritoneal lavage cytology without clear peritoneal metastases, the treatment options will be inconclusive. The prevailing treatment option is radical resection combined with postoperative adjuvant chemotherapy, and the safety and efficacy of this method have been supported by several studies [3]. Systemic chemotherapy is important in the treatment of abdominal lavage cytology-positive gastric cancer [10]. If chemotherapy can alleviate the lesion effectively, especially if the abdominal cytology result can be converted to negative before surgery, it can effectively improve the patient's prognosis [11-15]. Previous studies on whether preoperative and postoperative adjuvant chemotherapy can provide a survival benefit for gastric cancer patients with peritoneal metastases are very scarce [2,3]. This retrospective study analyzes the efficacy of preoperative chemotherapy and postoperative adjuvant chemotherapy in gastric cancer patients with CY1P0.

3. Methods

3.1. Patients and Methods

We retrospectively collect 120 patients with gastric cancer who have always attended the Cancer Hospital of Chinese Academy of Medical Sciences from 2013 to 2018. All patients have positive preoperative peritoneal lavage cytology results and no clear peritoneal metastases or distant metastases are found (CY1P0). After preoperative lavage cytology, all patients underwent radical surgical resection with postoperative pathological findings of adenocarcinoma. 26 patients received preoperative chemotherapy and 84 patients received postoperative adjuvant chemotherapy. 26 patients who received preoperative chemotherapy have positive peritoneal lavage cytology prior to radical resection. All patients are retrospectively followed and checked for overall survival time and recurrence-free survival time, while univariate and multivariate analyses are performed using Cox proportional risk models to predict the factors affecting prognosis. We compare the OS and RFS of patients in the group receiving preoperative chemotherapy/no preoperative chemotherapy and in the group receiving postoperative adjuvant chemotherapy/no postoperative adjuvant chemotherapy, respectively. By using and analyzing Nomograms, we assess the predictive value of some meaningful indicators in patients' OS and RFS.

3.2. Statistical Analysis

Statistical analysis is also performed using R software 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria) and The SPSS 22.0 (SPSS Inc., Chicago, IL, USA). Every test is bilateral, and a difference of $P<0.05$ indicates statistical significance.

4. Results

Patient characteristics

The clinical characteristics of the patients are shown in Table 1. 26 patients received preoperative chemotherapy and 84 patients received postoperative adjuvant chemotherapy. However, there is no significant difference in clinicopathological characteristics between patients in the group receiving postoperative adjuvant chemotherapy and those in the group not receiving postoperative adjuvant chemotherapy.

OS and RFS for Preoperative chemotherapy+/-, Adjuvant chemotherapy+/-

The median survival for all patients is 19.0 months. The 1-year survival rate and 3-year survival rate are 73.1% and 21.3%, respectively.

Preoperative chemotherapy does not improve OS (median OS 19.00 vs. 19.87 months, p =0.620) (Figure 1A) and RFS (median RFS 16.00 vs. 15.00 months, p =0.843) (Figure 1B) of patients. However, postoperative chemotherapy improves the OS (median OS 23.00 vs. 14.00 months, p =0.001) (Figure 2A) and RFS (median OS 19.50 vs. 10.00 months, p =0.02) (Figure 2B) of patients.

Univariate analysis and Multivariate analysis of clinicopathologic variables in relation to OS and RFS

Table 2 and Table 3:

Univariate analyses that adjuvant chemotherapy (P = 0.001), vascular invasion (P = 0.004), pT4a-ab disease (P = 0.004) pN3b disease ($p<0.001$), are significant risk factors for OS. Tumor location (P = 0.008) adjuvant chemotherapy (P = 0.002), vascular invasion (P = 0.006), pT4a-ab disease (P = 0.002) pN3b disease ($p<0.001$), are significant risk factors for RFS. Multivariate analyses that adjuvant chemotherapy, vascular invasion and pN3b disease are significant independent risk factors for OS and RFS.

Result of Nomograms

Figure 3A and Figure 3B:

Adjuvant chemotherapy, Vascular invasion, pT4a-ab disease, pN3b disease play major roles in predicting OS and RFS in patients, especially Vascular invasion and pN3b disease.

Table 1: Patient characteristics (n = 120).

Characteristics	Adjuvant chemotherapy +(n = 83)	Adjuvant chemotherapy - (n = 37)	P value
Gender Male Female	 61 22	 28 9	0.801
Family history of cancer No Yes	 54 29	 24 13	0.983
Smoking history No Yes	 44 39	 18 19	0.866
Tumor location U M L	 11 20 52	 1 8 28	
Bormann classification Type 1 Type 2 Type 3 Type 4	 8 16 38 21	 2 10 13 12	0.491
Lauren's classification Type 1 Type 2 Type 3	 19 36 28	 7 17 13	0.887
Vascular invasion No Yes	 15 68	 3 34	0.158
pT stage Group 2-3 Group 4a-4b	 17 66	 5 32	0.362
Stage of lymph node metastasis Group 0-3a Group 3b	 44 39	 14 23	0.125

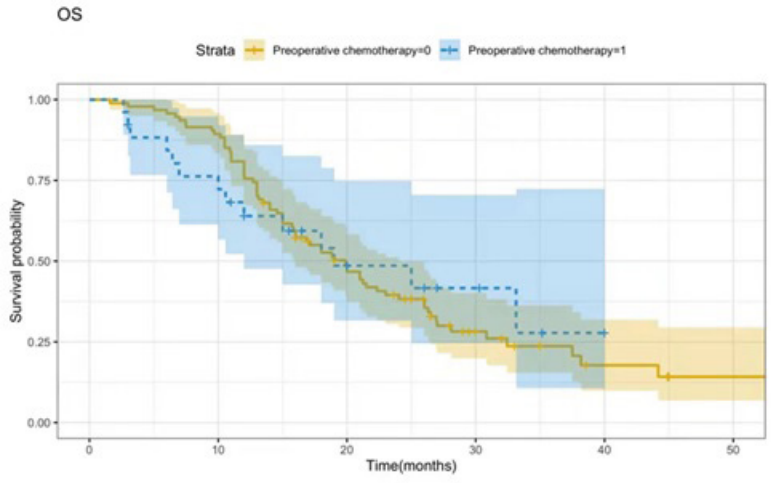

Figure 1A: OS in 94 patients (group 0, Preoperative chemotherapy-), 26 patients (group 1, Preoperative chemotherapy+), (median OS 19.00 vs. 19.87 months, p =0.620).

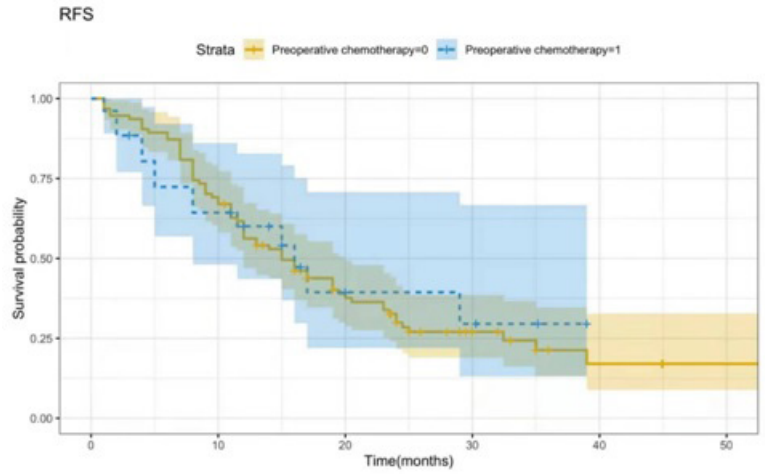

Figure 1B: RFS in 94 patients (group 0, Preoperative chemotherapy-), 26 patients (group 1, Preoperative chemotherapy+), (median RFS 16.00 vs. 15.00 months, p =0.843).

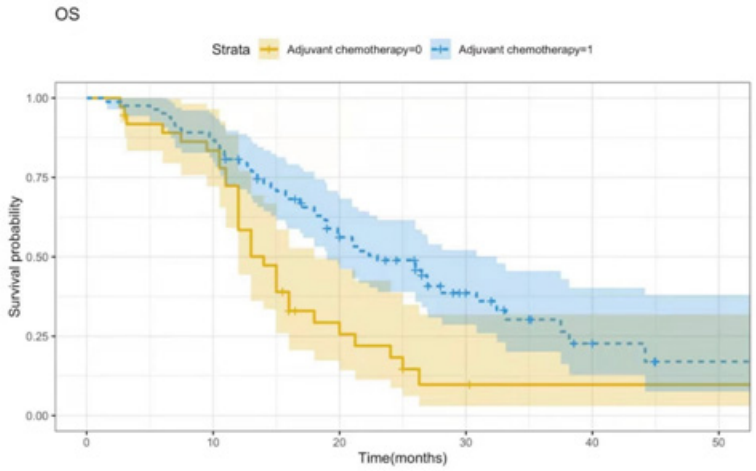

Figure 2A: OS in 37 patients (group 0, Adjuvant chemotherapy-), 83 patients (group 1, Adjuvant chemotherapy+), (median OS 23.00 vs. 14.00 months, p =0.001).

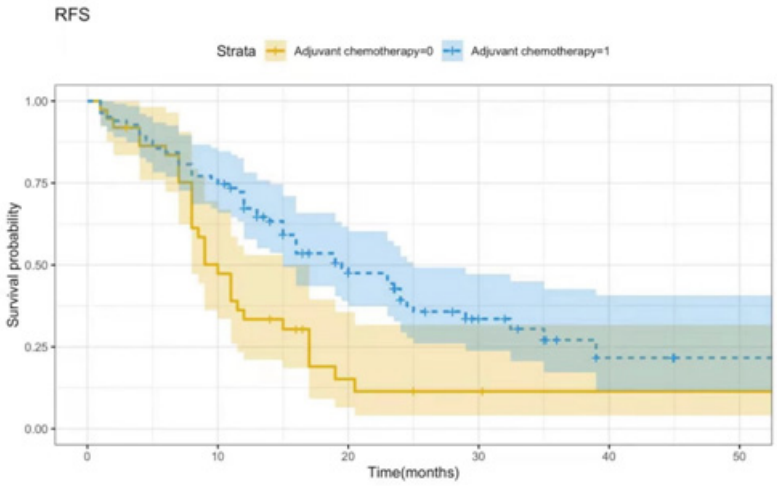

Figure 2B: RFS in 37 patients (group 0, Adjuvant chemotherapy-), 83 patients (group 1, Adjuvant chemotherapy+), (median OS 19.50 vs. 10.00 months, p =0.02).

Table 2: Univariate analysis and Multivariate analysis of clinicopathologic variables in relation to OS.

Clinicopathological features	case	Univariate analysis	P value	Multivariate analysis	P value
Gender					
Male	89		0.735		
Female	31				
Tumor location					
U	12	Reference			
M	28		0.684		
L	80		0.053		
Preoperative chemotherapy					
No	94		0.783		
Yes	26				
Adjuvant chemotherapy					
No	37	Reference	0.001	Reference	0.002
Yes	83	0.454(0.286-0.721)		0.475(0.296-0.762)	
Vascular invasion					
No	18	Reference	0.004	Reference	0.006
Yes	102	3.188(1.458-6.968)		3.047(1.371-6.771)	
Smoking history					
No	57		0.588		
Yes	63				
Family history of cancer					
No	78		0.141	Reference	0.048
Yes	42			1.600(1.003-2.551)	
pT stage					
Group 2-3	22	Reference	0.004		0.075
Group 4a-4b	98	3.124(1.439-6.782)			
Stage of lymph node metastasis					
Group 0-3a	58	Reference	＜0.001	Reference	＜0.001
Group 3b	62	2.966(1.858-4.735)		2.899(1.806-4.654)	

Table 3: Univariate analysis and Multivariate analysis of clinicopathologic variables in relation to RFS.

Clinicopathological features	case	Univariate analysis	P value	Multivariate analysis	P value
Gender					
Male	89		0.685		
Female	31				
Tumor location					
U	12	Reference			
M	28		0.108		
L	80	0.411(0.213-0.794)	0.008		
Preoperative chemotherapy					
No	94		0.812		
Yes	26				
Adjuvant chemotherapy					
No	37	Reference	0.002	Reference	0.007
Yes	83	0.483(0.305-0.765)		0.524(0.328-0.839)	
Vascular invasion					
No	18	Reference	0.006	Reference	0.048
Yes	102	2.979(1.367-6.493)		2.235(1.008-4.957)	
Smoking history					
No	57		0.437		
Yes	63				
Family history of cancer					
No	78		0.133		0.078
Yes	42				
T stage					
Group 2-3	22	Reference	0.002		0.052
Group 4a-4b	98	3.325(1.531-7.223)			
Stage of lymph node metastasis					
Group 0-3a	58	Reference	＜0.001	Reference	＜0.001
Group 3b	62	3.006(1.880-4.808)		2.811(1.748-4.521)	

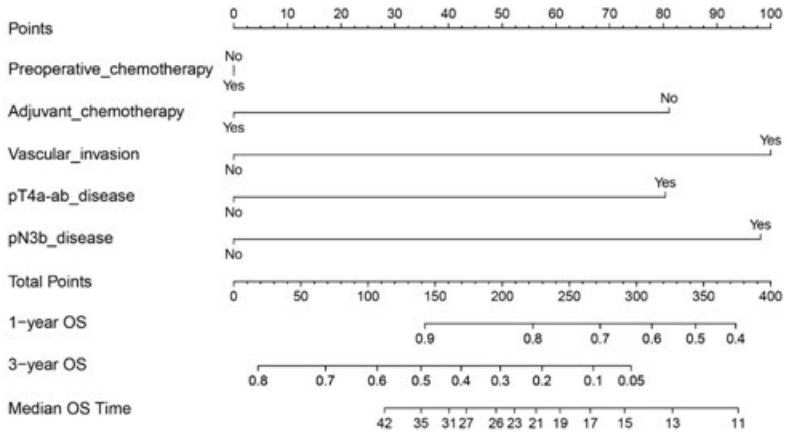

Figure 3A: Predictive value of Preoperative chemotherapy, Adjuvant chemotherapy, Vascular invasion, pT4a-ab disease, pN3b disease for OS.

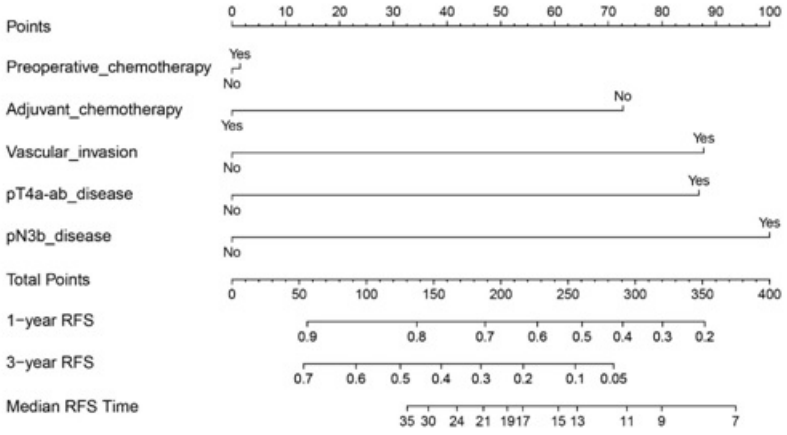

Figure 3B: Predictive value of Preoperative chemotherapy, Adjuvant chemotherapy, Vascular invasion, pT4a-ab disease, pN3b disease for RFS.

5. Discussion

At present, for patients with progressive gastric cancer, a comprehensive treatment plan of radical surgical resection combined with neoadjuvant chemotherapy and neoadjuvant radio (chemo-) therapy is mainly adopted in most situations. However, due to the lack of data from a large sample of prospective randomized controlled clinical studies, treatment options for patients with abdominal washout cytology-positive gastric cancer are relatively inconclusive [16].

Radical surgery combined with postoperative adjuvant chemotherapy has long been widely used in patients with progressive gastric cancer [17-25]. A multi-center retrospective study investigated the prognosis of patients with abdominal washout cytology (CY1) positive or limited peritoneal metastases (P1a) without macroscopically visible lesions with gastric cancer receiving different treatments. 506 patients who met the inclusion criteria underwent radical surgery, but all patients did not receive preoperative neoadjuvant therapy. Overall survivals are 29.5, 24.7, 25.4 and 9.9 months in the S-1 chemotherapy group, the S-1 combined with cisplatin chemotherapy group, the other chemotherapy regimen group, and the no chemotherapy group, respectively [3]. This result suggests that adjuvant chemotherapy can provide a survival benefit for such patients. Another clinical study also confirms the significance of adjuvant chemotherapy with S-1 after radical surgery in the treatment of patients with positive peritoneal lavage cytology. Kano K, et al. [26] observes that the survival and prognosis of 36 cytology-positive patients undergoing radical surgery and postoperative S-1 monotherapy adjuvant treatment with a median OS of 22.3 months, and the investigators confirm the efficacy of

this treatment regimen. A long-term follow-up with patients with positive abdominal washout cytology who underwent radical D2 surgery and postoperative S-1 monotherapy adjuvant therapy is made and the result has exceeded the investigators' expectations with a 2-year survival rate of 46%, a 5-year overall survival rate of 26%, and a recurrence-free survival rate of 21% [10]. According to many previous findings, radical surgery combined with postoperative adjuvant chemotherapy remains the cornerstone of treatment for progressive gastric cancer, and postoperative adjuvant chemotherapy is very essential to prolong the survival of patients with positive abdominal washout cytology.

Can preoperative chemotherapy also prolong survival for eligible CY1P0 gastric cancer patients? The investigators compare two treatment regimens of preoperative neoadjuvant chemotherapy followed by radical surgery and radical surgery followed by S-1 single-agent adjuvant chemotherapy, yielding a statistically and seemingly insignificant 5-year survival rate of 15% in both groups. The study also shows that the efficacy of preoperative chemotherapy and the extent of lymph node involvement have a significant impact on patient prognosis [27]. For these patients with positive peritoneal lavage cytology and no definite peritoneal metastases on laparoscopic exploration, chemotherapy is administered firstly and peritoneal metastases are re-evaluated by laparoscopy when gastroscopy and/or CT suggest tumor response to chemotherapy. If peritoneal lavage cytology turns negative, gastrectomy with radical lymph node dissection will be used as conversion therapy to achieve R0 resection. This treatment model is supported by much of the literature [2]. For poor prognosis type IV or type III gastric cancer larger than 8 cm in diameter, the 3-year survival rate after successful conversion therapy is 76.9%, even if the lavage cytology is positive. In contrast, the 3-year survival rates of patients undergoing palliative chemotherapy and palliative gastrectomy are 10.5% and 0%, separately [13]. A Japanese investigator has administered chemotherapy with S-1 combined with cisplatin to 41 patients with peritoneal metastases (30 of whom are positive for free abdominal cancer cells), and 19 patients had successful remission of peritoneal metastases. The median survival of these successfully converted patients undergoing radical surgery is extended from 12.6 months to 43.2 months [14]. It indicates that patients with good translational therapy may selectively benefit from radical surgery. The findings of a meta-analysis noted that negative cytologic findings after chemotherapy are associated with a significant increase in overall survivals [28].

Our study examined the role of preoperative chemotherapy versus postoperative adjuvant chemotherapy. The median survival of all patients who met the criteria for inclusion in the study is 19.0 months, suggesting a poor prognosis for this group of patients. Compared with the median survival of 9.9-12.6 months for patients treated with chemotherapy alone [29,30], surgical treatment may provide a survival benefit for patients [4]. Our study concluded that postoperative adjuvant chemotherapy is essential and crucial to prolong patients' survival. Because it is a retrospective study, peritoneal lavage cytology is performed after the completion of preoperative chemotherapy, and patients with positive results at this time suggest that preoperative chemotherapy in these patients does not improve prognosis. We therefore recommend that chemotherapy be administered to eligible patients firstly, and if the cytologic results of the reexamined peritoneal washings turn negative, radical surgical resection will be performed and the patient will likely have a significantly longer survival period. Adjuvant chemotherapy is a very necessary measure after surgery [31]. Besides, we find that vascular invasion and pN3b disease are significant independent risk factors for OS and RFS. More aggressive treatment measures should be taken for these patients. It has been reported in the literature that high postoperative neutrophil–lymphocyte ratio, low preoperative lymphocyte-monocyte ratio and low albumin levels are all associated with prognosis in CY1P0 patients [32,33].

It is clearly noted that there are still some limitations of our study, first of all, chemotherapy regimens are not explored. This study does not explore the conversion to negative peritoneal lavage cytology results after preoperative chemotherapy. The prognosis of patients with successful conversion is significantly improved according to previous literature. The number of cases included in the study is limited and it was retrospective, so the level of evidence credibility for the results is not high. Hyperthermic intraperitoneal chemotherapy has shown a unique application in the treatment of peritoneal metastatic cancer, and scholars at home and abroad have conducted a large number of basic and clinical studies, fully affirming the safety and efficacy of HIPEC [34,35]. This treatment is not discussed in our study.

6. Conclusion

The prognosis of gastric cancer patients with CY1P0 is poor and the principles of treatment are still inconclusive. Preoperative chemotherapy may not improve patients' prognosis if the patients' peritoneal lavage cytology remains positive after preoperative chemotherapy. For gastric cancer patients with CY1P0, postoperative adjuvant chemotherapy is a necessary help and can effectively prolong survival. Vascular invasion and pN3b disease are significant and independent risk factors for OS and RFS. Vascular invasion and pN3b disease also play major roles in predicting OS and RFS.

7. Funding

Supported by National Natural Science Foundation of China, No.81772642

References

1. Smyth EC, Nilsson M, Grabsch HI, van Grieken NC, Lordick F. Gastric cancer. Lancet. 2020; 396: 635-648.
2. Yamaguchi T, Takashima A, Nagashima K, Terashima M, Aizawa M, Ohashi M, et al. Impact of preoperative chemotherapy as initial treatment for advanced gastric cancer with peritoneal metastasis limited to positive peritoneal lavage cytology (CY1) or localized peritoneal metastasis (P1a): a multi-institutional retrospective study. Gastric Cancer. 2021; 24 (3): 701-709.
3. Yamaguchi T, Takashima A, Nagashima K, Makuuchi R, Aizawa M, Ohashi M, et al. Efficacy of Postoperative Chemotherapy After Resection that Leaves No Macroscopically Visible Disease of Gastric Cancer with Positive Peritoneal Lavage Cytology (CY1) or Localized Peritoneum Metastasis (P1a): A Multicenter Retrospective Study. Ann Surg Oncol 2020, 27 (1): 284-292.
4. Kang WZ, Zhong YX, Ma FH, Xue LY, Xiong JP, Ma S, et al. Survival outcomes and prognostic indicators for gastric cancer patients with positive peritoneal wash cytology but no peritoneal metastasis after radical gastrectomy. World J Gastrointest Oncol. 2021, 13 (1):24-36.
5. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, Jemal A, et al. Cancer statistics in China, 2015. CA Cancer J Clin. 2016;66 (2): 115-132.
6. Allen CJ, Blumenthaler AN, Das P, Minsky BD, Blum M, Roy-Chowdhuri S, Ajani JA, Ikoma N, Mansfield PF, Badgwell BD. Staging laparoscopy and peritoneal cytology in patients with early stage gastric adenocarcinoma. World J Surg Oncol. 2020; 18 (1): 39.
7. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 3rd English edition. Gastric Cancer 2011; 14: 101-112.
8. Japanese gastric cancer treatment guidelines 2018 (5th edition). Gastric Cancer. 2021; 24(1):1-21.
9. He Q, Zhu J, Wang A, Ji K, Ji X, Zhang J, et al J. A decision analysis comparing three strategies for peritoneal lavage cytology testing in staging of gastric cancer in China. Cancer Med. 2020; 9 (23): 8940-8949.
10. Kodera Y, Ito S, Mochizuki Y, Ohashi N, Tanaka C, Kobayashi D, et al. Longterm follow up of patients who were positive for peritoneal lavage cytology: final report from the CCOG0301 study. Gastric Cancer. 2012; 15 (3): 335-337.
11. Ishigami H, Yamaguchi H, Yamashita H, Asakage M, Kitayama J. Surgery after intraperitoneal and systemic chemotherapy for gastric cancer with peritoneal metastasis or positive peritoneal cytology findings. Gastric Cancer. 2017; 20: 128-134.
12. Shinkai M, Imano M, Chiba Y, Hiraki Y, Kato H, Iwama Met al. Intraperitoneal Administration of Paclitaxel Followed by Paclitaxel, Cisplatin, and S-1 Chemotherapy for Cytology-positive Gastric Cancer: A Feasibility Study. Anticancer Res. 2018, 38(10):5969-5974.
13. Yasufuku I, Nunobe S, Ida S, Kumagai K, Ohashi M, Hiki N, et al. Conversion therapy for peritoneal lavage cytology-positive type 4 and large type 3 gastric cancer patients selected as candidates for R0 resection by diagnostic staging laparoscopy. Gastric Cancer. 2020; 23(2): 319-327.
14. Okabe H, Ueda S, Obama K, Hosogi H, Sakai Y. Induction chemotherapy with S-1 plus cisplatin followed by surgery for treatment of gastric cancer with peritoneal dissemination. Ann Surg Oncol. 2009; 16 (12): 3227-3236.
15. Satoh S, Okabe H, Teramukai S, Hasegawa S, Ozaki N, Ueda S, et al. Phase II trial of combined treatment consisting of preoperative S-1 plus cisplatin followed by gastrectomy and postoperative S-1 for stage IV gastric cancer. Gastric Cancer. 2012; 15 (1): 61-69.
16. Cabalag CS, Chan ST, Kaneko Y, Duong CP. A systematic review and meta-analysis of gastric cancer treatment in patients with positive peritoneal cytology. Gastric Cancer. 2015;18 (1):11-22.
17. Yamashita K. Reduced preoperative serum albumin and absence of peritoneal dissemination may be predictive factors for long-term survival with advanced gastric cancer with positive cytology test. Eur J Surg Oncol. 2015; 41: 1324-1332.
18. Ishigami H. Phase III trial comparing intraperitoneal and intravenous paclitaxel plus S-1 versus cisplatin plus S-1 in patients with gastric cancer with peritoneal metastasis: PHOENIX-GC trial. J Clin Oncol. 2018; 36 (19): 1922-1929.
19. Manzanedo I. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) for gastric cancer with peritoneal carcinomatosis: multicenter study of spanish group of peritoneal oncologic surgery (GECOP). Ann Surg Oncol. 2019; 26(8): 2615-2621.
20. Okabe H. A phase 2 study of induction chemotherapy using docetaxel, cisplatin, and S1 for gastric cancer with peritoneal metastasis (KUGC06). Ann Surg Oncol. 2019; 26 (6): 1779-1786.
21. Kawazoe A. Safety and efficacy of pembrolizumab in combination with S-1 plus oxaliplatin as a first-line treatment in patients with advanced gastric/gastroesophageal junction cancer: Cohort 1 data from the KEYNOTE-659 phase IIb study. Eur J Cancer. 2020；129: 97-106.
22. Boku N. Safety and efficacy of nivolumab in combination with S-1/capecitabine plus oxaliplatin in patients with previously untreated, unresectable, advanced, or recurrent gastric/gastroesophageal junction cancer: interim results of a randomized, phase II trial (ATT RACTION-4). Ann Oncol. 2019; 30 (2): 250-258.
23. Kang Y. A phase III study of TAS-118 plus oxaliplatin versus S-1 plus cisplatin as first-line chemotherapy in patients with advanced gastric cancer (SOLAR study). Ann Oncol. 2019; 30(4): 153.
24. Fujitani K. Gastrectomy plus chemotherapy versus chemotherapy alone for advanced gastric cancer with a single non-curable factor (REGATTA): a phase 3, randomised controlled trial. Lancet Oncol. 2016; 17(3): 309-318.
25. Satoh S. Phase II trial of combined treatment consisting of preoperative S-1 plus cisplatin followed by gastrectomy and postoperative S-1 for stage IV gastric cancer. Gastric Cancer. 2012; 15(1):61-69.
26. Kano K. The survival and prognosticators of peritoneal cytolo-

gy-positive gastric cancer patients who received upfront gastrectomy and subsequent S-1 chemotherapy. Int J Clin Oncol. 2017; 22: 887-896.

27. Yamamoto M. Comparison of Neoadjuvant Chemotherapy to Surgery Followed by Adjuvant Chemotherapy in Japanese Patients with Peritoneal Lavage Cytology Positive for Gastric Carcinoma. Anticancer Res. 2015; 35 : 4859-4863.
28. Jamel S. Prognostic significance of peritoneal lavage cytology in staging gastric cancer: systematic review and meta-analysis. Gastric Cancer. 2018; 21: 10-18.
29. Yamada Y. Phase III study comparing oxaliplatin plus S-1 with cisplatin plus S-1 in chemotherapy-naive patients with advanced gastric cancer. Ann Oncol. 2015; 26:141-148
30. Nakayama I. Retrospective comparison of S-1 plus cisplatin versus S-1 monotherapy for the treatment of advanced gastric cancer patients with positive peritoneal cytology but without gross peritoneal metastasis. Int J Clin Oncol. 2017; 22: 1060-1068
31. Shim HJ, Kim HJ, Lee SH, Bae WK, Hwang EC, Cho SH. Observational Study of Peritoneal Washing Cytology-Positive Gastric Cancer without Gross Peritoneal Metastasis in Patients who Underwent Radical D2 Gastrectomy. Sci Rep 2020; 10 (1): 9549.
32. Sato S, Kunisaki C, Takahashi M, Kubo H, Tsuchiya N, Sato Ket al. High postoperative neutrophil-lymphocyte ratio and low preoperative lymphocyte-monocyte ratio predict poor prognosis in gastric cancer patients receiving gastrectomy with positive lavage cytology: a retrospective cohort study. Langenbecks Arch Surg. 2021.
33. Yamashita K, Ushiku H, Katada N, Hosoda K, Moriya H, Mieno H, et al. Reduced preoperative serum albumin and absence of peritoneal dissemination may be predictive factors for long-term survival with advanced gastric cancer with positive cytology test. Eur J Surg Oncol. 2015, 41 (10):1324-1332.
34. Coccolini F. Effect of intraperitoneal chemotherapy and peritoneal lavage in positive peritoneal cytology in gastric cancer. Systematic review and meta-analysis. Eur J Surg Oncol 2016; 42: 1261-1267.
35. Ishigami H. Phase II study of weekly intravenous and intraperitoneal paclitaxel combined with S-1 for advanced gastric cancer with peritoneal metastasis. Ann Oncol. 2010; 21: 67-70.