

The Multi-Disciplinary Management of Gastric Adenocarcinoma: The Retrospective Analysis of Outcomes of Patients Treated at Vajira Hospital

Bandidwattanawong C, MD¹, Kantrakornkiti P, MD²

¹ Division of Medical Oncology, Department of Internal Medicine, Faculty of Medicine, Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand

² Department of Internal Medicine, Faculty of Medicine, Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand

Background: Gastric adenocarcinoma is an uncommon gastrointestinal cancer in Thailand. The pathological features, pattern of relapses, treatments, and outcomes have not been explored systemically.

Objective: The primary outcome was to determine overall survival (OS) of patients. The secondary outcomes were to explore pathological features, pattern of relapses, outcomes of adjuvant and palliative treatments, and prognostic factors of survival.

Materials and Methods: The investigators conducted a retrospective analysis of patients with gastric cancer diagnosed between January 1, 2010 and December 31, 2015 and received medical attention at Vajira Hospital. Demographic data including gender, age, health schemes, histologic types, staging, surgical methods, paradigms of adjuvant treatment, metastatic sites, and chemotherapy regimens.

Results: There were 90 gastric cancer patients with adequate clinical data. The median age was 60 years (IQR 50 to 69). Most of them had infiltrative (poorly differentiated or signet-ring cell) histology (67, 74.4%) and presented with metastatic disease (42, 46.7%). The median OS of patients with stage 1/2, 3, and 4 were 85 months (IQR 19 to NR), 25 months (IQR 13 to 43), and 5 months (IQR 2 to 15), respectively. The investigators did not find the OS difference between patients receiving adjuvant chemoradiation compared to adjuvant chemotherapy. Among patients with non-metastatic diseases, patients who underwent total gastrectomy and patients with T3 to T4 were the independent factors of poor disease-free survival. Peritoneal carcinomatosis was the most common site of metastasis.

Conclusion: The outcomes of patients with gastric cancer in Thailand was poor due to the advanced stage at presentation. Compared to other parts of the world, gastric cancer in Thailand has many different features.

Keywords: Gastric cancer, Survival, Multi-disciplinary treatment, Thailand

Received 20 Feb 2020 | Revised 6 Apr 2020 | Accepted 7 Apr 2020

J Med Assoc Thai 2020;103(6):577-84

Website: <http://www.jmatonline.com>

Gastric cancer is one of the world most common gastrointestinal cancers and the leading cause of death especially in Eastern Asian countries like Japan and

Korea⁽¹⁾. In Thailand, gastric cancer is less common. It is the third most common gastrointestinal cancer behind colorectal and liver cancers⁽²⁾. Surgery with curative intent and adjuvant treatment is the mainstay of management. Gastrectomy with D2 lymph node dissection is at present the widely acceptable standard⁽³⁾. However, no worldwide consensus regarding the most proper adjuvant treatment existed. In the USA, postoperative chemoradiation is commonly used⁽⁴⁾. Among the European countries, perioperative chemotherapy is the current standard^(5,6). In Japan and Korea, postoperative chemotherapy without radiation has been proved to be the optimal option, especially after curative surgery with D2 lymph node dissection⁽⁷⁾. In Thailand, postoperative adjuvant chemoradiation with INT-0116 protocol was once the most commonly applied. However, since

Correspondence to:

Bandidwattanawong C.

Faculty of Medicine, Vajira Hospital, 681 Samsen Road, Vajiraphayaban, Dusit, Bangkok 10300, Thailand.

Phone: +66-2-2443467, **Fax:** +66-2-6687061

Email: chanyootmd@gmail.com

How to cite this article:

Bandidwattanawong C, Kantrakornkiti P. The Multi-Disciplinary Management of Gastric Adenocarcinoma: The Retrospective Analysis of Outcomes of Patients Treated at Vajira Hospital. *J Med Assoc Thai* 2020;103:577-84.

doi.org/10.35755/jmedassocthai.2020.06.11093

the results from the adjuvant chemoradiotherapy in stomach tumors (ARTIST) trial⁽⁸⁾ has demonstrated that postoperative adjuvant chemoradiation did not significantly reduce recurrence rate after D2 dissection, this paradigm is currently less popular. One of the most concerning issue of adoption of clinical practice guidelines from foreign countries is the different natural history of the same disease. Intestinal type is the most common gastric cancer cell type found in the Western and Eastern Asian countries, on the other hand, infiltrative type is the most common gastric cancer cell type found in Thailand. The investigators conducted a retrospective study to estimate the overall survival (OS) of gastric cancer patients treated at Vajira Hospital. The correlation between histopathology and patterns of recurrences or metastases was explored. The paradigms of adjuvant treatment were reported, and its outcomes were compared. The outcomes of patients with metastatic diseases were determined.

Materials and Methods

The present report was a retrospective study. The participants were the patients with gastric cancer aged from 18 years old up who received medical attention in Vajira Hospital, Navamindradhiraj University between January 1, 2010 and December 31, 2015. Baseline characteristics including age, gender, staging according to AJCC Staging System, Seventh Edition, histopathologic cell types (infiltrative versus intestinal), types of surgery, paradigms of adjuvant treatment, patterns of recurrences and sites of metastasis, and received chemotherapy in palliative setting were recorded. The data were retrieved from the hospital's electronic medical database and written medical records. The patients who had complete official pathological reports and surgical records were eligible for OS outcome evaluation. The participants who also had regular visits were eligible to determine both disease-free survival (DFS) and OS. Among participants with stage IV gastric cancer, the metastatic site(s), and palliative chemotherapy regimens used were recorded. The adjuvant therapies categorized into postoperative chemoradiation and adjuvant chemotherapy. Only participants with metastatic diseases who had confirmed radiological reports subsequently after initiation of a chemotherapy regimen were included in progression-free survival (PFS) and OS analysis, the rest were included only in OS analysis. The survival outcomes were analyzed in intent-to-treat fashion. The data were censored on December 31, 2017. The

exact date of death was determined by requesting Ministry of Interior's Census database. The present study was approved by the Ethics Committee on Medical Research, Navamindradhiraj University and funded by the Research facilitation Division, Faculty of Medicine Vajira Hospital (COA no.36/2559).

Definitions of the variables

1) DFS was determined among patients with stage 1 to 3 at presentation and calculated as the time from the date of the official pathological diagnosis was revealed as shown on the pathological report until the date of reported documentation of recurrence or metastasis or death from any causes was revealed, no matter what happened first. It was reported in months and interquartile range (IQR); 2) OS was calculated as the time from the date of the official pathological diagnosis reported to date of death from any causes. It was reported in months and IQR; 3) Histopathologic classification was based on Lauren's criteria⁽⁹⁾ classifying gastric cancer histopathology into two major subtypes, intestinal and diffuse subtypes.

Objectives

The primary objective was to evaluate the OS of all patients with gastric cancer and the OS stratified according to stages at diagnosis. The secondary objectives included 1) the DFS and OS between patients with early and locally advanced diseases (stage 1 to 3) who received adjuvant chemoradiation and who received adjuvant chemotherapy, 2) DFS of patients with stage 1 to 3, 3) OS of patients with metastatic diseases (divided into de novo metastasis group and recurrent metastasis group) who received palliative chemotherapy, and 4) the pattern of metastasis and correlation between histology classification and the pattern of metastasis.

Statistical analysis

Based on the study by Chen et al⁽⁹⁾, at least 90 patients were required to determine survival outcomes. The investigators collected demographic data including age, gender, TNM staging, histopathology, exact date of pathologic diagnosis, date of documented recurrence or metastasis and death, paradigms of adjuvant treatment (postoperative chemoradiation versus post-operative adjuvant chemotherapy), and regimens of chemotherapy in the palliative setting. The descriptive statistics were reported as mean and standard deviation or median and IQR as appropriate. Comparing the demographic data between the different groups of interest with Fisher's exact test.

Table 1. Baseline characteristics of the participants

Baseline characteristics	n (%)	Baseline characteristics	n (%)
Sex		N staging	n (%)
Male	41 (45.6)	N0	13 (14.4)
Female	49 (54.4)	N1	12 (13.3)
Age (years); median (interquartile range)	60 (50 to 69)	N2	19 (21.1)
Health scheme		N3	11 (12.2)
UC	40 (44.4)	Not known	35 (38.9)
SS	25 (27.8)	M staging	
CS	23 (25.6)	M0	48 (53.3)
Self-paid	2 (2.2)	M1	42 (46.7)
Histology		Metastatic sites	
Intestinal	18 (20.0)	Liver	6 (6.7)
Infiltrative (poorly differentiated/signet ring)	67 (74.4)	Peritoneum	33 (36.7)
Not indicated	5 (5.6)	Both	2 (2.2)
Staging		Other	1 (1.1)
Stage 1	7 (7.8)	NA*	48 (53.3)
Stage 2	11 (12.2)	Surgery	
Stage 3	30 (33.3)	Subtotal gastrectomy	24 (26.7)
Stage 4	42 (46.7)	Total gastrectomy	20 (22.2)
T staging		Laparoscopic	14 (15.6)
T1	2 (2.2)	Not done	32 (35.6)
T2	8 (8.9)	Adjuvant treatment	
T3	21 (23.3)	CCRT	12 (13.3)
T4	22 (24.4)	CMT	26 (28.9)
Unknown	37 (41.1)	Not done	10 (11.1)
		NA**	42 (46.7)

UC=universal coverage; SS=social security; CS=civil servant; NA=not applicable; CCRT=concurrent chemoradiation therapy; CMT=chemotherapy

* Presented with early/locally advanced disease, ** Presented with metastatic disease

Kaplan-Meier method was used to estimate the survival outcomes. DFS, PFS, and OS were calculated using log rank test and reported as median and IQR. Hazard ratio (HR) of DFS, PFS, and OS between different groups of interest were calculated using Cox proportional hazard model. All of the statistical data were evaluated using IBM SPSS Statistics software, version 23.0 (IBM Corp., Armonk, NY, USA). The p-value of less than 0.05 was considered significant.

Results

There were 90 patients (41 men and 49 women) included in the present analysis. Median time of follow-up was 53 months (IQR 37 to 70). Most of the patients presented with one or a combination of the following symptoms, early satiety, dyspepsia,

unexplained weight loss, and iron-deficiency anemia. Incidental abdominal finding on the gastroscopy for determining the site of the gastrointestinal hemorrhage was rarely found (five of the 90 patients, 5.55%). The investigators did not find any particular symptoms that associated with earlier or more advanced disease (data not shown). The median age at diagnosis was 60-year-old (IQR 50 to 69). Fifty-eight patients (64.44%) underwent surgery. Most of the patients (67 patients, 74.4%) had diffuse histology. Intestinal histology was less common (18 patients, 20.0%). The rest of the participants (five patients, 5.6%) had unidentified histology. Most of the patients (42 patients, 46.67%) had metastatic disease (stage 4) at presentation. Thirty (33.3%), 11 (12.2%), and seven (7.8%) patients had stage 3, 2, and 1 at presentation, respectively. The median OS of patients with stage

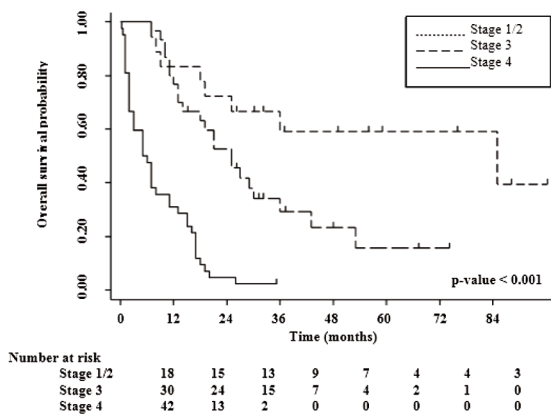


Figure 1. Kaplan-Meier curves of OS stratified by stages at diagnosis.

1/2, 3, and 4 were 85 months (IQR 19 to not reached [NR]), 25 months (IQR 13 to 43), and five (IQR 2 to 15), respectively. Peritoneal metastasis (33, 86.84%) was the most common distant site. Liver metastasis (7, 18.42%) was less common. Fifteen patients who presented with early and locally advanced disease and received curative surgery developed subsequent relapses. The systemic site was much more common than the locoregional site. Four of them had peritoneal, three of them had liver, one of them had lung, and six of them had multiple sites of metastases. Only one patient had locoregional recurrence (Table 1). The OS of patients who subsequently developed metastasis (n=14) proportionally short, the OS was seven months (IQR 4 to 12) (Figure 1).

Among patients with early diseases (stage 1 to 2; 18 patients), the DFS was 30 months (IQR 19 to 59). The DFS of patients with locally advanced disease (stage 3, 30 patients) was only 14 months (IQR 11 to 31). Adjuvant treatment was applied in 38 out of 48 patients. Adjuvant chemotherapy was the most commonly used (26 of 48 patients). Twelve of the 48 patients received adjuvant chemoradiation. Among the patients who received adjuvant treatment, the investigators found that DFS among the patients who received adjuvant chemotherapy [DFS 22 months (IQR 12 to 37)] was longer than those who received chemoradiation [DFS 12 months (IQR 11 to 59)]. However, it was not statistically different. Ten of them never received any adjuvant treatment. The reasons of not receiving adjuvant treatment were that they were very early disease (pT1-2N0M0) in two and deteriorating post-operative conditions in the rest. Figure 2 shows the Kaplan-Meier curves of DFS of patients receiving either adjuvant chemoradiation or

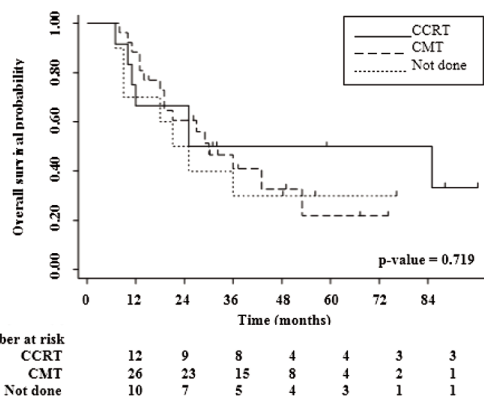


Figure 2. The Kaplan-Meier curves of DFS comparing adjuvant chemotherapy and chemoradiation.

chemotherapy and those not receiving any adjuvant treatment. Due to the small cohort of patients and retrospective design, the investigators did not find any particular paradigm with better outcome.

Patients that underwent total gastrectomy [DFS 12 months (IQR 9 to 18), adjusted HR 2.18 (95% CI 1.07 to 4.42), $p=0.031$] and patients with T3 to T4 [DFS 17 (11 to 32); adjusted HR 2.24 (95% CI 1.02 to 4.90), $p=0.044$] were significantly associated with poor DFS (Table 3). The Lauren's diffuse type adenocarcinoma was the most common histology. Nearly three fourths (74.4%) accounted for this type. Only one fifth (20%) had intestinal type. The rest had no pathologic report of classification. The investigators found no DFS differences between the patients with diffuse [DFS 22 months (IQR 11 to 37)] and intestinal subtype [DFS 19 months (IQR 13 to 74)] (Table 2).

Among patients with a metastatic disease at presentation, the peritoneal site (28/32, 87.5%) tended to be more common among patients with diffuse histology, however, no significant co-relation between histology and the preferential site of metastasis was demonstrated. There were 56 patients with metastatic (either de novo or subsequent) disease. Those who received palliative chemotherapy [n=38, OS 8 months (IQR 5 to 16)] lived longer ($p<0.001$) than those who did not [n=16; OS 2 months (IQR 1 to 3)]. The most commonly used chemotherapy regimens used was platinum (cisplatin or carboplatin or oxaliplatin) plus a fluoropyrimidine (5-FU or capecitabine).

Discussion

Gastric cancer is a less common GI cancer in Thailand compared with the Eastern Asian countries.

Table 2. Disease-free survival stratified by various baseline characteristics

Variables	n	DFS time (months)		Univariable analysis			Multivariable analysis		
		50%	IQR	HR	95% CI	p-value	HR _{adj}	95% CI	p-value
Overall	48	22	11 to 37						
Sex									
Female	25	27	11 to 48	1.00	Reference				
Male	23	19	9 to 31	1.14	0.63 to 2.06	0.662			
Age (year)									
≥50	36	22	11 to 37	1.00	Reference				
<50	12	17	10 to 32	1.34	0.68 to 2.63	0.395			
Histology									
Intestinal	12	19	13 to 74	1.00	Reference				
Infiltrative poorly differentiated/signet ring	35	22	11 to 37	2.10	0.95 to 4.64	0.068			
Not indicated	1	-	-	2.02	0.25 to 16.63	0.513			
Staging									
Stage 1/2	18	30	19 to 39	1.00	Reference		1.00	Reference	
Stage 3	30	14	11 to 31	2.22	1.17 to 4.20	0.014	1.64	0.71 to 3.79	0.247
T staging									
T1 to T2	10	49	26 to 73	1.00	Reference		1.00	Reference	
T3 to T4	38	17	11 to 32	2.38	1.13 to 5.05	0.023	2.24	1.02 to 4.90	0.044
N staging									
N0	13	30	19 to 49	1.00	Reference				
N1 to N3	35	17	11 to 37	1.24	0.65 to 2.37	0.509			
Surgery									
Subtotal gastrectomy	21	32	17 to 59	1.00	Reference		1.00	Reference	
Laparoscopic	11	26	11 to 39	1.70	0.79 to 3.68	0.176	1.87	0.86 to 4.06	0.115
Total gastrectomy	16	12	9 to 18	2.67	1.33 to 5.36	0.006	2.18	1.08 to 4.42	0.031
Adjuvant treatment									
CCRT	12	12	11 to 59	1.00	Reference				
CMT	26	22	12 to 37	1.68	0.79 to 3.59	0.178			
Not done	10	19	9 to 48	1.50	0.62 to 3.63	0.370			

DFS=disease-free survival; IQR=interquartile range; HR=hazard ratio; HR_{adj}=adjusted hazard ratio; CI=, confidence interval; CCRT=concurrent chemoradiation therapy; CMT=chemotherapy

The investigators demonstrated some adverse characteristics. Most of the Thai patients presented with advanced stage at presentation with peritoneum as the most common site of metastasis. Since INT-0116 by Macdonald et al⁽⁴⁾ had been published, the postoperative chemoradiation was the established standard of adjuvant treatment. The updated analysis⁽¹⁰⁾ demonstrated the persistent benefits of adjuvant chemoradiation compared to no treatment after curative surgery (R0 resection) in terms of relapse-free survival [27 versus 19 months, HR 1.51 (95% CI 1.25 to 1.83), p<0.001] and OS [35 versus 27 months, HR 1.32 (95% CI 1.10 to 1.60), p=0.0046].

Nevertheless, the intergroup study had many flaws. Most of the enrolled patients underwent suboptimal surgery (36% received D1 lymph node dissection and 54% received a less than D1 dissection). Moreover, only 65% of the patients in the adjuvant arm completed the planned chemoradiation. Later, the ARTIST trial⁽⁸⁾ demonstrated that the addition of chemoradiation after the widely-accepted optimal surgery (gastrectomy with D2 dissection) did not significantly reduce recurrence. However, in the subgroup of patients with pathologic lymph node metastasis at the time of surgery, the addition of postoperative chemoradiation improved (DFS). The

updated result⁽¹¹⁾ showed no significant difference in OS between both arms [5-year OS were 73% and 75% in the adjuvant chemotherapy only and adjuvant chemoradiation and chemotherapy, respectively, HR 1.130 (95% CI 0.775 to 1.647); p=0.5272]. The updated analysis of outcomes from CLASSIC study⁽¹²⁾ also demonstrated the persistent OS benefit from adjuvant chemotherapy only [5-year OS 78% (95% CI 74 to 82)] compared to observation [5-year OS 69% (95% CI 64 to 73)] after the optimal surgery with curative intent [HR 0.66 (95% CI 0.51 to 0.85), p=0.0015]. The investigators found that the outcomes in Thai patients were inferior to the pivotal trials' participants. Among participants in the present analysis who received adjuvant chemoradiation, the 3-year OS was 50% (95% CI 20.9 to 73.6) and the OS was only 25 months (IQR 11 to NR). Among participants who received adjuvant chemotherapy only, the 3-year OS was 40.9% (95% CI 20.7 to 60.1) and the OS was only 30 months (IQR 18 to 53). The investigators did not demonstrate the significant DFS and OS benefits between both paradigms. The explanations of inferior outcomes would be the worse physical and nutritional statuses compared to the participants enrolled in the pivotal trials. The quality of surgery may be a subject to be discussed. Due to the uncommon disease and no established guideline at the time of patients receiving treatment, most Thai surgeons were still unfamiliar to D2 dissection. The present study was a retrospective analysis. All of the patients were treated based on a patient's physical fitness, health scheme, and preference. Any patients who were older, unfit, and delayed time to recover after surgery tended to receive either adjuvant chemotherapy only or observation. Any patients with impaired renal function seemed to receive carboplatin rather than cisplatin and 5-fluorouracil rather than capecitabine or receive only 5-fluorouracil/leucovorin only. The investigators found only a subgroup of patients that underwent total gastrectomy and they had independent worse survival outcome. The investigators speculated that the extent of the tumor at presentation and the histologic type were rather the determinant factors of a surgical technique in particular. It is widely accepted that diffuse type requires wider surgical margins⁽¹³⁾. That is why any larger tumors at the body and the antrum with diffuse type adenocarcinoma need total gastrectomy.

Regarding the analysis of Lauren's histo-clinical outcomes, the investigators found that around three fourths of the participants had the diffuse type adenocarcinoma. This was an unusually high

prevalence of diffuse type compared to other parts of the world. According to the literature, intestinal type is the most common histologic type across the globe. In the Western countries, Polkowski et al⁽¹⁴⁾ reported a frequency of 54% for intestinal type, 32% for diffuse type, and 15% for indeterminate type. In Singapore, Teh et al⁽¹⁵⁾ denoted that 62.5% of the gastric cancer patients had intestinal type, 31.79% had diffuse type, and 5.7% had mixed type. However, in China, Qiu et al⁽¹⁶⁾ stated that the diffuse type was slightly more common. Diffuse type accounted for 49.2%, whereas intestinal type accounted for 43.7%. Muñoz et al⁽¹⁷⁾ suggested that the intestinal subtype seemed to be more common in areas with a high-risk for gastric cancer, whereas diffuse type was relatively more common in low risk area. In 1965, Lauren⁽¹⁸⁾ first proposed a histo-clinical classification. He found that the intestinal type was most commonly seen in men and older patients and the diffuse type was more frequent in women and rather younger ones. Several studies⁽¹⁹⁻²¹⁾ have demonstrated that the diffuse type had poorer prognosis. The more dismal prognosis of diffuse type is partly explained by the fact that this type usually presents with deeper invasion and propensity to migrate to peritoneum earlier. Moreover, the biomarker analyses showed that the diffuse type harbored different molecular features. Some of them were associated with worse outcomes and less immunogenic⁽¹⁸⁾. In a recent retrospective analysis of Chinese patients, diffuse type was significantly associated with younger age, female preponderance, distal location, advanced pT, advanced pN, and advanced TNM stage. Besides advanced T and N stages, diffuse type was also the independent adverse survival factor⁽¹⁶⁾. The investigators found that among patients with early and locally advanced (stage 1 to 3) stages included in the present analysis, both types had no significant difference in OS. However, among patients with metastatic diseases at presentation, peritoneal site tended to be more common among patients with diffuse histology.

Due to the retrospective study design, the investigators had to search the clinical data of patients back to 2010 to have enough power to determine the survival of the cohort. The association between *Helicobacter pylori* and disease manifestation, histology, and outcomes could not be determined due to the incomplete data. Thong-Ngam et al⁽²²⁾ reported the gastric cancer cases in King Chulalongkorn Memorial Hospital between 1994 and 1998. They found *H. pylori* infection in 17 of 25 patients with documented testing (68%). Compared to their

study, the investigators demonstrated the outcomes of multi-modality treatment established during the 2010s era. From the treatment paradigm without any adjuvant treatment to adjuvant chemo-radiation and adjuvant chemotherapy-only after D2 operation, the investigators speculated that the survival outcome was gradually improving as a result of the multi-disciplinary approach and adoption of good surgical practices. The investigators found the trend towards D2 gastrectomy and adjuvant chemotherapy among participants treated during the more recent period. The investigators also excluded the patients with gastric lymphoma and leiomyosarcoma that had unique clinical outcomes and different paradigm of management. Also noted, the leiomyosarcoma cases reported by Thong-Ngam et al⁽²²⁾ would be rather gastrointestinal stromal tumor (GIST), instead.

Conclusion

In conclusion, the investigators demonstrated the unique characteristics of gastric cancer patients in Thailand. Most of the patients presented with metastatic disease. Diffuse histology was far more common than intestinal type. Due to an uncommon disease without specific warning symptoms, the screening program for gastric cancer in Thailand is not possible. Experiences of surgeon and harmonization of the optimal surgical techniques and adjuvant treatment would lead to the improved outcomes.

What is already known on this topic?

Surgery is the mainstay of curative treatment of early or locally advanced gastric cancer. However, to improve survival, most of such patients need effective adjuvant treatment.

What this study adds?

Unfortunately, Thai gastric cancer patients usually present with advanced stage. Peritoneal carcinomatosis is the common site of metastasis. The investigators suggest that laparoscopic evaluation of peritoneal disease should be performed prior to determining further aggressive managements.

Acknowledgement

The present study has been accomplished due to the generous assistances of the surgeons, pathologists, and medical record staffs who provided crucial information.

Conflicts of interest

The authors declare no conflict of interest.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68:394-424.
2. Virani S, Bilheem S, Chansaard W, Chitapanarux I, Daoprasert K, Khuanchana S, et al. National and subnational population-based incidence of cancer in Thailand: Assessing cancers with the highest burdens. *Cancers (Basel)* 2017;9.
3. Tamura S, Takeno A, Miki H. Lymph node dissection in curative gastrectomy for advanced gastric cancer. *Int J Surg Oncol* 2011;2011:748745.
4. Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med* 2001;345:725-30.
5. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006;355:11-20.
6. Ychou M, Boige V, Pignon JP, Conroy T, Bouche O, Lebreton G, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCO multicenter phase III trial. *J Clin Oncol* 2011;29:1715-21.
7. Bang YJ, Kim YW, Yang HK, Chung HC, Park YK, Lee KH, et al. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. *Lancet* 2012;379:315-21.
8. Lee J, Lim DH, Kim S, Park SH, Park JO, Park YS, et al. Phase III trial comparing capecitabine plus cisplatin versus capecitabine plus cisplatin with concurrent capecitabine radiotherapy in completely resected gastric cancer with D2 lymph node dissection: the ARTIST trial. *J Clin Oncol* 2012;30:268-73.
9. Chen K, Xu X, Mou Y, Pan Y, Zhang R, Zhou Y, et al. Totally laparoscopic distal gastrectomy with D2 lymphadenectomy and Billroth II gastrojejunostomy for gastric cancer: short- and medium-term results of 139 consecutive cases from a single institution. *Int J Med Sci* 2013;10:1462-70.
10. Smalley SR, Benedetti JK, Haller DG, Hundahl SA, Estes NC, Ajani JA, et al. Updated analysis of SWOG-directed intergroup study 0116: a phase III trial of adjuvant radiochemotherapy versus observation after curative gastric cancer resection. *J Clin Oncol* 2012;30:2327-33.
11. Park SH, Sohn TS, Lee J, Lim DH, Hong ME, Kim KM, et al. Phase III trial to compare adjuvant chemotherapy with capecitabine and cisplatin versus concurrent chemoradiotherapy in gastric cancer: Final

- report of the adjuvant chemoradiotherapy in stomach tumors trial, including survival and subset analyses. *J Clin Oncol* 2015;33:3130-6.
12. Noh SH, Park SR, Yang HK, Chung HC, Chung IJ, Kim SW, et al. Adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): 5-year follow-up of an open-label, randomised phase 3 trial. *Lancet Oncol* 2014;15:1389-96.
 13. Meyer HJ, Holscher AH, Lordick F, Messmann H, Monig S, Schumacher C, et al. Current S3 guidelines on surgical treatment of gastric carcinoma. *Chirurg* 2012;83:31-7.
 14. Polkowski W, van Sandick JW, Offerhaus GJ, ten Kate FJ, Mulder J, Obertop H, et al. Prognostic value of Lauren classification and c-erbB-2 oncogene overexpression in adenocarcinoma of the esophagus and gastroesophageal junction. *Ann Surg Oncol* 1999;6:290-7.
 15. Teh M, Lee YS. Intestinal and diffuse carcinoma of the stomach among the ethnic and dialect groups in Singapore. *Cancer* 1987;60:921-5.
 16. Qiu MZ, Cai MY, Zhang DS, Wang ZQ, Wang DS, Li YH, et al. Clinicopathological characteristics and prognostic analysis of Lauren classification in gastric adenocarcinoma in China. *J Transl Med* 2013;11:58.
 17. Muñoz N, Correa P, Cuello C, Duque E. Histologic types of gastric carcinoma in high- and low-risk areas. *Int J Cancer* 1968;3:809-18.
 18. Ma J, Shen H, Kapesa L, Zeng S. Lauren classification and individualized chemotherapy in gastric cancer. *Oncol Lett* 2016;11:2959-64.
 19. Yamashita K, Sakuramoto S, Katada N, Futawatari N, Moriya H, Hirai K, et al. Diffuse type advanced gastric cancer showing dismal prognosis is characterized by deeper invasion and emerging peritoneal cancer cell: the latest comparative study to intestinal advanced gastric cancer. *Hepatogastroenterology* 2009;56:276-81.
 20. Kim KH, Chi CH, Lee SK, Lee D, Kubo T. Histologic types of gastric carcinoma among Koreans. *Cancer* 1972;29:1261-3.
 21. Stemmermann GN, Brown C. A survival study of intestinal and diffuse types of gastric carcinoma. *Cancer* 1974;33:1190-5.
 22. Thong-Ngam D, Tangkijvanich P, Mahachai V, Kullavanijaya P. Current status of gastric cancer in Thai patients. *J Med Assoc Thai* 2001;84:475-82.