Current Problems in Cancer 44 (2020) 100577

Contents lists available at ScienceDirect

Current Problems in Cancer

journal homepage: www.elsevier.com/locate/cpcancer

Delaying adjuvant chemotherapy in advanced gastric cancer patients: Risk factors and its impact on survival outcome

Bochao Zhao[a,*], Wu Lv[b], Jie Lin[b,*]

[a] Department of Surgical Oncology, First Affiliated Hospital of China Medical University, Shenyang, PR China
[b] Department of General Surgery, Cancer Hospital of China Medical University, Liaoning Cancer Hospital and Institute, Shenyang, PR China

ABSTRACT

Adjuvant chemotherapy following the curative resection could improve the survival outcome of advanced gastric cancer (GC) patients. However, it is unclear whether delayed initiation of adjuvant chemotherapy had a negative impact on survival outcome in GC patients. The purpose of this study was to review current published literature about the impact of delaying adjuvant chemotherapy on survival outcome and summarize risk factors for delaying adjuvant chemotherapy. Delayed initiation of adjuvant chemotherapy was quite frequent in GC patients who underwent gastrectomy due to postoperative complications, poor nutritional status, comorbid diseases and socioeconomic status. Therefore, it is important for these patients to have a sufficient and smooth transition from surgery to initiation of adjuvant chemotherapy. Based on current available evidence, there is no specific timing interval for the initiation of adjuvant chemotherapy in GC patients. Earlier initiation of adjuvant chemotherapy (<4 weeks) may not be mandatory for GC patients who underwent curative resection. However, the patients should be recommended to receive adjuvant chemotherapy within 6-8 weeks if their performance status and nutritional status were deemed to be appropriate. Minimizing postoperative complications and providing requisite nutritional advice may be helpful for timely initiation of adjuvant chemotherapy.

☆ Conflict of interest: ECS reports honororia for advisory role from BMS, Celgene and Servier outside the submitted work.

☆☆ Funding: None.

* Correspondence to: Bochao Zhao, MD, Department of Surgical Oncology, First Affiliated Hospital of China Medical University, No. 155 Nanjing North Street, Heping District, Shenyang 110001, PR China; Jie Lin, MD, Department of General Surgery, Cancer Hospital of China Medical University, Liaoning Cancer Hospital and Institute, No. 44 Xiaoheyan Road, Dadong District, Shenyang 110042, PR China

E-mail addresses: summerain2010@126.com (B. Zhao), Jielin2019_700410@163.com (J. Lin).

https://doi.org/10.1016/j.currproblcancer.2020.100577
0147-0272/

ARTICLE INFO

Keywords: Gastric cancer; Adjuvant chemotherapy; Time to initiation; Postoperative complication; Survival

Introduction

Although the survival outcome of gastric cancer patients has been significantly improved, it still is the third leading cause of cancer-related deaths in the world.[1] Curative resection with adequate lymphadenectomy is the most powerful treatment method for advanced gastric cancer patients.[2] However, a substantial proportion of these patients experience tumor recurrence even after curative resection, which makes it important to consider adjuvant treatment.[3,4] To date, increased evidence has demonstrated that gastric cancer patients with stage II-III could gain a survival benefit from adjuvant chemotherapy following the curative resection.[5,6] In East Asian countries, capecitabine plus oxaliplatin for 6 months or S-1 monotherapy for 1 year has become the standard treatment regimens, with a promising result.[6-8]

In routine clinical practice, physicians are frequently asked by their patients when adjuvant chemotherapy should be administrated after surgery. The patients concerned that delayed initiation of adjuvant chemotherapy could impair their survival. Actually, there is no specific timing interval from radical operation to initiation of adjuvant chemotherapy for gastric cancer patients. In general, adjuvant chemotherapy should be initiated within 4-8 weeks after curative resection according to the current guidelines and clinical trials.[8,9] However, whether adjuvant chemotherapy beyond a time cutoff-point has a negative impact on survival outcome of cancer patients remains controversial. Delayed initiation of adjuvant chemotherapy has been reported to be related to poorer survival outcome in colorectal cancer patients,[10,11] ovarian cancer patients,[12] breast cancer patients[13] and gastric cancer patients.[14,15] However, a few studies have demonstrated that time to initiation of adjuvant chemotherapy has no impact on tumor recurrence or cancer-related death.[16-20] In a retrospective study involving 7942 gastric cancer patients from the National Cancer Database, Greenleaf et al showed adjuvant chemotherapy the following curative resection remained effective even the starting time beyond 12 weeks.[21]

Clinical trials that determine the impact of delaying adjuvant chemotherapy on survival outcome in gastric cancer patients are not ethically permissible. In view of no consensus on this topic, more research evidence need to be provided to help us better understand this important clinical concern. In the present study, we systematically searched and reviewed current published literature about the impact of delaying adjuvant chemotherapy on the survival outcome of gastric cancer patients, and summarized risk factors for delayed initiation of adjuvant chemotherapy.

Evidence acquisition

To identify related studies, systematic search strategy was performed using PubMed, Embase and Cochrane Library databases until the end of October, 2019. The following keywords and search terms were used for this search strategy: “gastric cancer,” “adjuvant chemotherapy,” “time to initiation” and “timing for initiation.” Through these combined keywords, the primary collection of studies was defined. Besides, the reference lists of relevant articles were manually searched to identify additional relevant studies. There was no language limitation for the identification of published literature. The titles and abstracts of each retrieved studies were scanned by investigators for evaluating the topic relevance. The full text of potentially relevant studies was obtained and further assessed.

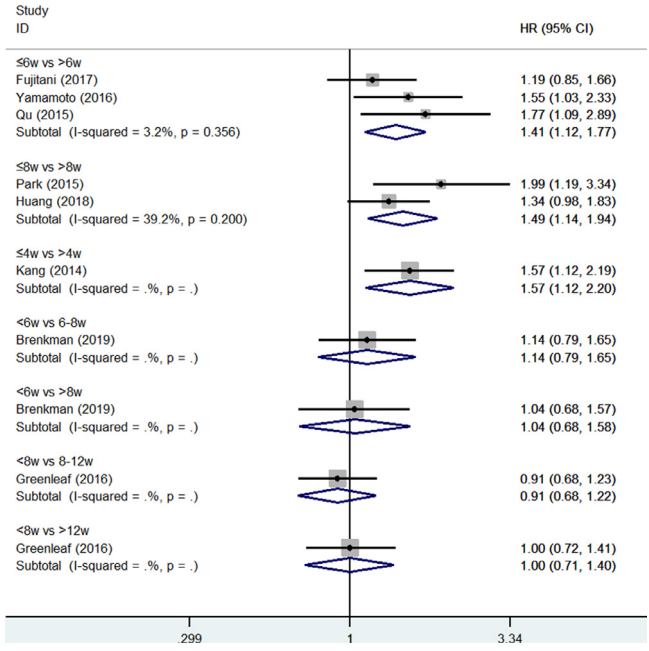

Fig. 1. Impact of delaying adjuvant chemotherapy on overall survival (OS) in gastric cancer patients.

Impact of delayed initiation of adjuvant chemotherapy on survival outcome in gastric cancer patients

A total of 11 studies have evaluated the relationship between time to initiation of adjuvant chemotherapy and survival or recurrence in gastric cancer patients. The main characteristics and detailed results of these studies were summarized in Table 1. Among these studies, 2 studies compared the prognostic difference between the initiation of adjuvant chemotherapy ≤4 weeks and >4 weeks. Lee et al showed that the initiation of adjuvant chemotherapy beyond 4 weeks had no negative impact on the recurrence-free survival (RFS) relative to the initiation of adjuvant chemotherapy within 4 weeks (HR:1.04, 95% CI: 0.62-1.74, $P > 0.05$).[22] However, Kang et al reported a significant association between delaying adjuvant chemotherapy (>4 weeks) and poorer survival in gastric cancer patients (HR:1.63, 95% CI: 1.17-2.26, $P < 0.05$).[14] In addition, the authors also used 3 weeks as the cutoff time point to distinguish between early and delayed initiation of adjuvant chemotherapy, but the results indicated that gastric cancer patients could not gain a benefit from earlier initiation of adjuvant chemotherapy (<3 weeks vs ≥3 weeks; HR:1.13, 95% CI: 0.85-1.49, $P > 0.05$).14

Three studies used 6 weeks as the cutoff point for evaluating the impact of delayed initiation of adjuvant chemotherapy on survival outcome in gastric cancer patients. Fujitani et al reported that overall survival (OS) of the patients who initiated adjuvant chemotherapy beyond 6 weeks was not different from that of those who initiated adjuvant chemotherapy within 6 weeks.[23] However, the results of Yamamoto et al and Qu et al indicated that the initiation of adjuvant chemotherapy within 6 weeks was beneficial for improved survival in gastric cancer patients who underwent curative gastrectomy.[15,24] The pooled results of 3 studies showed a similar finding that the patients with initiation of adjuvant chemotherapy beyond 6 weeks had a worse OS than those who started adjuvant chemotherapy within this interval (HR:1.41, 95% CI: 1.12-1.77, $P< 0.001$) (Fig 1).

Three studies evaluated the impact of the initiation of adjuvant chemotherapy at an 8-week interval, the pooled results indicated that delaying adjuvant chemotherapy beyond 8 weeks was

Table 1
The main characteristics and detailed results of relevant studies.

Study	Country	Inclusion period	Sample size	TNM stage	Follow-up median (range)	Time to chemotherapy median (range)	Cutoff value	Outcome and HR (95%CI)	Chemotherapy regimen	Quality
Qu et al[24]	China	2004-2013	266	I-III	28 mo (7-139)	42.5 d (12-115 d)	<45 d; ≥45 d	OS, HR:1.77(1.09-2.89)	S-1,XELOX,5-FU-based	7
Kang et al[14]	Korea	1996-2004	410	II-III	150 mo (97-195)	21 d (7-80 d)	<21 d; ≥21 d <28 d; ≥28 d	OS, HR:1.13(0.85-1.49) OS, HR:1.57(1.12-2.19)	5FU+MMC+PSK	7
Yamamoto et al[15]	Japan	2003-2013	113	II-III	47.6 mo (4.6-116)	N/A	≤6 wk; >6 wk	OS, HR:1.55(1.03-2.33)	S-1	7
Lee et al[22]	Korea	2008-2014	460	II-III	48 mo (3-101)	5 wk (2-9 wk)	≤4 wk; >4 wk	RFS, HR:1.04(0.62-1.74)	S-1,XELOX	7
Ahmed et al[25]	Canada	2002-2007	174	I-IV	18 mo (9-37)	29 d (1-109 d)	<56 d; ≥56 d	DFS, HR:1.16(0.58-2.32)	5-FU-based	6
Park et al[27]	Korea	2005-2011	840	II-III	34 mo (1-96)	5 wk (2-21 wk)	<4 wk, 4-8 wk, >8 wk;	RFS, HR:0.94(0.74-1.20) RFS, HR:1.77(1.09-2.89) OS, HR:1.10(0.83-1.45) OS, HR:2.24(1.30-3.86)	S-1,XELOX,S-1+DDP,5-FU+DDP	7
Greenleaf et al[21]	United States	2003-2012	2332	I-III	N/A	N/A	<8 wk, 8-12 wk, ≥12 wk	OS, HR:0.91(0.68-1.23) OS, HR:1.00(0.72-1.41)	N/A	6
Fujitani et al[23]	Japan	2008-2010	498	II-III	N/A	6 wk (2-20 wk)	≤6 wk; >6 wk	OS, HR:0.84(0.60-1.18)	S-1	7
Nakanishi et al[28]	Japan	2010-2014	401	II-III	45.5 mo (3.8–94)	6 wk	<6 wk, 6-8 wk, >8 wk	RFS, HR:1.19(0.77-1.81) RFS, HR:2.05(1.22-3.36)	S-1	7
Huang et al[26]	China	2006-2013	538	II-III	42.4 mo	6 wk	≤8 wk; >8 wk	RFS, HR:1.46(1.02-2.09) OS, HR:1.34(0.98-1.83)	S-1,XELOX,5-FU or 5-FU+cisplatin-based	7
Brenkman et al[30]	Netherlands	2010-2014	463	I-III	34.1 mo	6.1 wk	<6 wk, 6-8 wk, >8 wk	OS, HR:1.14(0.79-1.65) OS, HR:1.04(0.68-1.57)	epirubicin, cisplatin or oxalipatin, and capecitibine or fluorouracil	7

DDP, cisplatin; DFS, disease-free survival; 5-FU, 5-fluorouracil; HR, hazard ratio; LV, leucovorin; MMC, mitomycin-C; OS, overall survival; PSK, polysaccharide; RFS, relapse-free survival; S-1, oral fluoropyrimidine; XELOX, capeitabine plus oxaliplatin.

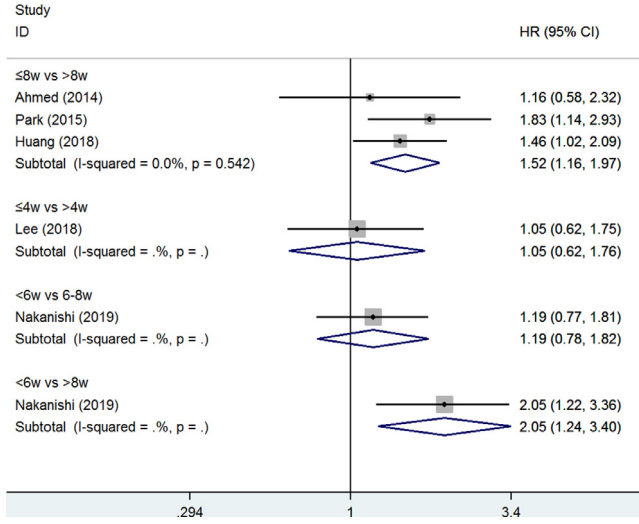

Fig. 2. Impact of delaying adjuvant chemotherapy on recurrence-free survival (RFS) in gastric cancer patients.

associated with increased risk of recurrence or death compared with the initiation within 8 weeks (Figs 1 and 2).[25-27] Similarly, Nakanishi et al reported that there was no significant prognostic difference between the starting adjuvant chemotherapy <6 weeks and 6-8 weeks in terms of RFS, but the administration of adjuvant chemotherapy beyond 8 weeks showed a higher risk of recurrence.[28]

The objective of adjuvant chemotherapy is to eradicate remaining micrometastatic cancer cells and reduce tumor recurrence. Previous animal models and studies have shown that the removal of the primary tumor could promote entry of tumor cells into the circulation and tumor angiogenesis.[29] The increased interval between operation and adjuvant chemotherapy may result in an exponential growth of cancer cells. Theoretically, adjuvant chemotherapy should be administrated as soon as possible after surgery. However, there was a time discrepancy among gastric cancer patients for the initiation of adjuvant chemotherapy, because biological behaviors of tumor, histopathological type, disease stage and postoperative recovery were various. It is difficult to determine what optimal timing for the initiation of adjuvant chemotherapy in these patients. To date, there have been no convincing evidence to support that early initiation of adjuvant chemotherapy could improve the survival outcome in gastric cancer patients. Therefore, earlier initiation of adjuvant chemotherapy (<4 weeks) may not be mandatory for gastric cancer patients who underwent curative resection. In fact, decreased interval between operation and the initiation of adjuvant chemotherapy could be detriment to the recovery of gastrointestinal function and physical condition, which further could result in a poor tolerance for adjuvant chemotherapy. Unlike breast cancer and lung cancer patients, the patients who underwent abdominal operation had a longer recovery period. Those patients who received subtotal or total gastrectomy often required a long transition period from liquid diet to normal diet. Therefore, prompt initiation of adjuvant chemotherapy seems unrealistic for gastric cancer patients. It is important to encourage them to have sufficient recovery time before the initiation of adjuvant chemotherapy. Of course, this did not mean that the protective effect of adjuvant chemotherapy could be occur irrespective of when it was initiated. Based on current available evidence, adjuvant chemotherapy should be initiated within 6-8 weeks for gastric cancer patients if their performance status and nutritional status were deemed to be appropriate. However, whether adjuvant chemotherapy beyond a certain time window had little or no impact on survival outcome of gastric cancer patients remains controversial. Brenkman et al reported that the initiation of adjuvant chemotherapy beyond 8 weeks was not associated with poorer survival outcome in gastric cancer patients.[30] Similarly, Greenleaf et al showed that delayed initiation of adjuvant

chemotherapy did not affect the prognosis of gastric cancer patients even when it was administrated later than 12 weeks after surgery.[21] They concluded that the patients who received adjuvant chemotherapy at any postoperative interval had a better prognosis than those who failed to receive systematic chemotherapy.[21] In the future, further research need be performed to answer this clinical concern.

Risk factors for delayed initiation of adjuvant chemotherapy

Aggressive efforts should be made to timely initiate adjuvant chemotherapy, but not all gastric cancer patients could fulfill treatment plan in a prescriptive timing interval. Many studies emphasized that the presence of postoperative complications was the most important risk factor for delaying adjuvant chemotherapy,[27,28,31] and severe postoperative complications increased the risk of failure to receive adjuvant chemotherapy.[32,33] Merkow et al reported that colorectal cancer patients who had severe postoperative complications were more than twice as likely to experience the omission of adjuvant chemotherapy or delayed initiation of adjuvant chemotherapy ($\geq$10 weeks).[32] It is well established that gastric cancer patients could gain a survival benefit from D2 lymph node dissection,[34,35] but a high incidence of postoperative complications and hospital mortality were reported.[36,37] Recently, some studies showed that the presence of postoperative complications, especially for severe postoperative complications such as anastomotic leakage and intra-abdominal infection, could have a negative impact on tumor recurrence and long-term survival in gastric cancer patients.[38-40] Systemic inflammatory response and immune suppression caused by surgical trauma may partially explain why postoperative complications are associated with poor survival outcome.[39,41] A large amount of cytotoxic mediators released by activated leukocytes (eg: TNF-α, IL-1, and IL-6) could provide a favorable microenvironment for the growth and invasion of residual cancer cells, resulting in a tumor recurrence.[39,42]

In a recent retrospective study, Jin et al reported an interaction between postoperative complications and failure to receive adjuvant chemotherapy. The results indicated that at least 50% of gastric cancer patients who experienced postoperative complications were less likely to receive adjuvant chemotherapy following the curative resection.[43] Compared with those patients who had no postoperative complications, the combination of postoperative complications and failure to receive adjuvant chemotherapy increased the risk of death more than 200%.[43] However, the adverse effect of postoperative complications on OS became nonsignificant for those patients who experienced postoperative complications but received adjuvant chemotherapy.[43] These results suggested that poor survival may be partially attributable to the presence of postoperative complications and not receiving adjuvant chemotherapy, empathizing the necessity of adjuvant chemotherapy and reducing postoperative complications for gastric cancer patients. A previous study demonstrated that isolated tumor cells and micrometastases were vulnerable to preoperative or postoperative chemotherapy.[44] The administration of neoadjuvant chemotherapy has been reported to improve R0 resection rate and the survival outcome of locally advanced gastric cancer patients by downstaging the tumor and eliminating micrometastases.[45,46] One particular concern was the potential increased risk of postoperative complications after neoadjuvant chemotherapy. However, increasing evidence regarding this issue have shown that neoadjuvant chemotherapy could not affect the incidence of postoperative complications.[47,48] Recently, Eto et al reported that neoadjuvant chemotherapy could abolish the poor prognosis induced by postoperative complications via eliminating micrometastases and suppressing the growth of residual tumor cells.[49] Similarly, some studies showed a prophylactic effect of neoadjuvant chemotherapy on postoperative complications in gastric cancer patients.[50,51] Therefore, preoperative and postoperative chemotherapy have an important clinical significance for the patients with high risk of postoperative complications.

On the other hand, improved surgical procedures could be helpful to reduce the incidence of postoperative complications. In the recent decade, laparoscopic gastrectomy for gastric cancer has become increasingly popular.[52,53] In the past, the primary indication for laparoscopic gastrectomy was early gastric cancer (cT1N+/-M0). Recently, laparoscopic surgery has been ap-

Table 2
Risk factors for delaying adjuvant chemotherapy identified in literature.

Treatment-related factors	Patient-related factors
Postoperative complications	Advanced age
Prolonged recovery	Comorbidities
Surgical procedure	Body weight loss (or nutritional status)
	Performance status
	Socioeconomic status
	Education level

plied to the treatment of advanced gastric cancer.[54-56] Laparoscopic gastrectomy had more advantages than open gastrectomy such as decreased surgical trauma and pain, fewer amount of intraoperative blood loss and faster recovery.[52,56,57] Some studies reported that the patients who underwent laparoscopic surgery had a shorter hospital stay and earlier initiation of adjuvant chemotherapy than those who underwent open abdominal surgery.[31,58] To accelerate the postoperative recovery and initiation of adjuvant chemotherapy, laparoscopic gastrectomy is optional for gastric cancer patients.

In addition to postoperative complications and surgical procedure, Katio et al reported that body weight loss following the gastrectomy was associated with delayed initiation of adjuvant chemotherapy.[31] Unlike other surgeries, the patients who underwent gastrectomy often lost approximately 10%-20% of their body weight after surgery, especially for those who underwent total gastrectomy.[59-61] Insufficient caloric intake was quite frequent in gastric cancer patients who underwent gastrectomy due to limited absorption of nutrients, reflux esophagitis and dumping syndrome. Body weight loss following the operation may represent a poor nutritional status and could result in a decline in postoperative quality of life.[62] The nutritional status at the initial several months was very important for the administration of adjuvant chemotherapy. The patients with poor nutritional status could delay the initiation of adjuvant chemotherapy, and even not complete chemotherapy as treatment schedule.[63] What's more, the malnutrition might increase the potential toxicity of chemotherapy drugs and chemotherapy-related adverse events.[64,65] Aoyama et al reported that the patients with body weight loss $\geq$15% had a lower 6-month continuation rate of S-1 treatment than those with body weight loss $<$15% (36.4% vs 66.4%).[63] About half of patients with body weight loss $\geq$ 15% terminated S-1 treatment due to chemotherapy-induced adverse events.[63] Some researchers believed that gastric cancer patients with severe body weight loss could gain little or no benefit from S-1 adjuvant treatment.[66] Sufficient nutritional support may improve the response to chemotherapy and radiotherapy, and provide a potential survival benefit for cancer patients. Recently, a randomized controlled trial (RCT) involving 358 digestive or lung cancer patients with body weight loss was performed to evaluate the effect of nutritional intervention before the start of chemotherapy, and the results indicated that the patients who gained weight had a better survival outcome than those who did not.[67] Therefore, the assessment of nutritional status and nutritional support should be indispensable for those patients undergoing the transition from surgery to adjuvant chemotherapy. Providing nutritional advice, dietary counseling and the prescription of oral nutritional supplement for these patients may be helpful to improve oral intake, nutritional status and even survival outcome.[68-70] In the future, RCTs involving the patients at risk of malnutrition could be designed for evaluating the impact of nutritional support on treatment toxicities and clinical outcomes during adjuvant chemotherapy.

Other patient-related factors, including advanced age, severe comorbid diseases and poor performance status, have been reported to be associated with delay or failure to receive adjuvant chemotherapy (Table 2).[58,71,72] There was a significant increase in hospital stays, the incidence of postoperative complications and re-admission with increasing age. This could inevitably impede the administration of adjuvant chemotherapy. In addition, comorbid diseases and patient performance status were another important concerns when considering the administration of adjuvant chemotherapy. It has been shown that chronic diseases, such as congestive heart fail-

ure, cerebrovascular problems, chronic obstructive pulmonary disease, renal and hepatic dysfunction, had a negative impact on decision-making and administration of adjuvant chemotherapy.[73,74] The patients with poor performance status and severe comorbid diseases were less likely to timely receive adjuvant chemotherapy. Moreover, supplemental insurance, economic status, the level of education, marital status, delayed referral and increased waiting times for oncological treatment were potential reasons for delay or failure to receive adjuvant chemotherapy.[58,75,76] These illustrated the potential impact of socioeconomic factors on timely treatment. In many institutions, the plans for adjuvant chemotherapy are based on final pathological reports of patients and are determined by collective discussion from a multidisciplinary treatment team. The clinicians explain the necessity of adjuvant chemotherapy and predict the risk of tumor recurrence for patients after the operation. This mode may avoid a delay in referral and shorten waiting times for oncological treatment. In general, the clinicians are more likely to recommend those with high recurrence risk to receive adjuvant chemotherapy. However, whether or not to receive adjuvant chemotherapy is largely depended on patients and their families. Some patients may refuse further treatment or not complete all treatment plans due to socioeconomic reasons. In fact, these factors may indirectly reflect the impact of patient compliance on therapeutic outcome of adjuvant chemotherapy in some manners. In the ESPAC-3 study evaluating optimal timing and duration of adjuvant chemotherapy, the results demonstrated that pancreatic cancer patients who completed all 6 cycles of adjuvant chemotherapy had a better survival outcome than those who failed to complete treatment plan.[77] The researchers confirmed that treatment completion rather than early initiation of adjuvant chemotherapy was associated with improved survival of these patients.[77] Similarly, Bartolomeo et al reported that failure to complete planned treatment had a negative effect on the recurrence and OS in gastric cancer patients. However, delayed initiation of adjuvant chemotherapy, at least, did not worsen the survival outcome.[78]

Limitations

Current studies evaluating the impact of delaying adjuvant chemotherapy on survival outcome in gastric cancer patients were single-center, small sample size and retrospective design. Due to basic ethical consideration and treatment needs, prospective cohort studies and RCTs were unlikely to be performed. Therefore, the level of current available evidence is relatively low. In addition, whether delayed initiation of adjuvant chemotherapy is associated with poor prognosis remain controversial. Various cutoff thresholds for delay time of adjuvant chemotherapy may limit direct comparison between different studies and result in a significant heterogeneity. It also should be noted that different studies were relatively heterogeneous in patient demographics, tumor stage, chemotherapy regimens and the dose of anticancer drugs, which might have affect the prognostic assessment for gastric cancer patients. On the other hand, many confounding factors could play a potential role in evaluating the impact of delaying adjuvant chemotherapy on survival outcome. The presence of postoperative complication was the strongest factor for delaying adjuvant chemotherapy and failure to receive adjuvant chemotherapy. Based on current retrospective studies, it is unclear that postoperative complications or delayed initiation of adjuvant chemotherapy directly impair survival of gastric cancer patients. Besides, the patients with advanced age or with multiple comorbidities or with poor nutrition status had a higher risk of postoperative complications and a higher rate of delaying adjuvant chemotherapy than other patients. Therefore, it is difficult to determine the association between delaying adjuvant chemotherapy and poor survival should be attributable to patient-specific conditions (eg: poor performance status, severe comorbidities and advanced age) or delay initiation itself. These factors were inevitable bias when evaluating the time to initiation of adjuvant treatment. A previous meta-analysis indicated that initiation of adjuvant chemotherapy per 4-week delay was associated with a significant decrease in OS but not RFS for colorectal cancer patients.[75] It is reasonable to assume that the patients with poor performance status or severe comorbidities or advanced age might have a higher risk of noncancer related deaths than other patients. In the future, further accumulation of data and high-quality studies need to be per-

formed to explore the potential association between delaying adjuvant chemotherapy and survival outcome of gastric cancer patients.

Conclusions

Delayed initiation of adjuvant chemotherapy is quite frequent in gastric cancer patients who underwent gastrectomy due to postoperative complications, poor nutritional status, comorbid diseases and socioeconomic status. Therefore, it is important for gastric cancer patients to have a sufficient and smooth transition from surgery to initiation of adjuvant chemotherapy. Earlier initiation of adjuvant chemotherapy (<4 weeks) may not be mandatory for all gastric cancer patients. However, the patients should be recommended to receive adjuvant chemotherapy within 6-8 weeks if their performance status and nutritional status were deemed to be appropriate. Minimizing postoperative complications and providing requisite nutritional advice may be helpful for timely initiation of adjuvant chemotherapy.

References

1. Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. *CA Cancer J Clin*. 2015;65:87–108.
2. Brar S, Law C, McLeod R, et al. Defining surgical quality in gastric cancer: a RAND/UCLA appropriateness study. *J Am Coll Surg*. 2013;217 347-57.e1.
3. Ychou M, Boige V, Pignon JP, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. *J Clin Oncol*. 2011;29:1715–1721.
4. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med*. 2006;355:11–20.
5. Noh SH, Park SR, Yang HK, 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;15:1389–1396.
6. Sasako M, Sakuramoto S, Katai H, et al. Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer. *J Clin Oncol*. 2011;29:4387–4393.
7. Nakamura Y, Yamanaka T, Chin K, et al. Survival outcomes of two phase 2 studies of adjuvant chemotherapy with S-1 plus oxaliplatin or capecitabine plus oxaliplatin for patients with gastric cancer after D2 gastrectomy. *Ann Surg Oncol*. 2019;26:465–472.
8. Bang YJ, Kim YW, Yang HK, et al. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. *Lancet*. 2012;379:315–321.
9. Japanese Gastric Cancer Association treatment guidelines 2010 (ver. 3). *Gastric Cancer*. 2011;14:113–123.
10. Biagi JJ, Raphael MJ, Mackillop WJ, et al. Association between time to initiation of adjuvant chemotherapy and survival in colorectal cancer: a systematic review and meta-analysis. *Jama*. 2011;305:2335–2342.
11. Nachiappan S, Askari A, Mamidanna R, et al. The impact of adjuvant chemotherapy timing on overall survival following colorectal cancer resection. *Eur J Surg Oncol*. 2015;41:1636–1644.
12. Hofstetter G, Concin N, Braicu I, et al. The time interval from surgery to start of chemotherapy significantly impacts prognosis in patients with advanced serous ovarian carcinoma - analysis of patient data in the prospective OVCAD study. *Gynecol Oncol*. 2013;131:15–20.
13. Chavez-MacGregor M, Clarke CA, Lichtensztajn DY, et al. Delayed initiation of adjuvant chemotherapy among patients with breast cancer. *JAMA Oncol*. 2016;2:322–329.
14. Kang SY, Ahn MS, Song GW, et al. Does the timing of adjuvant chemotherapy for gastric cancer influence patient outcome? *Acta Oncol*. 2015;54:1231–1234.
15. Yamamoto M, Sakaguchi Y, Kinjo N, et al. S-1 Adjuvant chemotherapy earlier after surgery clinically correlates with prognostic factors for advanced gastric cancer. *Ann Surg Oncol*. 2016;23:546–551.
16. Peixoto RD, Kumar A, Speers C, et al. Effect of delay in adjuvant oxaliplatin-based chemotherapy for stage III colon cancer. *Clin Colorectal Cancer*. 2015;14:25–30.
17. Feng Z, Wen H, Bi R, et al. Prognostic impact of the time interval from primary surgery to intravenous chemotherapy in high grade serous ovarian cancer. *Gynecol Oncol*. 2016;141:466–470.
18. Liu Y, Zhai X, Li J, et al. Is there an optimal time to initiate adjuvant chemotherapy to predict benefit of survival in non-small cell lung cancer? *Chin J Cancer Res*. 2017;29:263–271.
19. Saeed H, Hnoosh D, Huang B, et al. Defining the optimal timing of adjuvant therapy for resected pancreatic adenocarcinoma: a statewide cancer registry analysis. *J Surg Oncol*. 2016;114:451–455.
20. Salazar MC, Rosen JE, Wang Z, et al. Association of delayed adjuvant chemotherapy with survival after lung cancer surgery. *JAMA Oncol*. 2017;3:610–619.
21. Greenleaf EK, Kulaylat AN, Hollenbeak CS, et al. Timing of adjuvant chemotherapy and impact on survival for resected gastric cancer. *Ann Surg Oncol*. 2016;23:4203–4213.
22. Lee Y, Min SH, Park KB, et al. Effect of early adjuvant chemotherapy on survival of advanced gastric cancer patients: a propensity score-matched analysis. *J Gastric Cancer*. 2018;18:58–68.
23. Fujitani K, Kurokawa Y, Takeno A, et al. Time to initiation or duration of S-1 adjuvant chemotherapy; which really impacts on survival in stage II and III gastric cancer? *Gastric Cancer*. 2018;21:446–452.

24. Qu JL, Qu XJ, Li X, et al. Early initiation of fluorouracil-based adjuvant chemotherapy improves survival in patients with resectable gastric cancer. *J buon*. 2015;20:800–807.
25. Ahmed S, Iqbal N, Yadav S, et al. Time to adjuvant therapy and other variables in localized gastric and gastroesophageal junction (GEJ) cancer (IJGC-D-13-00162). *J Gastrointest Cancer*. 2014;45:284–290.
26. Huang SM, Chen YC, Chen WY, et al. Optimal timing for postsurgical adjuvant therapy in patients with gastric cancer: a propensity score matching study. *J Cancer*. 2019;10:332–340.
27. Park HS, Jung M, Kim HS, et al. Proper timing of adjuvant chemotherapy affects survival in patients with stage 2 and 3 gastric cancer. *Ann Surg Oncol*. 2015;22:224–231.
28. Nakanishi K, Kanda M, Ito S, et al. Delay in initiation of postoperative adjuvant chemotherapy with S-1 monotherapy and prognosis for gastric cancer patients: analysis of a multi-institutional dataset. *Gastric Cancer*. 2019;22:1215–1225.
29. Fisher B, Gunduz N, Coyle J, et al. Presence of a growth-stimulating factor in serum following primary tumor removal in mice. *Cancer Res*. 1989;49:1996–2001.
30. Brenkman HJF, van Putten M, Visser E, et al. Timing of postoperative chemotherapy in patients undergoing perioperative chemotherapy and gastrectomy for gastric cancer. *Surg Oncol*. 2018;27:421–427.
31. Kaito A, Kinoshita T, Shitara K, et al. Timing of initiation of adjuvant chemotherapy for gastric cancer: a case-matched comparison study of laparoscopic vs. open surgery. *Eur J Surg Oncol*. 2017;43:801–807.
32. Merkow RP, Bilimoria KY, Tomlinson JS, et al. Postoperative complications reduce adjuvant chemotherapy use in resectable pancreatic cancer. *Ann Surg*. 2014;260:372–377.
33. Kim IY, Kim BR, Kim YW. Factors affecting use and delay (>/=8 weeks) of adjuvant chemotherapy after colorectal cancer surgery and the impact of chemotherapy-use and delay on oncologic outcomes. *PLoS One*. 2015;10.
34. Randle RW, Swords DS, Levine EA, et al. Optimal extent of lymphadenectomy for gastric adenocarcinoma: a 7-institution study of the U.S. gastric cancer collaborative. *J Surg Oncol*. 2016;113:750–755.
35. Seevaratnam R, Bocicariu A, Cardoso R, et al. A meta-analysis of D1 versus D2 lymph node dissection. *Gastric Cancer*. 2012;15(Suppl 1):S60–S69.
36. Songun I, Putter H, Kranenbarg EM, et al. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. *Lancet Oncol*. 2010;11:439–449.
37. Mocellin S, McCulloch P, Kazi H, et al. Extent of lymph node dissection for adenocarcinoma of the stomach. *Cochrane Database Syst Rev*. 2015.
38. Hayashi T, Yoshikawa T, Aoyama T, et al. Impact of infectious complications on gastric cancer recurrence. *Gastric Cancer*. 2015;18:368–374.
39. Sierzega M, Kolodziejczyk P, Kulig J. Impact of anastomotic leakage on long-term survival after total gastrectomy for carcinoma of the stomach. *Br J Surg*. 2010;97:1035–1042.
40. Fujiya K, Tokunaga M, Mori K, et al. Long-term survival in patients with postoperative intra-abdominal infectious complications after curative gastrectomy for gastric cancer: a propensity score matching analysis. *Ann Surg Oncol*. 2016;23:809–816.
41. Goldfarb Y, Sorski L, Benish M, et al. Improving postoperative immune status and resistance to cancer metastasis: a combined perioperative approach of immunostimulation and prevention of excessive surgical stress responses. *Ann Surg*. 2011;253:798–810.
42. Diakos CI, Charles KA, McMillan DC, et al. Cancer-related inflammation and treatment effectiveness. *Lancet Oncol*. 2014;15:e493–e503.
43. Jin LX, Sanford DE, Squires 3rd MH, et al. Interaction of postoperative morbidity and receipt of adjuvant therapy on long-term survival after resection for gastric adenocarcinoma: results from the U.S. Gastric Cancer Collaborative. *Ann Surg Oncol*. 2016;23:2398–2408.
44. Eguchi T, Kodera Y, Nakanishi H, et al. The effect of chemotherapy against micrometastases and isolated tumor cells in lymph nodes: an in vivo study. *In Vivo*. 2008;22:707–712.
45. Schuhmacher C, Gretschel S, Lordick F, et al. Neoadjuvant chemotherapy compared with surgery alone for locally advanced cancer of the stomach and cardia: European Organisation for Research and Treatment of Cancer randomized trial 40954. *J Clin Oncol*. 2010;28:5210–5218.
46. Al-Batran SE, Homann N, Pauligk C, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. *Lancet*. 2019;393:1948–1957.
47. Ahn HS, Jeong SH, Son YG, et al. Effect of neoadjuvant chemotherapy on postoperative morbidity and mortality in patients with locally advanced gastric cancer. *Br J Surg*. 2014;101:1560–1565.
48. Fuentes E, Ahmad R, Hong TS, et al. The impact of neoadjuvant therapy for gastroesophageal adenocarcinoma on postoperative morbidity and mortality. *J Surg Oncol*. 2016;113:560–564.
49. Eto K, Hiki N, Kumagai K, et al. Prophylactic effect of neoadjuvant chemotherapy in gastric cancer patients with postoperative complications. *Gastric Cancer*. 2018;21:703–709.
50. Vicente D, Ikoma N, Chiang YJ, et al. Preoperative therapy for gastric adenocarcinoma is protective for poor oncologic outcomes in patients with complications after gastrectomy. *Ann Surg Oncol*. 2018;25:2720–2730.
51. Hayashi M, Yoshikawa T, Yura M, et al. Does neoadjuvant chemotherapy cancel out the negative survival impact induced by surgical complications after gastrectomy? *Gastric Cancer*. 2019;22:1274–1284.
52. Kim W, Kim HH, Han SU, et al. Decreased morbidity of laparoscopic distal gastrectomy compared with open distal gastrectomy for stage I gastric cancer: short-term outcomes from a multicenter randomized controlled trial (KLASS-01). *Ann Surg*. 2016;263:28–35.
53. Hu Y, Ying M, Huang C, et al. Oncologic outcomes of laparoscopy-assisted gastrectomy for advanced gastric cancer: a large-scale multicenter retrospective cohort study from China. *Surg Endosc*. 2014;28:2048–2056.
54. Kim HH, Han SU, Kim MC, et al. Long-term results of laparoscopic gastrectomy for gastric cancer: a large-scale case-control and case-matched Korean multicenter study. *J Clin Oncol*. 2014;32:627–633.
55. Park DJ, Han SU, Hyung WJ, et al. Long-term outcomes after laparoscopy-assisted gastrectomy for advanced gastric cancer: a large-scale multicenter retrospective study. *Surg Endosc*. 2012;26:1548–1553.

56. Bo T, Peiwu Y, Feng Q, et al. Laparoscopy-assisted vs. open total gastrectomy for advanced gastric cancer: long-term outcomes and technical aspects of a case-control study. *J Gastrointest Surg*. 2013;17:1202–1208.
57. Lin JX, Lin JL, Zheng CH, et al. Short- and long-term outcomes of laparoscopy-assisted versus open total gastrectomy for gastric cancer: a propensity score-matched analysis. *Oncotarget*. 2017;8:80029–80038.
58. Malietzis G, Mughal A, Currie AC, et al. Factors implicated for delay of adjuvant chemotherapy in colorectal cancer: a meta-analysis of observational studies. *Ann Surg Oncol*. 2015;22:3793–3802.
59. Abdiev S, Kodera Y, Fujiwara M, et al. Nutritional recovery after open and laparoscopic gastrectomies. *Gastric Cancer*. 2011;14:144–149.
60. Lee HH, Park JM, Song KY, et al. Survival impact of postoperative body mass index in gastric cancer patients undergoing gastrectomy. *Eur J Cancer*. 2016;52:129–137.
61. Fein M, Fuchs KH, Thalheimer A, et al. Long-term benefits of Roux-en-Y pouch reconstruction after total gastrectomy: a randomized trial. *Ann Surg*. 2008;247:759–765.
62. Ryu SW, Kim IH. Comparison of different nutritional assessments in detecting malnutrition among gastric cancer patients. *World J Gastroenterol*. 2010;16:3310–3317.
63. Aoyama T, Yoshikawa T, Shirai J, et al. Body weight loss after surgery is an independent risk factor for continuation of S-1 adjuvant chemotherapy for gastric cancer. *Ann Surg Oncol*. 2013;20:2000–2006.
64. Extermann M, Boler I, Reich RR, et al. Predicting the risk of chemotherapy toxicity in older patients: the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score. *Cancer*. 2012;118:3377–3386.
65. Andreyev HJ, Norman AR, Oates J, et al. Why do patients with weight loss have a worse outcome when undergoing chemotherapy for gastrointestinal malignancies? *Eur J Cancer*. 1998;34:503–509.
66. Aoyama T, Sato T, Maezawa Y, et al. Postoperative weight loss leads to poor survival through poor S-1 efficacy in patients with stage II/III gastric cancer. *Int J Clin Oncol*. 2017;22:476–483.
67. Baldwin C, Spiro A, McGough C, et al. Simple nutritional intervention in patients with advanced cancers of the gastrointestinal tract, non-small cell lung cancers or mesothelioma and weight loss receiving chemotherapy: a randomised controlled trial. *J Hum Nutr Diet*. 2011;24:431–440.
68. Ravasco P, Monteiro-Grillo I, Vidal PM, et al. Dietary counseling improves patient outcomes: a prospective, randomized, controlled trial in colorectal cancer patients undergoing radiotherapy. *J Clin Oncol*. 2005;23:1431–1438.
69. Baldwin C, Spiro A, Ahern R, et al. Oral nutritional interventions in malnourished patients with cancer: a systematic review and meta-analysis. *J Natl Cancer Inst*. 2012;104:371–385.
70. Cox S, Powell C, Carter B, et al. Role of nutritional status and intervention in oesophageal cancer treated with definitive chemoradiotherapy: outcomes from SCOPE1. *Br J Cancer*. 2016;115:172–177.
71. Wheeler SB, Carpenter WR, Peppercorn J, et al. Predictors of timing of adjuvant chemotherapy in older women with hormone receptor-negative, stages II-III breast cancer. *Breast Cancer Res Treat*. 2012;131:207–216.
72. Wildes TM, Kallogjeri D, Powers B, et al. The benefit of adjuvant chemotherapy in elderly patients with stage III colorectal cancer is independent of age and comorbidity. *J Geriatr Oncol*. 2010;1:48–56.
73. Gross CP, McAvay GJ, Guo Z, et al. The impact of chronic illnesses on the use and effectiveness of adjuvant chemotherapy for colon cancer. *Cancer*. 2007;109:2410–2419.
74. Aoyama T, Yoshikawa T, Hayashi T, et al. Risk factors for 6-month continuation of S-1 adjuvant chemotherapy for gastric cancer. *Gastric Cancer*. 2013;16:133–139.
75. Des Guetz G, Nicolas P, Perret GY, et al. Does delaying adjuvant chemotherapy after curative surgery for colorectal cancer impair survival? A meta-analysis. *Eur J Cancer*. 2010;46:1049–1055.
76. Lima IS, Yasui Y, Scarfe A, et al. Association between receipt and timing of adjuvant chemotherapy and survival for patients with stage III colon cancer in Alberta, Canada. *Cancer*. 2011;117:3833–3840.
77. Valle JW, Palmer D, Jackson R, et al. Optimal duration and timing of adjuvant chemotherapy after definitive surgery for ductal adenocarcinoma of the pancreas: ongoing lessons from the ESPAC-3 study. *J Clin Oncol*. 2014;32:504–512.
78. Di Bartolomeo M, Pietrantonio F, Rulli E, et al. Impact on survival of timing and duration of adjuvant chemotherapy in radically resected gastric cancer. *Tumori*. 2016;102:e15–e19.