

Could Adjuvant Chemotherapy after Surgery Benefit Elderly Patients with Advanced Gastric Cancer?

Jin Woon Jeong, In Gyu Kwon, Young-Gil Son, and Seung Wan Ryu

Department of Surgery, Keimyung University School of Medicine, Daegu, Korea

Purpose: The aim of this study was to evaluate tolerance to adjuvant chemotherapy, and to compare survival between treatments using only surgery and using surgery with adjuvant chemotherapy, in elderly patients with advanced gastric cancer who were ≥ 75 years of age.

Materials and Methods: Patients ≥ 75 years of age who were diagnosed with pathological stage II or III gastric cancer were identified retrospectively and categorized into the surgery only and surgery with adjuvant chemotherapy groups. Clinicopathological and survival data were compared between these two groups.

Results: Among the 130 patients studied, 67 patients underwent curative surgery only, and 63 patients received adjuvant chemotherapy after curative surgery. In the latter group, adverse events were reported in 24 patients (38.1%). The treatments were discontinued in 19 patients (30.2%) owing to any reason. The overall 5-year survival rates of the surgery only and the surgery with adjuvant chemotherapy groups did not differ significantly (44.1% vs. 30.7%, respectively; $P=0.804$). Among 90 death events, deaths from recurrences of gastric cancer occurred in 42 patients. Multivariate analyses revealed that the American Society of Anesthesiologists score and the depths of tumor invasions were related to survival, and the addition of adjuvant chemotherapy after surgery did not influence survival.

Conclusions: The decision for the addition of adjuvant chemotherapy for elderly patients should be taken after considering the condition of individual patients and their life expectancies.

Key Words: Aged; Chemotherapy; Adjuvant; Gastrectomy; Stomach neoplasms

Introduction

Most cancers are primarily a disease of aged people. For most cancers, including gastric cancer, the incidence rates are rising with increasing ages of patients.^{1,2} Moreover, life expectancy is increasing steadily, both in developing and developed countries. In Korea, the proportion of people who were aged 65 years or older was reported to be 13% in 2015; this is expected to in-

crease up to 21% in 2026.³ Consequently, the number of elderly patients with cancer is rapidly increasing, and there is a growing need to optimize management strategies in these patients.

An aging society stands, not only for increases in chronological age, but also for improvements in general performance status at the same age. In the past, because a greater proportion of elderly patients frequently had poor health conditions and short life expectancies at the time of their cancer diagnoses, physicians were apt to treat them with only supportive care, rather than with surgery and chemotherapy.^{4,5} In contrast, physicians currently attempt to treat these patients with more aggressive modalities, if their body functions are preserved, in spite of their advanced age. Furthermore, improvements in surgical techniques and systemic chemotherapeutic agents have contributed in making the choice to treat elderly patients diagnosed with gastric

Correspondence to: Seung Wan Ryu
Department of Surgery, Keimyung University School of Medicine, 56 Dalseong-ro, Jung-gu, Daegu 41931, Korea
Tel: +82-53-250-7386, Fax: +82-53-250-7322
E-mail: gsman@dsmc.or.kr
Received October 21, 2016
Revised October 26, 2016
Accepted October 27, 2016

© This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0>) which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

cancer. Several researchers have reported that curative surgery for gastric cancer in the elderly is feasible, and has acceptable operative morbidity and mortality.^{6,7}

Several randomized control trials and meta-analyses have demonstrated the positive effects of adjuvant chemotherapy in patients with advanced gastric cancer, in terms of cancer recurrence and patient survival.⁸⁻¹³ However, chemotherapy is toxic, and could result in severe side effects. Furthermore, age is considered a risk factor for increased toxicity and poorer tolerance to chemotherapy.¹⁴ In spite of the elevation in the mean age of patients, until recently the clinical data for elderly patients, especially for those over 75 years of age, have been limited. Even large-scale clinical trials have either included only a small number of elderly patients or excluded extremely elderly patients.¹⁵⁻¹⁸

Thus, management strategies for elderly patients with gastric cancer are still controversial, and till date the treatment guidelines for these patients are lacking. The aim of this study was to evaluate the tolerance to adjuvant chemotherapy, and to compare survival between elderly patient groups (aged ≥ 75 years) with advanced gastric cancer undergoing surgery only or surgery with adjuvant chemotherapy.

Materials and Methods

1. Patients

From January 1998 to December 2013, 307 patients ≥ 75 years of age underwent gastrectomy for histologically proven gastric adenocarcinomas. We retrospectively reviewed their medical records. Among them, 130 patients with stage II or III gastric cancer were deemed suitable to the purpose of our study. We excluded patients who had stage I gastric cancer, or had undergone palliative surgery. Cases with postoperative mortality (in cases of death within 1 month after surgery) were also excluded from our analysis. A total of 63 patients received adjuvant chemotherapy after gastrectomy (surgery with adjuvant chemotherapy group), while the other 67 patients underwent gastrectomy only (surgery only group) (Fig. 1). This study was approved by the Institutional Review Board in Keimyung University Dongsan Medical Center, Korea (IRB No. 2015-10-020).

2. Treatment (surgical procedure and chemotherapy)

All of the patients underwent distal or total gastrectomy. Billroth I or Billroth II anastomosis was performed in distal gastrectomy, and Roux-en-Y esophagojejunostomy in total gas-

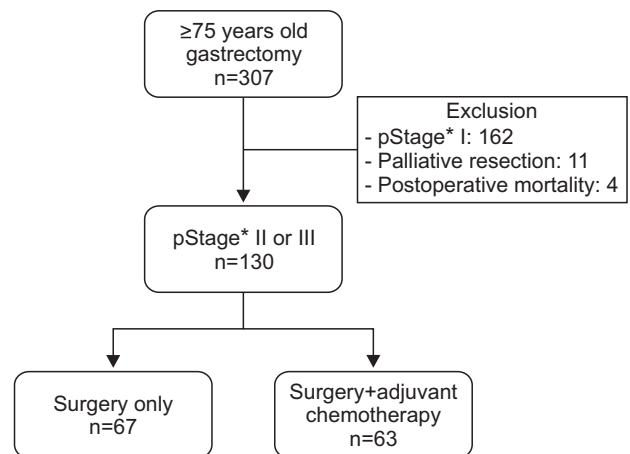


Fig. 1. Flowchart for inclusion of patients in this study. *Classification according to the American Joint Committee on Cancer 7th edition.

trectomy. Although the extent of lymph node dissections were determined with respect to the general condition of patients, at least D1+ lymph node dissection was performed for all patients.

Among the 63 patients in the surgery with adjuvant chemotherapy group, 51 patients were treated with oral 5-fluorouracil derivatives, on an outpatient basis. The regimens of the remaining 12 patients contained intravenous chemotherapeutic agents, such as 5-fluorouracil, mitomycin-C, and oxaliplatin.

3. Follow-up

For the patients in the study, physicians recommended visits to an outpatient clinic every 3 months or 6 months after finishing treatment. In compliant patients, computed tomography scans were taken every 6 months after surgery. In addition to medical records, survival records were checked and confirmed through the Statistics Korea, a national administrative institution, especially for patients who were lost to follow-up. We were able to get data on whether these patients were dead or alive, and the dates and causes of their deaths, from the Statistics Korea. The data on whether the patients were dead or alive and their dates of death were well matched, whereas the data for causes of death were uncertain or even wrong, in several cases. Therefore, in cases where medical records before deaths were inconclusive, the causes of deaths were classified as “unknown.”

4. Statistical analysis

Clinicopathological features were analyzed using the Student's t-test for continuous variables, and the chi-square test or the Fisher's exact test for categorical variables. The cumulative

survival rates were estimated by the Kaplan–Meier method. Patient survivals between the surgery only and the surgery with adjuvant chemotherapy groups were compared by log–rank test. In the estimation of disease–specific survival, only death owing to gastric cancer recurrence was regarded as a death event. Cox proportional regression test was performed to identify the impact of each factor on overall survival. In multivariate analysis for patient survival, all variables that were used for univariate analysis, and were known to be important to survival, were included. A P–value of <0.05 was considered statistically significant. All statistical analyses were performed using the IBM SPSS Statistics ver. 23 (IBM Co., Armonk, NY, USA).

Results

The mean age of patients in this study was 78.0 ± 2.7 years, and 31 patients were >80 years of age. The mean ages of the surgery only and the surgery with adjuvant chemotherapy groups were 78.4 ± 2.9 years and 77.7 ± 2.4 years, respectively. There were no statistically significant differences between the two groups, in terms of other clinicopathological findings, including sex, the American Society of Anesthesiologists (ASA) scores, body mass indexes (BMIs), types of gastrectomy, histological types, and TNM stages (Table 1).

Among the 63 patients in the surgery with adjuvant chemotherapy group, adverse events were reported in 24 patients (38.1%). Two patients (3.2%) had grade 3 or grade 4 adverse events. Discontinuations of treatments owing to any reasons occurred in 19 patients (30.2%). The reasons for withdrawal of adjuvant chemotherapeutic treatments included recurrences (in 6 patients), adverse events (in 5 patients), transfers to other hospitals (in 3 patients), poor general condition of patients (in 2 patients), presence of malignancies other than gastric cancer (in 1 patient), surgical complications (in 1 patient), and decisions of patients (in 1 patient).

There were 90 death events during the follow–up period. The overall 5–year survival rates of the surgery only and the surgery with adjuvant chemotherapy groups were similar (44.1% vs. 30.7%, respectively; $P=0.804$ by log–rank test). The disease–specific 5–year survivals were 66.7% in surgery only group, and 54.1% in surgery with adjuvant chemotherapy group, which were not statistically different ($P=0.582$). Fig. 2 shows cumulative overall and disease–specific survival graphs.

Forty–two patients died owing to recurrences of gastric cancer,

Table 1. The clinicopathologic characteristics of patients in the surgery only and the surgery with adjuvant chemotherapy groups

| Characteristic | Surgery only (n=67) | Surgery with adjuvant chemotherapy (n=63) | P-value |
|--------------------------|------------------------|----------------------------------------------------|---------|
| Age (yr) | 78.4 ± 2.9 | 77.7 ± 2.4 | 0.122 |
| <80 | 47 (70.1) | 52 (82.5) | 0.098 |
| ≥80 | 20 (29.9) | 11 (17.5) | |
| Sex | | | 0.519 |
| Male | 42 (62.7) | 36 (57.1) | 0.098 |
| Female | 25 (37.3) | 27 (42.9) | |
| ASA score | | | 0.098 |
| 1 or 2 | 47 (70.1) | 52 (82.5) | 0.503 |
| 3 or 4 | 20 (29.9) | 11 (17.5) | |
| BMI (kg/m ²) | 21.8 ± 3.1 | 22.1 ± 2.8 | 0.503 |
| Type of gastrectomy | | | 0.143 |
| Subtotal | 56 (83.6) | 46 (73.0) | 0.741 |
| Total | 11 (16.4) | 17 (27.0) | |
| Lauren classification | | | 0.741 |
| Intestinal | 32 (47.8) | 27 (42.9) | 0.502 |
| Diffuse | 34 (50.7) | 34 (54.0) | |
| Mixed | 1 (1.5) | 2 (3.2) | |
| Depth of invasion* | | | 0.502 |
| T1b | 1 (1.5) | 3 (4.8) | 0.555 |
| T2 | 5 (7.5) | 7 (11.1) | |
| T3 | 24 (35.8) | 24 (38.1) | |
| T4a | 35 (52.2) | 29 (46.0) | |
| T4b | 2 (3.0) | 0 (0.0) | |
| Lymph node metastasis* | | | |
| N0 | 15 (22.4) | 10 (15.9) | 0.254 |
| N1 | 15 (22.4) | 11 (17.5) | |
| N2 | 12 (17.9) | 16 (25.4) | |
| N3 | 25 (37.3) | 26 (41.3) | |
| Overall stage* | | | 0.254 |
| IIa | 11 (16.4) | 15 (23.8) | 0.254 |
| IIb | 15 (22.4) | 8 (12.7) | |
| IIIa | 12 (17.9) | 7 (11.1) | |
| IIIb | 11 (16.4) | 17 (27.0) | 0.254 |
| IIIc | 18 (26.9) | 16 (25.4) | |

Values are presented as mean±standard deviation or number (%). ASA = American Society of Anesthesiologists; BMI = body mass index. *Classification according to the American Joint Committee on Cancer 7th edition.

9 owing to malignancies other than gastric cancer, and 5 owing to cardiovascular or cerebrovascular diseases. The causes of death according to the times after surgery are shown in Fig. 3. The

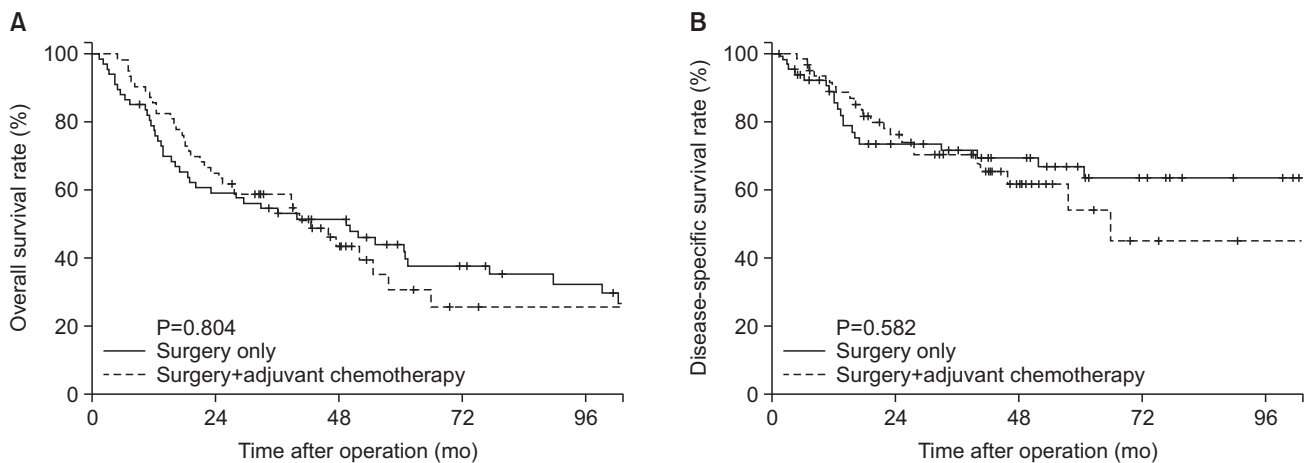


Fig. 2. Survival graphs. Comparison of (A) cumulative overall survival, and (B) cumulative disease-specific survival between the surgery only and surgery with adjuvant chemotherapy groups.

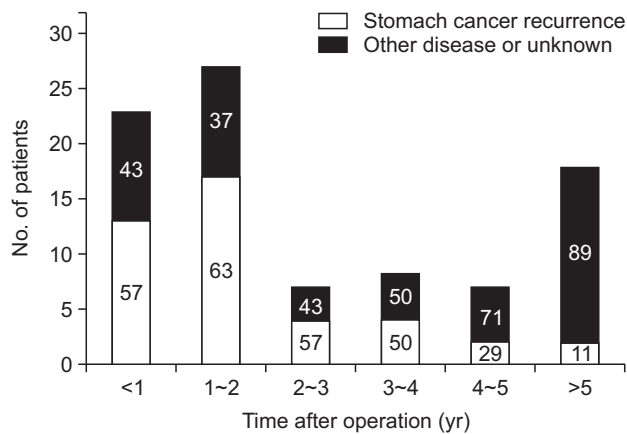


Fig. 3. The causes of deaths with respect to the times after surgery. The values are represented percent in the graph.

proportions of deaths from diseases other than stomach cancers were directly proportional to times after surgery.

The Cox regression test was performed for patient survival with respect to age, sex, ASA score, BMI, type of gastrectomy, depth of tumor invasion, lymph node metastasis, and adjuvant chemotherapy. In univariate analysis, high ASA scores, total gastrectomy, and serosa invasion were identified as risk factors for poor survival. A multivariate analysis revealed that the ASA scores and depths of tumor invasions were related to survival; however, addition of adjuvant chemotherapy after surgery did not influence survival (Table 2).

Discussion

In this study on patients aged ≥ 75 years, it appeared that the tolerance to chemotherapeutic agents in elderly patients may be

similar to that seen in younger patients. However, the addition of adjuvant chemotherapy after curative gastrectomy for these elderly patients did not improve survival beyond the values obtained by treatment with only surgery.

Oncologists are hesitant to prescribe adjuvant chemotherapy to elderly patients because of concerns regarding the high risks of complications and the low evidence of efficacy. The Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC) study demonstrated that adjuvant chemotherapy after curative gastrectomy with D2 dissection for gastric cancer improves the overall survival. A subgroup analysis revealed that the survival benefit appeared only in patients <70 years of age.¹¹ Although demographic studies define the elderly as being ≥ 65 years of age, the conditions of patients between 60 and 70 years of age generally do not have an effect on choosing the treatment strategies in most countries. Therefore, we conducted a study on patients who were aged ≥ 75 years.

The ASA score has a strong correlation with postoperative morbidity and mortality in patients treated using surgery.¹⁹ The score is determined by the severity of the underlying disease. In accordance with previous studies, in this study also high ASA scores were found to be associated with a poor prognosis. Additionally, we found that the proportion of deaths caused by diseases other than gastric cancer is high even within 3 years after surgery. Moreover, the proportion of deaths by other diseases further increased as a function of time after surgery. Therefore, underlying diseases, general condition of patients, and their life expectancies should be evaluated before prescribing adjuvant chemotherapy to elderly patients.

Lymph node metastasis is a well-known prognostic factor

Table 2. Cox proportional hazard analyses for survival (univariate and multivariate)

| Variable | Univariate | | Multivariate | |
|--------------------------|---------------------|---------|---------------------|---------|
| | HR (95% CI) | P-value | HR (95% CI) | P-value |
| Age (yr) | | 0.544 | | 0.149 |
| <80 | 1 | | 1 | |
| ≥80 | 1.16 (0.71~1.89) | | 1.449 (0.876~23.95) | |
| Sex | | 0.942 | | 0.932 |
| Male | 1 | | 1 | |
| Female | 0.984 (0.637~1.519) | | 0.980 (0.620~1.549) | |
| ASA score | | 0.003 | | 0.016 |
| 1 or 2 | 1 | | 1 | |
| 3 or 4 | 1.986 (1.256~3.141) | | 1.842 (1.122~3.024) | |
| BMI (kg/m ²) | | 0.837 | | 0.320 |
| <23 | 1 | | 1 | |
| ≥23 | 0.837 (0.533~1.313) | | 0.787 (0.490~1.262) | |
| Type of gastrectomy | | 0.007 | | 0.087 |
| Subtotal | 1 | | 1 | |
| Total | 1.994 (1.205~3.299) | | 1.605 (0.934~2.757) | |
| Depth of invasion | | 0.004 | | 0.019 |
| Serosa (-) | 1 | | 1 | |
| Serosa (+) | 1.873 (1.221~2.873) | | 1.706 (1.091~2.667) | |
| Lymph node metastasis | | 0.134 | | 0.124 |
| No | 1 | | 1 | |
| Yes | 1.536 (0.876~2.692) | | 1.579 (0.883~2.826) | |
| Adjuvant chemotherapy | | 0.804 | | 0.325 |
| No | 1 | | 1 | |
| Yes | 1.058 (0.679~1.649) | | 1.275 (0.786~2.071) | |

HR = hazard ratio; CI = confidence interval; ASA = American Society of Anesthesiologists; BMI = body mass index.

for gastric cancer. Although we observed that hazard ratios increased with lymph node metastasis (Table 2), they did not reach statistical significance. In order to validate our findings with previous findings, the study of a larger sample size may be required.

The regimens comprising S-1 or capecitabine plus oxaliplatin as adjuvant chemotherapy after curative gastrectomy for stage II and III gastric cancer have become standard treatments based on the results of the ACTS-GC and the Capecitabine and Oxaliplatin Adjuvant Study in Stomach Cancer (CLASSIC) trials.^{11,20} The majority of patients in our study received adjuvant chemotherapy with chemotherapeutic agents and doses that were different from those used in recent standard protocols. Further investigations with more homogenous patient groups who are treated according to standard protocols for adjuvant chemotherapy are required for better evaluation of chemotherapeutic regimens.

The rate of adverse events owing to chemotherapy was reportedly lower in this study than in other well-designed prospective studies, especially for grade 3 or grade 4 cancers.^{10,12} This limitation may have occurred because the present study was

a retrospective study. However, both physicians and their elderly patients tend to withdraw treatment more easily because of concerns regarding fatal complications owing to cytotoxic agents. This fact might explain the fewer adverse events seen in our study. Furthermore, it is difficult to expect full compliance to regular follow-up in the elderly. The high rate of losses to follow-up in these elderly patients makes it difficult to confirm recurrences and the times to recurrences. Therefore, our study made an effort to compensate for this limitation by including supplementing data from the Statistics Korea, a national institution. Although the overall survival were completely accounted for by the additional data, the inaccuracy of the data regarding recurrences and causes of deaths still remains a limitation of our study.

In conclusion, although the addition of adjuvant chemotherapy after curative gastrectomy for gastric cancer in general shows potential survival benefit, the need for such treatment in elderly patients should be determined by considering the conditions of individual patients and their life expectancies.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

References

1. Edwards BK, Howe HL, Ries LA, Thun MJ, Rosenberg HM, Yancik R, et al. Annual report to the nation on the status of cancer, 1973-1999, featuring implications of age and aging on U.S. cancer burden. *Cancer* 2002;94:2766-2792.
2. Shin A, Kim J, Park S. Gastric cancer epidemiology in Korea. *J Gastric Cancer* 2011;11:135-140.
3. Korean Statistical Information Service. Statistical Database; Population/Household [Internet]. Daejeon: Korean Statistical Information Service; 2016 [cited 2016 Oct 21]. Available from: http://kosis.kr/statisticsList/statisticsList_01List.jsp?vwcd=MT_ZTITILE&parentId=A#SubCont.
4. Korenaga D, Moriguchi S, Baba H, Kakeji Y, Orita H, Hara-guchi M, et al. Surgery for gastric carcinoma is feasible for patients over 80 years of age. *World J Surg* 1991;15:642-647; discussion 647-648.
5. Hanazaki K, Wakabayashi M, Sodeyama H, Miyazawa M, Yokoyama S, Sode Y, et al. Surgery for gastric cancer in patients older than 80 years of age. *Hepatogastroenterology* 1998;45:268-275.
6. Jung HS, Park YK, Ryu SY, Jeong O. Laparoscopic total gastrec-tomy in elderly patients (≥ 70 years) with gastric carcinoma: a retrospective study. *J Gastric Cancer* 2015;15:176-182.
7. Kwon IG, Cho I, Guner A, Kim HI, Noh SH, Hyung WJ. Mini-mally invasive surgery as a treatment option for gastric cancer in the elderly: comparison with open surgery for patients 80 years and older. *Surg Endosc* 2015;29:2321-2330.
8. Yamada T, Hayashi T, Aoyama T, Shirai J, Fujikawa H, Cho H, et al. Feasibility of enhanced recovery after surgery in gastric surgery: a retrospective study. *BMC Surg* 2014;14:41.
9. Yamada Y, Higuchi K, Nishikawa K, Gotoh M, Fuse N, Sugi-moto N, et al. Phase III study comparing oxaliplatin plus S-1 with cisplatin plus S-1 in chemotherapy-naïve patients with advanced gastric cancer. *Ann Oncol* 2015;26:141-148.
10. Sakuramoto S, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A, et al. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. *N Engl J Med* 2007;357:1810-1820.
11. Sasako M, Sakuramoto S, Katai H, Kinoshita T, Furukawa H, Yamaguchi T, 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.
12. 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, ran-domised controlled trial. *Lancet* 2012;379:315-321.
13. GASTRIC (Global Advanced/Adjuvant Stomach Tumor Re-search International Collaboration) Group, Paoletti X, Oba K, Burzykowski T, Michiels S, Ohashi Y, et al. Benefit of adjuvant chemotherapy for resectable gastric cancer: a meta-analysis. *JAMA* 2010;303:1729-1737.
14. Wedding U, Honecker F, Bokemeyer C, Pientka L, Höffken K. Tolerance to chemotherapy in elderly patients with cancer. *Cancer Control* 2007;14:44-56.
15. Murad AM, Santiago FF, Petroianu A, Rocha PR, Rodrigues MA, Rausch M. Modified therapy with 5-fluorouracil, doxo-rubicin, and methotrexate in advanced gastric cancer. *Cancer* 1993;72:37-41.
16. Glimelius B, Hoffman K, Haglund U, Nyrén O, Sjöden PO. Initial or delayed chemotherapy with best supportive care in advanced gastric cancer. *Ann Oncol* 1994;5:189-190.
17. Wagner AD, Unverzagt S, Grothe W, Kleber G, Grothey A, Haerting J, et al. Chemotherapy for advanced gastric cancer. *Cochrane Database Syst Rev* 2010;(3):CD004064.
18. Monfardini S, Sorio R, Boes GH, Kaye S, Serraino D. Entry and evaluation of elderly patients in European Organization for Research and Treatment of Cancer (EORTC) new-drug-development studies. *Cancer* 1995;76:333-338.
19. Kim MC, Kim W, Kim HH, Ryu SW, Ryu SY, Song KY, et al. Risk factors associated with complication following laparosco-py-assisted gastrectomy for gastric cancer: a large-scale korean multicenter study. *Ann Surg Oncol* 2008;15:2692-2700.
20. 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;15:1389-1396.