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Original Article

Safety and Efficacy of the Surgical Management of Hemodialysis Patients with Gastric Cancer

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This retrospective study evaluated the short- and long-term outcomes after surgical management for gastric cancer in hemodialysis patients compared to non-dialysis patients. Twelve hemodialysis patients were compared with a propensity score-matched cohort of 39 gastric cancer patients who had not undergone hemodialysis. Short- and long-term outcomes along with scores estimating physiological ability and surgical stress were evaluated in both groups. The incidence of postoperative morbidity according to the Clavien-Dindo classification was higher in the hemodialysis gastric cancer group than in the non-dialysis gastric cancer group. The 5-year overall survival rate in the non-dialysis group was 69.2% after surgical resection for gastric cancer and 22.2% in the hemodialysis group. Patients with preoperative risk scores ≥ 0.48 had significantly poorer survival outcomes compared to those with preoperative risk scores < 0.48 (5-year survival rate, 83.3% vs. 39.4%, respectively). Our analyses suggest that hemodialysis patients undergoing surgery for gastric cancer have a significantly poorer postoperative prognosis and an elevated risk of postoperative complications.

Key words: gastric cancer, surgery, hemodialysis, outcomes, prognosis, ESRD

Approximately 330,000 individuals in Japan currently undergo hemodialysis, a number that has been forecast to increase by 2% annually [The Japan Society for Hemodialysis Therapy: Current status of hemodialysis therapy and related clinical guideline. <http://www. jsdt. or. jp/currentstatus. html.>(accessed July, 2016). End-stage renal disease (ESRD) requiring hemodialysis is associated with poor health care outcomes, including a 10-fold increase in the risk of hospitalization and an expected lifespan shortened by 17-25% compared to that of the general population [1]. Fortunately, although the number of patients undergoing long-term hemodialysis has increased, the prognosis of hemodialysis patients has improved in recent years due to advances in areas such as dialysis technology, new drug approaches, and clinical developments [2].

Despite the well-described outcomes for ESRD in community-dwelling individuals, little is known about how long-term hemodialysis contributes to the risks of complications and death due to malignancies. A large nationwide study of ESRD patients undergoing dialysis in the US revealed a high cumulative incidence of cancer, with > 9% of such patients being diagnosed with cancer within 5 years of initiating hemodialysis therapy [3].

Gastric cancer is the second most common malignancy worldwide, and surgical treatment remains the only curative management option [4-6]. Although

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advances in surgical techniques and perioperative management have made it possible to perform a gastrectomy for gastric cancer safely, the outcomes for hemodialysis patients undergoing a gastrectomy have been unclear. We conducted the present retrospective study to evaluate the short- and long-term outcomes of hemodialysis patients after surgical management for gastric cancer, compared to non-dialysis gastric cancer patients with normal renal function. We also assessed the patients' immunological status, consisting of the 'inflammation status' and 'nutritional condition', as this is important for the survival of patients with various cancers. For the first time, the Estimation of Physiologic Ability and Surgical Stress (E-PASS) scoring system, originally developed for a comparative audit of general surgical patients, was used herein to test whether the E-PASS scores can predict long-term outcomes after gastrectomy in hemodialysis gastric cancer patients [7, 8].

Patients and Methods

Patients. The diagnosis of gastric cancer was made initially based on imaging and then confirmed by pathological analysis. We retrospectively reviewed the surgical pathology database of the Kochi Health Sciences Center (Kochi, Japan) to identify the patients who underwent a resection for gastric neoplasms from March 2005 to December 2014. The clinical characteristics evaluated included age, gender, parts of the tumor, size of the tumor, operative procedures, and pathological data. Our department followed the prognosis of each patient and obtained accurate outcome details. This series included patients with adenocarcinoma of the stomach and excluded those with gastrointestinal a stromal tumor, carcinoid, or neuroendocrine tumor.

Each surgically resected specimen was macroscopically examined to determine the maximum tumor diameter. We assessed the location of the gastric cancer, the size of the tumor, stage, the depth of invasion, the degree of differentiation, vascular invasion, lymphatic permeation, and lymph node metastasis according to the staging system of the TNM Committee of the Japanese classification of gastric cancer (3rd English edition) [9, 10]. This study was approved by the Ethics Committee of the Kochi Health Sciences Center, and all patients provided written informed consent for their specimens and data to be used and published.

Assessment. The study data were prospectively collected and retrospectively analyzed by a biostatistician (T. I.). A propensity score-matched analysis was performed to match the hemodialysis patients with the control, non-dialysis gastric cancer patients with normal renal function based on five values (gender, age, stage, type of surgery, and year of operation) that we speculated might impact the outcome of radical surgery. Surgical complications were determined from the patient records during hospitalization and within 30 days after surgery, and were then stratified according to the Clavien-Dindo (C-D) classification [11]. Overall survival was calculated from the date of curative surgery for gastric cancer until the date of documentation of recurrent disease or death. The prognostic nutritional index (PNI), a predictor of poor prognosis that is used to assess the immune-nutritional status of patients undergoing gastrointestinal surgery, was calculated from the complete blood count routinely performed before surgery [12-14].

The primary endpoint of this study was overall survival in patients with gastric cancer after intent-to-cure surgical management, compared between the group of hemodialysis patients and the control group of patients with normal renal function and therefore without dialysis. The secondary comparative endpoint was the incidence of postoperative morbidities. We also assessed the correlations between the incidence of postoperative complications and the preoperative risk score (PRS), the surgical stress score (SSS), and the comprehensive risk score (CRS) of the E-PASS scoring system in both groups of patients.

Statistical analysis. Patients alive in October 2015 were right-censored at the time of follow-up. We compared qualitative variables with the chi-square test or Fisher's test, whereas quantitative variables were analyzed using *t*-tests or a nonparametric test. Survival data were determined using a stratified log-rank test. All tests were two-sided, with a p-value < 0.05 considered significant. All analyses were performed using SPSS® software (SPSS, Chicago, IL, USA). Overall survival and disease-free survival were estimated using the Kaplan-Meier method [15].

Results

Patients. Among the 1,418 patients with gastric

cancer who underwent surgical resection at Kochi Health Sciences Center during the period described above, only 12 patients (10 males and 2 females) also underwent hemodialysis for ESRD. The mean duration of dialysis in these 12 patients was 6.5 years (range 1-33 years). Our comparison of these 12 hemodialysis patients with gastric cancer to the 39 non-dialysis patients with gastric cancer, matched for gender, age, stage, type of surgery, and year of operation revealed no difference in body mass index between the groups.

Table 1 summarizes the preoperative clinical profiles of the patients in both groups. Clinical symptoms were present in 21 of the control patients (53.8%) and in all of the hemodialysis patients. Interestingly, gastric cancer was discovered due to anemia and/or tarry stool in the hemodialysis patients, but in the non-dialysis patients the gastric cancer was discovered due to abdominal pain and/or during the group examination. There was no significant difference in the prevalence of complicated concurrent or previous diseases between the dialysis and non-dialysis patients.

The baseline preoperative values of all laboratory parameters were comparable between the groups, except for several parameters related to renal function, as expected. Serum albumin, hemoglobin, serum creatinine, and blood urea nitrogen levels in the non-dialysis patients were significantly preserved compared to those in the hemodialysis patients ($p < 0.001$). The PNI in the non-dialysis group was also significantly higher compared to the hemodialysis patients ($p < 0.05$). Moreover, both the PRS and CRS of the E-PASS scoring system were significantly greater in the hemodialysis patients compared to the control group ($p < 0.05$).

Operative characteristics and oncologic behavior. Table 2 summarizes the operative characteristics of the 51 patients who underwent gastric surgery (the 12 hemodialysis patients + the 39 non-dialysis patients). Distal gastrectomy was performed in 34 patients and

Table 1 Preoperative characteristics in patients with gastric cancer

Characteristics	GC (n = 39)	HD-GC (n = 12)	*P* value
Age, mean (range), years	72 (52–87)	72 (52–87)	matching
Gender (male/female)	36/3	10/2	matching
Body mass index	22.2 ± 3.1	21.9 ± 2.9	0.275
Clinical symptoms	21 (53.8)	12 (100.0)	0.004
Anemia	6 (15.4)	7 (58.3)	0.006
Abdominal pain	10 (25.6)	0 (0.0)	0.092
Body weight loss	3 (7.8)	0 (0.0)	1.000
Tarry stool	1 (2.6)	7 (58.3)	0.001
Group examination	17 (43.6)	0 (0.0)	0.004
Concurrent diseases			
Diabetes	14 (35.9)	3 (25.0)	0.728
Hypertension	13 (33.3)	3 (25.0)	0.730
Ischemic heart diseases	4 (10.3)	1 (8.3)	1.000
Respiratory diseases	3 (7.8)	3 (25.0)	0.134
Brain infarction	2 (5.2)	3 (25.0)	0.078
Preoperative parameters			
Albumin (g/dL)	3.9 ± 0.5	3.4 ± 0.8	0.073
Hemoglobin (g/dL)	12.2 ± 2.3	9.8 ± 1.5	< 0.001
Creatinine (mg/dL)	0.9 ± 0.2	7.1 ± 3.1	< 0.001
Blood urea nitrogen (mg/dL)	15.4 ± 5.3	36.5 ± 18.5	< 0.001
Hemoglobin A1c (%)	5.7 ± 0.8	5.3 ± 1.6	0.323
Prognostic nutritional index	47.7 ± 9.9	40.0 ± 8.9	0.023
E-PASS score			
Preoperative risk score	0.49 ± 0.20	0.58 ± 0.28	0.035
Surgical stress score	0.19 ± 0.14	0.17 ± 0.06	0.087
Comprehensive risk score	0.33 ± 0.27	0.45 ± 0.28	0.016

Values are mean ± SD, or n (%), unless otherwise indicated. GC matched gastric cancer patients, HD-GC hemodialysis patients with gastric cancer, *n* number of patients, E-PASS estimation of physiologic ability and surgical stress.

total gastrectomy in 17 patients. For all of the patients who underwent stomach resection, the gastrectomy consisted of attempted curative resection with regional lymphadenectomy. The operation time and volume of blood loss did not differ significantly between the non-dialysis and hemodialysis patient groups: operation time, 225 ± 97 min and 184 ± 41 min; blood loss volume, 175 ± 166 mL and 275 ± 224 mL, respectively; Table 2. The oncology of the resected tumors also did not differ significantly between these groups.

Short-term outcomes. There was no postoperative mortality in this series. The incidence of postoperative complications (*i.e.*, postoperative pneumonia and anastomotic leakage) was lower in the non-dialysis group than in the hemodialysis group, although the difference was not significant (Table 2). Overall, the incidence of postoperative morbidity according to the C-D classification was significantly higher in the hemodialysis group than in control patients ($p = 0.002$, Table 2). Notably, the hemodialysis gastric cancer patients required a length of hospitalization that was similar to that of the non-dialysis gastric cancer patients.

Long-term outcomes. The causes of death in this study are shown in Table 2. The hemodialysis gastric cancer patients had a significantly higher frequency of death due to other diseases rather than recurrence of gastric cancer compared to the non-dialysis gastric cancer patients ($p = 0.006$), especially for pneumonia (four hemodialysis patients *vs.* one non-dialysis patient). The length of patient follow-up as of October 2015 ranged from 3 to 101 months, with a median of 60.0 months (mean 43.9 months). The overall survival rate at 5 years

Table 2 Operative and postoperative characteristics in patients with gastric cancer

Characteristics	GC (n = 39)	HD-GC (n = 12)	*P* value
Type of surgery			matching
Distal gastrectomy	26	8	
Total gastrectomy	13	4	
Blood loss volume (mL)	175 ± 166	275 ± 224	0.184
Operation time (min)	225 ± 97	184 ± 41	0.072
Pathological findings			
Size of tumor (cm)	5.0 ± 5.6	5.0 ± 2.9	0.391
Depth of invasion			
pT1/pT2/pT3/pT4	11/8/4/3	5/4/2/1	0.965
Lymph node metastases	11	7	0.118
Vascular invasion	20	8	0.545
Lymphatic permeation	14	6	0.591
Liver metastasis	2	1	0.561
Pathological stage Ⅰ/Ⅱ/Ⅲ/Ⅳ	14/6/2/4	6/3/2/1	matching
Mortality	0	0	1.000
Morbidities			
Pneumonia	0	2	0.052
Anastomotic leakage	0	1	0.235
Delirium	2	0	1.000
Clavien-Dindo grade Ⅲ-Ⅴ	0	4	0.002
Hospital stay (days)	14 ± 5	15±154	0.313
Causes of death			
Cancer recurrence	9	3	1.000
Pneumonia	1	4	0.009
Other malignancies	1*	2**	0.134
Sudden cardiac arrest	0	1	0.235
Decrepitude	3	0	1.000

Values are mean±SD or the number of patients. GC matched gastric cancer patients, HD-GC hemodialysis patients with gastric cancer, *n* number of patients, pT1 tumor invasion into lamina propria, muscularis mucosae, or submucosa, pT2 tumor invasion into muscularis propria, pT3 tumor invasion into subserosa, pT4 tumor perforation of serosa, or invasion to adjacent organs. *colonic cancer in one patient after surgical resection for gastric cancer; **lung cancer in 2 patients after surgical resection for gastric cancer.

in the non-dialysis group was 69.2% after surgical resection for gastric cancer, but only 22.2% in the hemodialysis gastric cancer patients ($p=0.004$, Fig. 1).

Sub-group analyses. Our subgroup analyses of postoperative morbidities according to the patients' preoperative baseline characteristics showed no significant correlation of nutritional status, including PNI, PRS, SSS, and CRS, to postoperative complications in gastrectomized patients, regardless of the dialysis state. Fig. 2 illustrates the relationships among the PRS, the incidence of postoperative complications, and the grade of morbidity according to the C-D classification. A significant positive association was revealed between the PRS and the postoperative complications ($p<0.05$).

However, the subgroup analysis of survival according to the patients' preoperative baseline characteristics showed a significant difference between the non-dialysis and hemodialysis gastric cancer patients for PRS (Spearman product-moment correlation coefficient, $r=0.434$). A receiver operating characteristic curve analysis indicated that the optimal cut-off value for PRS was 0.48, yielding 87.5% sensitivity and 65.6% specificity for poor prognosis after surgical management ($p=0.015$). The patients with a PRS≥0.48 had significantly poorer survival outcomes compared to those with a PRS<0.48 (5-year survival rate, 39.4% vs. 83.3%, respectively, $p=0.003$, according to the log-rank test; Fig. 3).

Discussion

The overall survival curves were virtually identical in this study between hemodialysis patients and patients

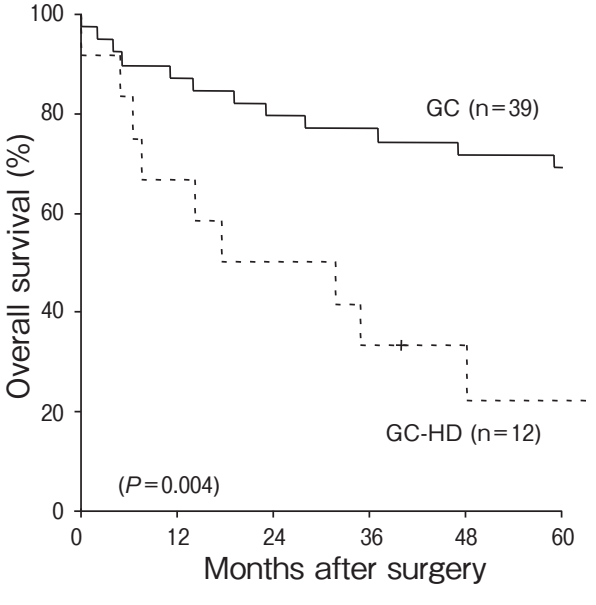

Fig. 1 Kaplan-Meier estimates of overall survival in patients undergoing hemodialysis (GC-HD) and matched non-dialysis patients (GC) after surgery for gastric cancer.

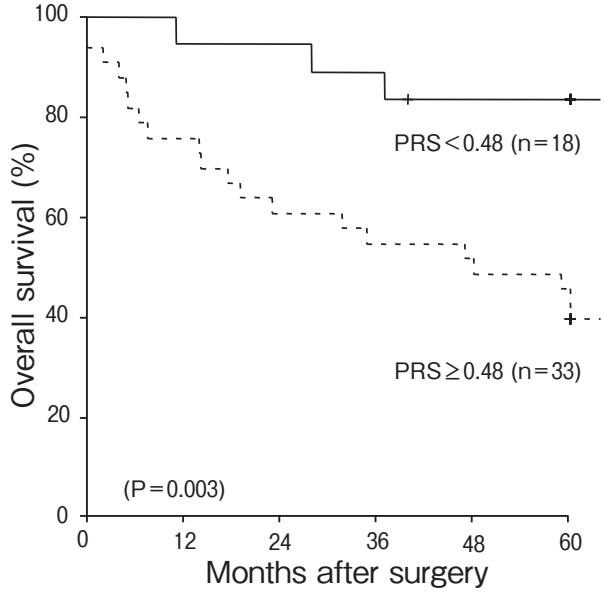

Fig. 2 Stacked bar chart showing the proportions of each morbidity score, according to the PRS.

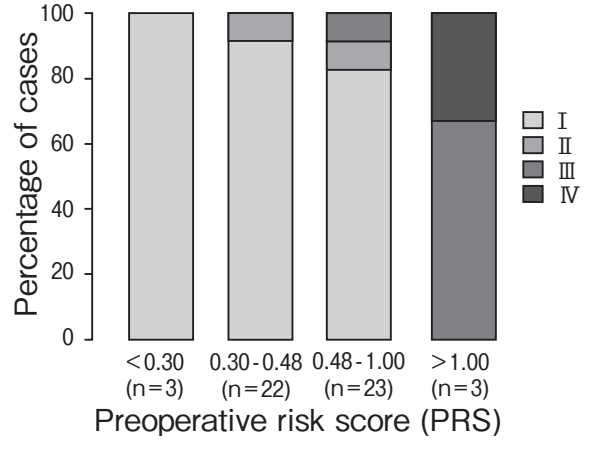

Fig. 3 Kaplan-Meier estimates of overall survival according to the preoperative risk score (PRS) of the E-PASS scoring system in patients undergoing surgery for gastric cancer.

with normal renal function after curative surgical treatment for gastric cancer. At the time of the data evaluation in this study, the participants included only hemodialysis patients with gastric adenocarcinoma who were matched to patients with normal renal function. Overall survival was worse in the hemodialysis patients compared to non-dialysis patients, and there was a significant difference in postoperative morbidity between the groups, according to the C-D classification. Potentially modifiable preoperative variables, such as PNI, PRS, SSS, and CRS, did not differentially affect the complication rates or the risk of postoperative mortality in the hemodialysis patients compared to the non-dialysis patients. However, our analysis demonstrated that a high PRS (≥ 0.48) was significantly associated with a poorer survival in gastrectomized patients.

In this series, excellent curative treatment was achieved for the patients with gastric cancer in the matched control cohort with normal renal function. The long-term prognosis after surgical resection of gastric cancer in the patients undergoing hemodialysis was unsatisfactory, due to a high recurrence rate of gastric cancer and to other causes of death, even when complete resection of the gastric cancer was attained pathologically. Once a complication occurred, the hemodialysis patients were less likely to survive compared to the non-dialysis patients. Pneumonia, stroke/cerebrovascular accident, myocardial infarction, and unplanned intubation appeared to be the most lethal complications in hemodialysis patients [16, 17].

Importantly, there was no significant difference between our 2 patient groups in the incidence of cancer recurrence after gastric resection. However, the incidence of death due to diseases other than the recurrence of gastric cancer after surgical management in the hemodialysis group was significantly higher than that in the non-dialysis group. To this end, our analyses of gastric cancer patients with and without hemodialysis has identified 2 possible independent risk factors for poor prognosis in hemodialysis patients after surgical resection for gastric cancer: the postoperative adjuvant setting and the systemic inflammation status according to the PRS.

The standard adjuvant regimens in Japan for advanced gastric cancer are the S-1 single or S-1/CDDP combined chemotherapy regimens that were verified in the JCOG 9912 and SPIRITS trials [18, 19]. However, no standard adjuvant chemotherapy has been established for patients on hemodialysis. Physicians treating such patients must arrange an individualized regimen for each patient taking into account the metabolic characteristics of each anti-cancer agent, although in the present study, none of the hemodialysis patients with advanced gastric cancer received adjuvant chemotherapy after surgical management.

The PRS from the E-PASS scoring system is based on the premise that morbidity and mortality rates can be correlated with the patient's physiological risk and the surgical stress applied [20]. Interestingly, our analyses suggested that a high PRS was significantly correlated with long-term outcomes in gastrectomized patients. The correlation between PRS and outcome might therefore enable surgeons to predict risks in each individual patient before surgery. The patient's nutritional intake and dietary patterns are also potential determinants of health outcomes in individuals undergoing dialysis. Postoperative malnutrition after gastrectomy is deemed inevitable, and gastrectomy *per se* may be a risk for mortality [21]. Although the PRS in the present study's patients was not significantly powerful in predicting the mortality and morbidity ranges, if the risk predicted by the PRS is high for a patient, this risk can then be discussed confidently with both the patient and relatives while gaining informed consent.

Our study had some limitations associated with errors and biases inherent in a small retrospective study design, where sample sizes are not large enough to perform analyses for each patient group. However, we believe that our report is valuable as a landmark for understanding the information and patient care required for hemodialysis patients undergoing gastric surgery for gastric cancer.

In conclusion, our findings suggest that hemodialysis patients undergoing surgery for gastric cancer have a significantly poorer postoperative prognosis and an elevated risk of postoperative complications and death compared to their non-dialysis counterparts. It also highlights that the significantly elevated risk of a poor outcome and death after surgery deserves an in-depth, preoperative discussion with each dialysis patient.

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References

1. Gajdos C, Hawn MT, Kile D, Robinson TN and Henderson WG: Risk of major nonemergent inpatient general surgical procedures in patients on long-term hemodialysis. JAMA Surg (2013) 148: 137–143.
2. Ayesh Haj Yousef MH, Bataineh A, Elamin E, Khader Y, Alawneh K and Rababah M: Adequate hemodialysis improves anemia by enhancing glucose-6-phosphate dehydrogenase activity in patients with end-stage renal disease. BMC Nephrol (2014) 15: 155.
3. Butler AM, Olshan AF, Kshirsagar AV, Edwards JK, Nielsen ME, Wheeler SB and Brookhart MA: Cancer incidence among US Medicare ESRD patients receiving hemohemodialysis, 1996–2009. Am J Kidney Dis (2015) 65: 763–772.
4. Brar SS, Mahar AL, Helyer LK, Swallow C, Law C, Paszat L, Seevaratnam R, Cardoso R, McLeod R, Dixon M, Yohanathan L, Lourenco LG, Bocicariu A, Bekaii-Saab T, Chau I, Church N, Coit D, Crane CH, Earle C, Mansfield P, Marcon N, Miner T, Noh SH, Porter G, Posner MC, Prachand V, Sano T, van de Velde C, Wong S and Coburn NG: Processes of care in the multidisciplinary treatment of gastric cancer: results of a RAND/UCLA expert panel. JAMA Surg (2014) 149: 18–25.
5. Shen L, Shan YS, Hu HM, Price TJ, Sirohi B, Yeh KH, Yang YH, Sano T, Yang HK, Zhang X, Park SR, Fujii M, Kang YK and Chen LT: Management of gastric cancer in Asia: resource-stratified guidelines. Lancet Oncol (2013) 14: e535–547.
6. Nakamura K, Kuwata T, Shimoda T, Mizusawa J, Katayama H, Kushima R, Taniguchi H, Sano T, Sasako M and Fukuda H: Determination of the optimal cutoff percentage of residual tumors to define the pathological response rate for gastric cancer treated with preoperative therapy (JCOG1004-A). Gastric Cancer (2015) 18: 597–604.
7. Ariake K, Ueno T, Takahashi M, Goto S, Sato S, Akada M and Naito H: E-PASS comprehensive risk score is a good predictor of postsurgical mortality from comorbid disease in elderly gastric cancer patients. J Surg Oncol (2014) 109: 586–592.
8. Abe H, Mafune K, Minamimura K and Hirata T: Validation of the Estimation of Physiologic Ability and Surgical Stress (E-PASS) score for maintenance hemodialysis patients undergoing elective abdominal surgery. Dig Surg (2014) 31: 269–275.
9. Sano T and Aiko T: New Japanese classifications and treatment guidelines for gastric cancer: revision concepts and major revised points. Gastric Cancer (2011) 14: 97–100.
10. Japanese Gastric Cancer Association: Japanese classification of gastric cancer: 3rd English edition. Gastric Cancer (2011) 14: 101–112.
11. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, de Santibañes E, Pekolj J, Slankamenac K, Bassi C, Graf R, Vonlanthen R, Padbury R, Cameron JL and Makuuchi M: The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg (2009) 250: 187–196.
12. Guthrie GJ, Charles KA, Roxburgh CS, Horgan PG, McMillan DC and Clarke SJ: The systemic inflammation-based neutrophil-lymphocyte ratio: experience in patients with cancer. Crit Rev Oncol Hematol (2013) 88: 218–230.
13. Templeton AJ, McNamara MG, Šeruga B, Vera-Badillo FE, Aneja P, Ocaña A, Leibowitz-Amit R, Sonpavde G, Knox JJ, Tran B, Tannock IF and Amir E: Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. J Natl Cancer Inst (2014) 106: dju124.
14. Sakurai K, Ohira M, Tamura T, Toyokawa T, Amano R, Kubo N, Tanaka H, Muguruma K, Yashiro M, Maeda K and Hirakawa K: Predictive potential of preoperative nutritional status in long-term outcome projections for patients with gastric cancer. Ann Surg Oncol (2016) 23: 525–533.
15. Kaplan EL and Meier P: Nonparametric estimation from incomplete observations. J. Am. Stat. Assoc. (1958) 53: 457.
16. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, Wanner C, Krane V, Cass A, Craig J, Neal B, Jiang L, Hooi LS, Levin A, Agodoa L, Gaziano M, Kasiske B, Walker R, Massy ZA, Feldt-Rasmussen B, Krairittichai U, Ophascharoensuk V, Fellström B, Holdaas H, Tesar V, Wiecek A, Grobbee D, de Zeeuw D, Grönhagen-Riska C, Dasgupta T, Lewis D, Herrington W, Mafham M, Majoni W, Wallendszus K, Grimm R, Pedersen T, Tobert J, Armitage J, Baxter A, Bray C, Chen Y, Chen Z, Hill M, Knott C, Parish S, Simpson D, Sleight P, Young A and Collins R; SHARP Investigators: The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet (2011) 377: 2181–2192.
17. Jamison RL, Hartigan P, Kaufman JS, Goldfarb DS, Warren SR, Guarino PD and Gaziano JM; Veterans Affairs Site Investigators: Effect of homocysteine lowering on mortality and vascular disease in advanced chronic kidney disease and end-stage renal disease: a randomized controlled trial. JAMA (2007) 298: 1163–1170.
18. Sakuramoto S, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A, Furukawa H, Nakajima T, Ohashi Y, Imamura H, Higashino M, Yamamura Y, Kurita A and Arai K; ACTS-GC Group: Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med (2007) 357: 1810–120.
19. Koizumi W, Narahara H, Hara T, Takagane A, Akiya T, Takagi M, Miyashita K, Nishizaki T, Kobayashi O, Takiyama W, Toh Y, Nagaie T, Takagi S, Yamamura Y, Yanaoka K, Orita H and Takeuchi M: S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. Lancet Oncol (2008) 9: 215–221.
20. Tang T, Walsh SR, Fanshawe TR, Gillard JH, Sadat U, Varty K, Gaunt ME and Boyle JR: Estimation of physiologic ability and surgical stress (E-PASS) as a predictor of immediate outcome after elective abdominal aortic aneurysm surgery. Am J Surg (2007) 194: 176–182.
21. Kobayashi D, Ishigure K, Mochizuki Y, Nakayama H, Sakai M, Ito S, Kojima H, Kajikawa M, Ando M and Kodera Y: Multi-institutional prospective feasibility study to explore tolerability and efficacy of oral nutritional supplements for patients with gastric cancer undergoing gastrectomy (CCOG1301). Gastric Cancer (2017) 20: 718–727.