Gastric Cancer Patients with End-stage Renal Disease Who Underwent Radical Gastrectomy

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Abstract. Background: Radical gastrectomy (RG) with lymph node (LN) dissection is a standard procedure for gastric cancer (GC). Patients with end-stage renal disease (ESRD) usually have high risk for any operative procedure. However, information for ESRD on RG for GC is limited. Patients and Methods: A total of 2,021 GC patients who underwent RG with LN dissection were retrospectively reviewed. Among them, 26 patients had ESRD. The clinicopathological features and surgical outcomes were compared between GC with ESRD (ESRD-GC group) and GC without ESRD (GC group). Results: ESRD-GC patients could be independently differentiated from GC patients by lower hemoglobin, negative lymph node (LN) involvement and higher postoperative complications. The overall survival rate of ESRD-GC group seemed better than that of GC group patients. Lesser depth of tumor invasion, LN metastasis and lymphatic invasion and early-staged tumor contributed to favorable prognosis of ESRD-GC group of patients. Conclusion: RG might be beneficial for GC-ESRD patients especially for early-stage disease; however, RG for GC patients with ESRD should be more cautiously performed, otherwise the benefit might be compromised by higher postoperative complications and even mortality.

The incidence of gastric cancer (GC) has gradually declined; however, it remains the 4th highest cancer in incidence and the second leading cause of cancer-related death worldwide. GC is common in Japan and China (1-3). In Taiwan, 3,612 new GC patients were diagnosed in 2007 accounting for an incidence

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of 15.73 per 100,000 in the population and the 7th common cancer. Surgery remains the treatment of choice against GC and offers a chance of cure (4). We previously reported that the overall cumulative 5-year survival rate of all resected GC patients was 45.6%; 57.0% after curative resection (5).

End-stage renal disease (ESRD) is the state when the kidneys are no longer able to work at a level needed for dayto-day life. ESRD patients are considered high-risk candidates for invasive treatments due to decreased glomerular filtration rate and this is associated with a wide range of disorders in other organ systems (6-8). The overall risk of cancer is increased in patients with end-stage renal disease (ESRD), including cancer of the kidney (risk, 3.6 times; range=3.45-3.76), bladder (risk, 1.50; range=1.42-1.57), thyroid and other endocrine organs (risk, 2.28; range=2.03-2.54). However, the overall risk of cancers of the lung, colorectum, prostate, breast and stomach are not consistently increased in ESRD patients (9); for the elderly ESRD patient, the risk of GC is especially increased (10). Because the total incidence of GC with ESRD is low, the information about treatment of GC in ESRD patient is still lacking.

Furthermore, the aim of the present study was to assess the safety, efficacy and clinical outcomes of radical gastrectomy in GC patients with ESRD.

Patients and Methods

Patients and patients' management. From 2000 to 2011, 2,021 consecutive patients with histologically-proven GC underwent gastric resection at the Department of Surgery, Chang Gung Memorial Hospital, Taipei, Taiwan. Gastrectomy with lymph node dissection number exceeding 15 is defined as intention curative surgery. Meanwhile, curative resection is defined as a negative resection margin observed by histopathological examination. All procedures were performed after written informed consent was obtained from the patients and this study was approved by the Institutional Review Board of our Hospital.

Patients with lesions that were pathologically-confirmed as nonneoplastic lesions, including hyperplastic polyps, intestinal metaplasia, gastrointestinal stomal tumor and neuroendocrine tumor were excluded from the study. Metastasis and palliative surgery were also excluded

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Table I. Clinical manifestations in 2,021 gastric cancer patients undergoing gastrectomy with or without ESRD.

Factors	Without ESRD (n=1995)	With ESRD (n=26)	p-Value	
Age (years)	64.3±13.4	67.9±9.4	0.059	
Gender				
Male	1248 (62.6)	15 (57.7)	0.611	
Female	747 (37.4)	11 (42.3)		
CEA (ng/ml)	10.3±66.1	3.74 ± 2.01	0.731	
Creatine	7.26 ± 3.45	0.71±0.56	< 0.001	
Hemoglobin (g/dl)	11.8±2.45	9.77 ± 2.1	< 0.0001	
Albumin (g/dl)	3.94 ± 0.6	3.7 ± 0.51	0.101	
Tumor size (cm)	4.3±3.0	4.3 ± 3.0	0.970	
Tumor location			0.423	
Upper	350 (17.5)	3 (11.5)		
Middle	400 (20.1)	3 (11.5)		
Lower	1156 (57.9)	18 (69.2)		
Diffuse	68 (3.4)	1 (3.8)		
Others	21 (1.1)	1 (3.8)		
HP-positive rate	385 (19.6)	3 (12.0)	0.451	
Pre-op comorbidity				
0	1247(62.5%)	0(0%)	< 0.001	
1	501(25.1%)	10(38.5%)		
2	170(8.5%)	7(26.9%)		
>=3	77(3.9%)	9(34.6%)		
Type of gastrectomy			0.672	
Total	554 (27.8)	6 (23.1)		
Subtotal	1407 (70.5)	20 (76.9)		
Others	34 (1.7)	0 (0.0)		
Complication	294 (14.7)	10 (38.5)	0.003	
Hospital mortality	56 (2.8)	3 (11.5)	0.038	
One month mortality	23 (1.2)	2 (7.7)	0.040	
Post-op chemotherapy	1137 (57.0)	8 (30.8)	0.007	

HP: Helicobacter pylori; ESRD: end-stage renal disease. Figures are numbers with percentages in parentheses, unless otherwise stated.

from this study. Patients receiving aspirin, antiplatelet or anti-coagulant agents were asked to stop the medications at least 5 days before the procedures. ESRD was defined as a patient having oliguria or anuria and receiving regular hemodialysis. The ESRD with peritoneal dialysis were excluded. Patients without either condition were designated as the control group.

Treatment of GC was performed with open radical gastrectomy with D-II lymph dissection (including total or subtotal gastrectomy). All patients had general supportive care after the procedure. When a complication was suspected clinically or radiographically, further computed tomography (CT) scans were undertaken. Surgical mortality was defined as death occurring within 1 month after surgery. In-hospital mortality was defined as death occurring after surgery without discharge. Laboratory tests were conducted on the day before surgery. Serum carcinoembryonic antigen (CEA) was measured by radioimmunoassay or enzyme-linked immunosorbent assay (ELISA). The tumors were evaluated preoperatively by panendoscopy, upper gastrointestinal (GI) series, abdominal ultrasonography (US), CT, magnetic resonance imaging (MRI) and endoscopic US, as appropriate. Tumor stage was defined according to the AJCC 7th edition of the pathological tumor-node-metastasis

Table II. Histopathological data for 2,021 gastric cancer patients undergoing gastrectomy with or without ESRD.

Factors	Without ESRD (n=1995)	With ESRD (n=26)	<i>p</i> -Value
Resection margins			1.000
Negative	1874 (93.9)	25 (96.2)	
Positive	121 (6.1)	1 (3.8)	
Differentiation			0.034
Well-differentiated	816 (40.9)	16 (61.5)	
Poorly differentiated	1179 (59.1)	10 (38.5)	
Vascular invasion	225 (11.5)	3 (3.8)	0.351
Lymphatic invasion	989 (50.2)	7 (26.9)	0.018
Perineural invasion	855 (43.5)	6 (24)	0.051
Lauren's classification			0.042
Intestinal	1023 (52.3)	20 (76.9)	
Diffuse	701 (35.8)	706 (35.6)	
Mixed	232 (11.9)	1 (3.8)	
T stage		, ,	0.065
T1	518 (26)	11 (42.3)	
T2	296 (14.8)	6 (23.1)	
T3	121 (6.1)	2 (7.7)	
T4	1060 (53.1)	7 (26.9)	
No. of LN retrieval,			0.259
<15	292 (14.6)	6 (23.1)	
>15	1703 (85.4)	20 (76.9)	
LN positive ratio	0.183±0.253	0.092±0.203	0.050
LN total number	30.70±16.35	23.50±11.33	0.025
N status			0.011
N0	815 (40.9)	19 (73.1)	
N1	299 (15)	2 (7.7)	
N2	304 (15.2)	2 (7.7)	
N3	577 (28.9)	3 (11.5)	
TNM stage	. ,	. /	0.009
I	636 (31.9)	14 (53.8)	
II	380 (19)	7 (26.9)	
III	979 (49.1)	5 (19.2)	

Figures are numbers with percentages in parentheses, unless otherwise stated. *ERSD: End-stage renal disease*.

(pTNM system) classification proposed by the International Union against Cancer (UICC). Adjuvant chemotherapy was systemically performed with a 5-fluorouracil-based regimen due to positive lymph node metastasis, local recurrence or systemic metastasis. Meanwhile, adjuvant radiotherapy was performed with external-beam radiotherapy due to positive lymph node (LN) metastasis.

Follow-up study. Follow-up evaluation included clinical physical examinations and blood chemistry tests at each visit. Additionally, serum CEA and CA19-9 were measured and the liver was examined with abdominal US every 3 months. When abdominal US detected a new lesion or when elevated CEA or CA 19-9 was noted, abdominal CT with contrast was performed. If any of the above procedures indicated recurrence, the patient was admitted for more comprehensive assessment, including panendoscopy and wholebody CT. Methods for treating recurrence included palliative surgery, systemic chemotherapy, external-beam radiotherapy, endoscopic stenting and conservative treatment as appropriate.

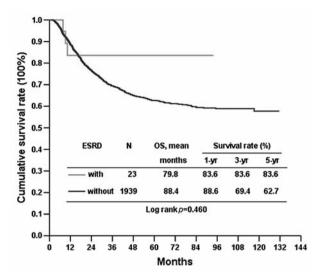


Figure 1. Overall survival rates for 1,939 gastric cancer (GC) patients who underwent gastrectomy without end-stage renal disease (ESRD) and 23 GC patients with ESRD.

Statistical analysis. All data are presented as percentage of patients or mean with standard deviation. All numerical continuous data were compared by the Student's independent t-test. Categorical data were compared by the Pearson's chi-square test or Fisher's exact test and multiple forward stepwise logistic regression analysis when appropriate. The overall survival rates were calculated with the Kaplan-Meier method. Seventeen clinicopathological variables were selected for survival analysis by the log-rank test. The Cox proportional hazards model was employed for multivariate regression analysis. The SPSS statistics software (version 10.0, Chicago, IL, USA) for Windows was used for the statistical analysis. p < 0.05 was considered statistically significant.

Results

Clinicopathological features. Among 2,021 GC patients who underwent radical gastrectomy, 26 (1.28%) had end-stage renal disease (ESRD-GC group). The clinicopathological features and outcome of 1,995 GC patients undergoing gastrectomy without ESRD (GC group) were used for comparisons. Tables I and II summarize demographic, laboratory data and pathological features between the two groups. The ESRD-GC group contained 15 men and 11 women, with a mean age of 67.9 years, while the GC group contained 1,248 men and 747 women, with mean age of 64.3 years. ESRD-GC patients were 4 years older than GC patients on average (p=0.059). Generally, the ESRD-GC group and GC group patients showed similar gender ratio, tumor marker values, tumor size, tumor location, T stage, rate of gastrectomy procedure and Helicobacter pylori positive rate. However, high pre-operative comorbidity and hemoglobin level less than 10 g/dl were more common in the ESRD-GC group than the GC group (Table I). In terms of histopathological features, ESRD-GC

Table III. Multivariate logistic regression analysis of ESRD** in gastric cancer.

Factors	Odds ratio	95% CI of odds ratio	<i>p</i> -Value
Hemoglobin* (g/dl)	0.715	0.592-0.863	< 0.001
Lauren's classification			0.248
Differentiation			0.253
Lymphatic invasion			0.675
Perineural invasion			0.267
N status			
N1/N0	0.236	0.049-1.129	0.071
N2/N0	0.148	0.019-1.164	0.069
N3/N0	0.139	0.030-0.644	0.012
Complication	3.918	1.488-10.318	0.006
Hospital mortality			0.302
Adjuvant chemotherapy	,		0.533

^{*}for an increase of 1 g/dL in hemoglobin the odds of ESRD are multiplied by 0.715. ESRD: End-stage renal disease.

group patients had more intestinal type of GC (76.9%) (Table II) and GC with lower rate of lymphatic, neural invasion, lymph node metastasis, lower rate of tumor de-differentiation and less advanced tumor stage (Tables I and II). ESRD-GC group patients had higher operative morbidity rate (38.5%), one month surgical mortality rate (7.7%) and hospital mortality rate (11.5%).

For the independent factor, the ESRD-GC group has a lower hemoglobin level and less N3 stage patients but higher postoperative complications; the data are demonstrated by multivariate analysis as Table III.

Complications and mortality in the ESRD-GC group. Out of the 26 ESRD-GC patients who underwent radical gastrectomy, there were a total of 10 complications, as summarized in Table IV. Overall, 7 patients had complications related to surgery and 3 patients to medical problems, such as cardiovascular and pulmonary problems. In terms of mortality, 2 patients had mortality related to surgical complications and 1 to cardiopulmonary failure. The most common complication was leakage and pancreatitis. The most common cause of mortality was leakage.

Survival impact and prognostic analysis for ESRD-GC patients. A total of 2,021 GC patients who had undergone gastrectomy received regular follow-up until death. Twenty-six patients (56 GC-group patients and 3 ESRD-GC-group patients) were excluded from the survival analysis because they died within 1 month after surgery. A total of 1,962 GC patients undergoing gastrectomy were enrolled in the survival analysis. Follow-up duration ranged from 2.1 to 131.54 months (median=30.29 months). Overall survival (OS) rates at 1, 3, 5 and 10 years were 88.8 %, 69.5%, 62.8 % and 57.8 %, respectively. Among them, 1,939 gastric cancer patients

Table IV. Causes of complications and mortality of the ERSD-GC group (10 patients).

Causes of complication	N	
Leakage	3	
Intra-abdominal infectionor abscess	2	
Pancreatitis	2	
Angina	2	
Cardiopulmonary failure	1	
Causes of mortality		
Leakage	2 (T4aN0, T4aN1)	
Cardiopulmonary failure	1 (T4bN3b)	

undergoing gastrectomy without ESRD had 1-, 3- and 5-year OS rates of 88.6 %, 69.4 % and 62.7 %, respectively. However, 23 GC patients undergoing gastrectomy with ESRD had 1-, 3- and 5-year OS rate of 83.6 %, 83.6 % and 83.6 %, respectively. Figure 1 depicts that 1-, 3- and 5-year OS rates were not significantly different when the patients had ESRD (Table V). For prognostic analysis, the ESRD-GC group of patients with less depth of tumor invasion, less LN metastasis, less lymphatic invasion and early-staged tumor had a favorable prognosis after radical gastrectomy (Table VI).

Discussion

Radical resection of GC remains the treatment of choice and provides a chance of cure, even if extended resection may be required (11). Age, tumor depth, nodal status, distant metastasis and resection margin are consistently reported as independent prognostic factors for GC patients undergoing curative resection (11). Our previous study confirmed that old age, lymph node metastasis, serosal invasion, peritoneal seeding, positive resection margin, liver metastasis, tumor size and lymphatic invasion were independent prognostic factors for GC patients undergoing radical resection. The 5-year survival rate for all resected patients was 45.6% and 57.0% for curative resection (5, 13). Although several large series reported the prognostic analysis on GC undergoing radical gastrectomy (14-16), the influence of associated ESRD on GC patients who underwent curative resection has not been well-clarified.

Impaired renal function may be combined with several medical diseases and have potential risks for operation. Mori *et al.* reported the safety and outcome of gastrectomy for GC patients with nonuremic renal failure (17). These patients could achieve similar operation time, blood loss, complications, hospital stay and survival rates to those without renal function impairment (17).

Regarding patients with uremic renal failure, higher risks for operative procedures, due to associated multiple systemic diseases, are always considered as an obstacle to any invasive procedure (6).

Table V. Overall survival difference between gastric cancer patients undergoing gastrectomy in terms of ESRD.

	ESRD*	N	Mean survival (months)	95% C.I.** of mean	<i>p</i> -Value
Whole series					0.460
	Without	1939	88.4	85.6-91.1	
	With	23	79.8	65.4-94.2	

ESRD: End stage renal disease; C.I.: confidence interval.

The incidence of cancer in ESRD patient is about threetimes higher than that of the normal population but the incidence of GC in ESRD patients is not significantly increased over that of the normal population (9), except elderly patients. As demonstrated in this study, the incidence of GC with ESRD was 1.28% (26/2,021). Because of the lower incidence, most surgeons have limited information for this kind of patients.

In the present report, it is worth noting that the ESRD patients with GC had distinct clinicopathological charactistics, including lower hemoglobin levels, high preoperative comorbidity, more early-stage tumors, less lymph node metastasis, less perineural invasion, more welldifferentiated tumors and more intestinal types. Stages I and II GC comprised of 53.8% (n=14/26) and 26.9% (n=7/26) of ESRD patients with GC respectively. In Taiwan, ESRD patients usually have regular hemodialysis three-times a week. Most patients of GC with ESRD were diagnosed with anemia or dizziness. Aggressive examination using panendoscope or colonofiberscope to discover the reason for anemia might partly explain the higher rate of early-staged GC in the ESRD-GC group patients of our study. This phenomenon is well-demonstrated by Japan's screen program for GC in Japan. In Japan, early-stage gastric cancer accounts for 72.6% of GC patients undergoing gastrectomy due to their screening system (18). In our study, early-stage gastric cancer in the ESRD-GC group (stages I and II) was about 80.7%. The incidence is similar to that in Japan (18). The early diagnosis of GC with ESRD might be attributed to the regular hemoglobin follow-up and aggressive investigation for blood loss in the gastrointestinal tract.

Unfortunately, the surgical morbidity and hospital mortality rates are higher for GC-ESRD patients than the GC group without ESRD (30.8%, 14.7% versus 11.5 %, 2.8%, respectively). The most common causes of complication's or mortality are leakage and post-operative pancreatitis. The TNM stage of the three cases with mortality was T4aN0M0, T4aN1M0 and T4bN3bM0, respectively. For these patients with advanced disease, extensive lymph node dissection

Table VI. Univariate and multivariate analysis of prognostic factors in ESRD gastric cancer.

Factors	Mean (months)	95 % C.I. of mean	<i>p</i> -Value
Age			0.521
<68 (n=11)	84.3	66.9-101.6	
>68 (n=12)	35.7	26.4-45.0	
Gender			0.152
Male (n=13)	52.6	37.2-68.0	
Female (n=10)	NA		
Hemoglobin (g/dl)			0.405
≤12 (n=14)	34.0	25.0-43.0	
>12 (n=3)	NA		
Gastrectomy			0.868
Total (n=5)	56.8	36.4-77.2	
Subtotal (n=18)	81.0	64.7-97.2	
Complications			0.975
No (n=16)	79.7	62.0-97.4	
Yes (n=7)	22.1	17.8-26.4	
Location			0.811
Upper (n=3)	32.3	14.7-49.9	
Middle (n=3)	NA		
Lower (n=16)	80.0	62.5-97.4	
Others (n=1)	NA		
Tumor size (cm)			0.702
≤3 (n=14)	77.4	57.1-97.7	
>3 (n=9)	61.0	47.4-74.6	
Differentiation			0.145
Yes (n=14)	86.7	73.7-99.8	
No (n=9)	19.2	13.1-25.3	
Lauren's classification			NA
Intestinal (n=18)	77.1	60.2-63.9	
Diffuse (n=4)	NA		
Mixed (n=1)	NA		
Depth of invasion			0.095
T1/T2 (n=17)	87.2	74.9-99.4	
T3/T4 (n=6)	29.6	14.8-44.4	
LN metastases			0.002
Negative (n=18)	88.1	77.6-98.6	
Positive (n=5)	13.8	5.2-22.5	
Stage			0.041
I (n=14)	NA		
II (n=6)	29.9	15.4-44.3	
III (n=3)	16.2	4.5-27.9	
Lymphatic invasion			0.005
No (n=17)	88.1	77.6-98.6	
Yes (n=6)	14.6	5.7-23.5	
Vascular invasion			0.667
No (n=22)	79.0	63.9-94.1	
Yes (n=1)	NA		
Perineural invasion			0.375
No (n=17)	82.5	68.0-96.5	
Yes (n=5)	17.3	11.9-22.7	
Helicobacter pylori infection			0.385
No (n=19)	82.7	68.5-96.9	
Yes (n=3)	14.8	10.3-19.4	
Chemotherapy			0.967
No (n=16)	79.6	61.7-97.4	
Yes (n=7)	58.5	40.9-76.2	

NA, not available; CI, confidence interval; ESRD: end-stage renal disease.

inducing blood supply insufficiency, especially for patients with renal failure, would produce poor healing process in the duodenum stump and pancreas capsule might explain technical difficulty. Impaired renal function combined with several medical diseases may partly contribute to the higher surgical morbidity or even mortality. For surgeons, the surgical technique for extensive dissection and degree of tumor invasion might mainly explain the reasons of complications. Post-operative pancreatitis is mostly caused by pancreatic tissue injury, while LN dissection or pancreatic anterior capsule dissection and leakage are determined by the quality of blood supply and invasion of tumor. Blood supply should be preserved if the invasiveness of the tumor is severe. Although it might be difficult to prevent injury of pancreas and blood supply of duodenum in advanced patients, delicate surgical skill is required to minimize the injury. Neoadjuvant chemotherapy for GC-ESRD in advanced stages to decrease morbidity and even mortality by tumor down-staging might be helpful; however, no report has been published to date. On the other hand, to balance surgical risk and oncological clearance, GC-ESRD patients with early-stage cancer status may undergo treatment to a lesser extent, such as endoscopic mucosal resection, endoscopic submucosal dissection or laparoscopic wedge resection, etc.

Regarding the impact of ESRD on survival for GC after radical gastrectomy, ESRD-GC and GC group patients had similar survival rates. However, the ESRD-GC group of patients tended to have better survival, although the trend was not significant due to the limited number of cases.

This information is important to surgeons when they encounter patients with GC associated with ESRD. The majority of the ESRD-GC group patients had early-stage GC but the surgical risk is high in advanced patients. Newman et al. reported that emergent abdominal surgery in patients (n=21) with chronic renal failure (CRF) was associated with poor survival rates. Surgical (30-day) mortality for patients with CRF receiving emergent surgery was 38% and 0% for patients with CRF receiving elective surgery (5 patients) (8). Martínez et al. emphasized that morbidity and mortality after GC surgery was influenced by preoperative conditions of patients. Statistically significant risk factors for mortality were the Goldman cardiac risk index, albumin, creatinine and total lymphocyte count (7). Thus, adequate pre-operative preparation for ESRD patients is important and can improve the post-operative survival rate. We should acomplish adequate pre-operative preparation, perform delicate surgery and excellent post-operative care to minimize and even eliminate surgical complications and mortality. This way, the ESRD-GC patients will have similar survival; even better survival than that for normal populations.

Although our results may support both benefit and feasibility for radical gastrectomy for GC-ESRD, especially in early-stage patients, several problems need to be addressed.

First, the case number of the study group is quite small. Second, this study is a retrospective case control study and, therefore, selection bias is inevitable. Third, we cannot compare treatment efficacy for ESRD-GC patients between surgery and conservative treatment due to lack of complete data, because some patients without surgery chose no treatment and are thus lost for follow-up. Sometimes, surgeons may consider patients with GC-ESRD for radical gastrectomy and this is probably less feasible due to multiple comorbidities and change to conservative treatment, especially for surgery in the presence of advanced disease stage. However, this is the first study to address this specific clinical issue.

In conclusion, radical gastrectomy is feasible and beneficial for GC-ESRD patients, especially in early stage, with thorough pre-operative evaluation and postoperative care. However, radical gastrectomy for the treatment of GC in the ESRD-patient group should be more cautiously considered, otherwise any benefit will be compromised by higher postoperative complications and even mortality.

Conflicts of Interests

The Authors declare that they have no competing interests.

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