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Perioperative, short-, and long-term outcomes of gastric cancer surgery: Propensity score-matched analysis of patients with or without prior solid organ transplantation

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ABSTRACT

Background: Details of perioperative outcomes and survival after gastric cancer surgery in prior transplant recipients have received minimal research attention.
Methods: We performed an observational cohort study using the database of 20,147 gastric cancer patients who underwent gastrectomy at a single gastric cancer center in Korea. Forty-one solid organ recipients [kidney (n = 35), liver (n = 5), or heart (n = 1)] were matched with 205 controls using propensity score matching.
Results: Operation time, blood loss, and postoperative pain were similar between groups. Short-term complication rates were similar between transplantation and control groups (22.0% vs. 20.1%, $P = 0.777$). Transplantation group patients with stage 1 gastric cancer experienced no recurrence, while those with stage 2/3 cancer had significantly higher recurrence risk compared to the controls ($P = 0.049$). For patients with stage 1 cancer, the transplantation group had a significantly higher rate of non-gastric cancer-related deaths compared to the controls (19.2% vs. 1.4%, $P = 0.001$). For those with stage 2/3 cancer, significantly lower proportion of the transplantation group received adjuvant chemotherapy compared to the control group (26.7% vs. 80.3%, $P < 0.001$). The transplantation group had a higher (albeit not statistically significant) rate of gastric cancer-related deaths compared to the controls (40.0% vs. 18.0%, $P = 0.087$).
Conclusion: Transplant recipients and non-transplant recipients exhibited similar perioperative and short-term outcomes after gastric cancer surgery. From long-term outcome analyses, we suggest active surveillance for non-gastric cancer-related deaths in patients with early gastric cancer, as well as strict oncologic care in patients with advanced cancer, as effective strategies for transplant recipients.

Introduction

The number of solid organ transplantations has increased, and the survival of transplant recipients has improved over the years [1,2]. Accordingly, long-term consequences after transplantation have become an important factor to consider. The increased risk of malignancy resulting from lifelong use of immunosuppressive

Abbreviations: GC, gastric cancer; BMI, body mass index; DM, diabetes mellitus (DM); POD, postoperative day (POD); CNI, calcineurin inhibitor (CNI); MMF, mycophenolate mofetil (MMF); IV, intravenous (IV).

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agents was reported from studies in the United States and the United Kingdom [3,4]. In South Korea, a recent population-based study showed increased incidence of *de novo* cancers in kidney and liver transplant recipients [5]. Especially, several studies reported higher incidence of gastric cancer (GC) in transplant recipients compared to the general population [6–9].

A recent large, population-based study reported that cancer-specific mortality among GC patients and other cancers was higher in solid organ recipients than in non-transplant recipients [10]. However, little is known about the postoperative outcomes of GC surgery in transplant recipients. Immunosuppressive agents are known have side effects such as infection, wound problems, and gastrointestinal disturbances [11,12], while the perioperative effects of corticosteroids that can improve postoperative pain and bowel motility are not fully established [13–19]. No prior study has comprehensively investigated the recovery and complication characteristics after gastrectomy in transplant recipients. Furthermore, long-term oncologic outcomes have not been previously compared between transplant recipients and non-transplant recipients with resectable GC.

Therefore, we conducted this study to investigate the short-term outcomes as primary objective, and long-term outcomes as secondary objective after GC surgery in solid organ recipients, and to compare these outcomes to those observed in a group of propensity score-matched non-transplant recipient controls.

Methods

Patients and materials

In this cohort study, we selected patients from a prospectively-collected database of 20,147 GC patients who underwent gastrectomy at Severance Hospital between January 1998 and December 2019. The exclusion criteria were as follows: 1) age <19 or ≥80 years, 2) noncurative resection, 3) preoperative chemotherapy, 4) conversion to open surgery during minimally invasive surgery, 5) perioperative corticosteroid use for any indication except transplantation, 6) combined resection involving another major abdominal organ (liver, colon, pancreas, kidney, or uterus), 7) transplantation after gastrectomy, and 8) insufficient data. Among eligible patients, 41 underwent previous solid organ transplantation surgery (transplantation group) (Fig. 1). This study was approved by the Institutional Review Board of Severance Hospital, Yonsei University Health System (IRB No.: 4-2019-1187), and was exempted from obtaining informed consent due to the study design.

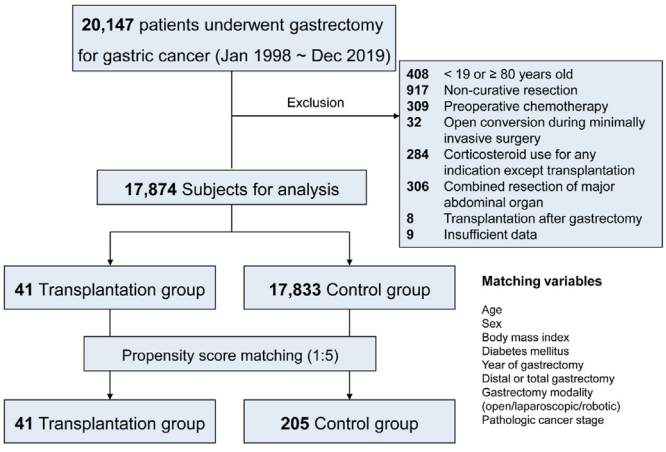

Fig. 1. Study population.

Propensity score matching

We matched the transplantation group patients (n = 41) to control group patients (n = 205) at a 1:5 ratio using the nearest neighbor method with a caliper set to a width of 0.25. The variables used to generate propensity scores were age, sex, body mass index (BMI), diabetes mellitus (DM), year of gastrectomy, gastrectomy modality (open, laparoscopic, or robotic), extent of gastrectomy (distal or total), and pathologic cancer stage. Hypertension was not matched since most of the transplantation group patients were kidney recipients with hypertension, so we regarded it as one of the natures of the transplantation group. Propensity score matching was achieved using the MatchIt package of R freeware v3.5.0 (R Foundation for Statistical Computing, Vienna, Austria) [20].

Short-term outcome data collection

The primary objective of our study was to compare postoperative complications between the transplant recipients and the controls. We collected data regarding the perioperative course from the GC database and medical records. The postoperative days of first gas expulsion, sips of water, and soft diet were recorded. Prolonged soft diet was defined as soft diet initiation after postoperative day (POD) 6, and prolonged hospital stay was defined as hospitalization ≥8 days; both criteria represented durations above the 75th percentile for all eligible study population. Postoperative pain was estimated using the numerical pain rating scale [21] and the number of analgesic doses administered during the first 5 postoperative days. Antiemetic administration was recorded. Complications were recorded by type and severity (based on the Clavien-Dindo classification) [22]. Laboratory values were also recorded, and prognostic nutritional index was calculated using the formula previously reported [23].

Long-term outcome data collection

Another purpose of our study was to compare long-term oncologic outcomes between the transplant recipients and the controls. We collected data from the GC database regarding adjuvant chemotherapy, long-term (>30 days post-gastrectomy) complications, GC recurrence, initial site of recurrence, and death. Mortality data were verified by linkage to the vital registration data from Statistics Korea [24]. We contacted the family members of patients for whom the cause of death was unclear in these sources. We defined death resulting from surgical complications or GC recurrence as “GC-related death,” and death from other causes as “non-GC-related death.”

Statistical analysis

Mann-Whitney *U* test was used to compare continuous variables; these data are presented as median (interquartile range). Chi-square test or Fisher's exact test was used to compare categorical variables; these data are presented as number (percentage). Survival outcomes were compared using Kaplan-Meier survival curves and log-rank test. All analyses were performed using SPSS v23.0 software (IBM, Armonk, NY, USA). $P < 0.05$ was considered statistically significant.

Results

Transplantation and immunosuppressants

In the transplantation group, thirty-five patients (85.4%) received a kidney, five (12.2%) received a liver, and one (2.4%) received a heart transplant. Among liver recipients, three had hepatocellular carcinoma while two had only liver cirrhosis before transplantation. None of the patients experienced recurrent or *de novo* liver cancer after liver transplantation. The median time from transplantation to *de novo* GC was 109 (65–200) months (Supplementary Fig. 1). All recipients had a functioning graft and were taking a calcineurin inhibitor (CNI) at the time of gastrectomy. The type of CNI was cyclosporin in 23 (56.1%) patients and tacrolimus in 18 (43.9%) patients. Nineteen (46.3%) patients were also treated with mycophenolate mofetil (MMF), while the remaining patients were taking only CNI and corticosteroids. Thirty-eight (92.7%) of the patients were taking oral corticosteroids at the time of gastrectomy (2.5–10 mg per day of prednisolone or an equivalent dose of methylprednisolone or deflazacort). Intravenous (IV) corticosteroids were administered around the time of gastrectomy in 36 (87.8%) transplant recipients, usually in daily dose of 50–100 mg methylprednisolone (100 mg hydrocortisone in four patients) for 1–4 days between the day before surgery and postoperative day 4. All patients continued taking oral CIN, and most resumed oral corticosteroids shortly after cessation of IV corticosteroids (one patient did not resume oral corticosteroids until 1 month after surgery). MMF was resumed within 7 days after gastrectomy in all patients receiving MMF preoperatively.

Baseline characteristics

As shown in Table 1, most of the patient demographics were similar between the two groups, including age, sex, operation era, BMI, and presence of DM. Hypertension was more frequent in the transplantation group for the reason mentioned in the Methods section. The type of gastrectomy was similar between groups, with 7.3% of patients in the transplantation group and 4.9% of patients in the control group undergoing total gastrectomy ($P = 0.524$). The most common operation modality was open surgery (transplantation vs. control: 48.8% vs. 49.3%), followed by laparoscopic surgery (26.8% vs. 31.7%) and robotic surgery (24.4% vs. 19.0%). The operation method ($P = 0.684$) and reconstruction method ($P = 0.469$) were not significantly different between groups. Regarding tumor pathology, histologic type ($P = 0.716$), Lauren classification ($P = 0.066$), and pathologic stage ($P = 0.520$) were also similar between the transplantation and control groups.

Perioperative recovery

As shown in Table 2, operation time and blood loss were similar between the transplantation group and control group, although intraoperative blood transfusion was more frequent in the former (7.3% vs. 0.5%, $P = 0.015$). Postoperatively, first gas expulsion day ($P = 0.878$) and first sips of water day ($P = 0.055$) were not significantly different between groups. However, the first soft diet

Table 1
Baseline characteristics.

Variables	Transplantation (n = 41)	Control (n = 205)	*P*
Age, y	57 (46–65)	58 (48–65)	0.543
Sex, male	32 (78.0)	168 (82.0)	0.559
Operation era			0.718
1998–2010	13 (31.7)	71 (34.6)	
2010–2019	28 (68.3)	134 (65.4)	
Body mass index, kg/m^2	22.2 (20.9–23.2)	22.5 (20.8–24.0)	0.246
Hypertension	34 (82.9)	101 (49.3)	<0.001
Diabetes mellitus	17 (41.5)	66 (32.2)	0.252
Type of gastrectomy			0.524
Total	3 (7.3)	10 (4.9)	
Subtotal	38 (92.7)	195 (95.1)	
Operation method			0.684
Open	20 (48.8)	101 (49.3)	
Laparoscopy	11 (26.8)	65 (31.7)	
Robot	10 (24.4)	39 (19.0)	
Reconstruction method			0.469
Gastroduodenostomy	17 (41.5)	110 (53.7)	
Gastrojejunostomy	19 (46.3)	80 (39.0)	
Roux en Y gastrojejunostomy	2 (4.9)	5 (2.4)	
Roux en Y esophagojejunostomy	3 (7.3)	10 (4.9)	
Tumor pathology			
Histologic type			0.716
Adenocarcinoma, well-differentiated	8 (19.5)	24 (11.7)	
Adenocarcinoma, moderately-differentiated	12 (29.3)	67 (32.7)	
Adenocarcinoma, poorly-differentiated	13 (31.7)	66 (32.2)	
Signet-ring cell	6 (14.6)	39 (19.0)	
Others[a]	2 (4.9)	9 (4.4)	
Lauren classification			0.066
Intestinal	17 (41.5)	98 (47.8)	
Diffuse	14 (34.1)	84 (41.0)	
Mixed	5 (12.2)	7 (3.4)	
Unknown	5 (12.2)	16 (7.8)	
Tumor stage			0.520
I	26 (63.4)	144 (70.2)	
II	10 (24.4)	34 (16.6)	
III	5 (12.2)	27 (13.2)	

Data are presented as numbers (percentage) or median (interquartile range), unless indicated otherwise.
[a] "Others" included papillary carcinoma, mucinous type, undifferentiated, and lymphoepithelioma-like carcinomas.

Table 2
Perioperative recovery data.

Variables	Transplantation (n = 41)	Control (n = 205)	*P*
Operation time	180 (141–222)	165 (133–200)	0.098
Blood loss, mL	100 (40–200)	60 (25–140)	0.187
Transfusion during operation	3 (7.3)	1 (0.5)	0.015
Gas out day	3 (3–4)	3 (3–4)	0.878
Sips-of-water start day	2 (2–3)	2 (2–4)	0.055
Soft-diet start day	5 (4–6)	4 (4–5)	<0.001
Hospital stay, days	9 (6–12)	6 (5–8)	<0.001
Anti-emetics administration	15 (36.6)	81 (39.5)	0.712
In-hospital mortality	0	0	–
Re-admission within 30 days	1 (2.4)	8 (3.9)	0.649

Data are presented as numbers (percentage) or median (interquartile range), unless indicated otherwise.

day was later (5 [IQR 4–6] vs. 4 [IQR 4–5] days, $P < 0.001$) and the hospital length of stay was longer (9 [IQR 6–12] vs. 6 [IQR 5–8] days, $P < 0.001$) in the transplantation group than in the controls. Delayed soft diet (≥POD 6) without postoperative complications (26.8% vs. 6.8%, $P = 0.001$) and prolonged hospital stay (≥POD 8) without postoperative complications (46.3% vs. 16.6%, $P < 0.001$) were more frequent in the transplantation group than in the control group. Antiemetic administration did not differ between groups ($P = 0.712$). No in-hospital mortality occurred in either group. The rate of readmission within 30 days after discharge was similar between groups (2.4% vs. 3.9%, $P = 0.649$). The distribution of the lengths of hospital stay are summarized in Supplementary Fig. 2.

Postoperative pain and laboratory results

As shown in Supplementary Fig. 3, the daily total number of analgesic doses from POD0 to POD5 did not differ between the transplantation and control groups. The mean numeric pain scores were also similar until POD3, but they were higher in the transplantation group than in the control group at POD5. Neutrophil count was higher in the transplantation group than in the controls, except on POD0. The transplantation group had a lower lymphocyte count preoperatively, on POD0, and on POD1, as well as a lower CRP on POD1. Hemoglobin, serum albumin, and prognostic nutritional index were lower in the transplantation group than in the control group preoperatively, and these remained lower throughout the first 30 days after gastrectomy.

Short-term complications

Within 30 days after gastrectomy, the total percentage of short-term complications was similar between groups (22.0% vs. 20.0%, $P = 0.777$) (Fig. 2a). Grade 3 and 4 complications occurred in 10 patients (4.9%) in the control group, which included gastric stasis (n = 1), anastomotic leakage (n = 4), intraabdominal fluid collection (n = 3), and bleeding (n = 2). However, none of the transplantation group patients experienced grade 3 and 4 complications. No differences were observed between groups when compared by the type of complications, including gastric stasis or ileus (7.3% vs. 3.4%, in the transplantation group and the control group, respectively, $P = 0.337$), anastomotic leakage (2.4% vs. 2.9%, $P = 0.670$), intraabdominal fluid collection (7.3% vs. 6.3%, $P = 0.518$), bleeding (0% vs. 1.5%, $P = 0.577$), wound infection (2.4% vs. 3.4%, $P = 0.604$), pulmonary infection (4.9% vs. 2%, $P = 0.262$), and other complications (2.4% vs. 1.5%, $P = 0.520$) (Fig. 2b).

Adjuvant chemotherapy and long-term complications

Among chemotherapy candidates whose GC stage was 2/3, the proportion of patients who received adjuvant chemotherapy was significantly lower in the transplantation group than in the control group (26.7% vs. 80.3%, $P < 0.001$) (Supplementary Fig. 4). Furthermore, only two (50%) of the four candidates in the transplantation group completed the planned adjuvant chemotherapy, whereas 41 (65.5%) of the 61 candidates in the control group completed the planned chemotherapy.

The total percentage of long-term (>30 days) complications did not differ significantly between the transplantation and control groups (4.9% vs. 1.0%, respectively, $P = 0.131$). Two patients in the transplantation group experienced a small bowel obstruction: one (grade 3) occurred at 3 months, and the other (grade 5) occurred at 7 months. In the control group, one patient developed acute pancreatitis (grade 2) at 2 months, and one had a small bowel

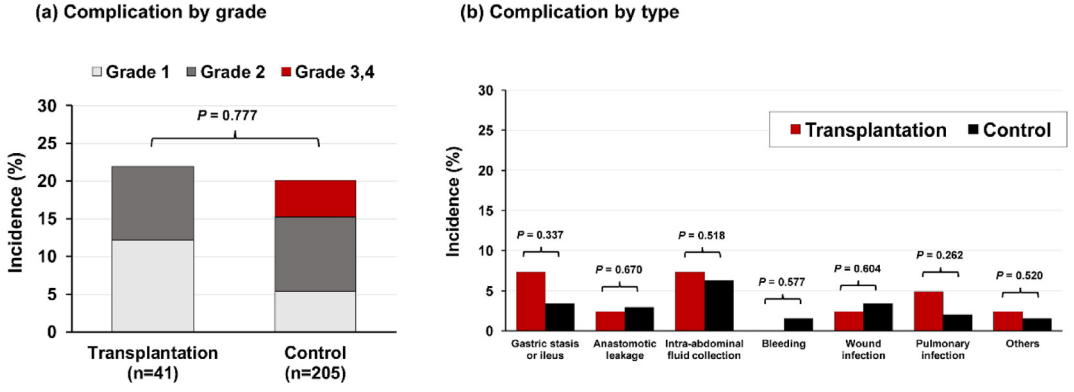

Fig. 2. Short-term complications after gastrectomy.
Comparison of complications by (a) Clavien-Dindo grade and (b) type.

obstruction (grade 2) at 14 months.

Gastric cancer recurrence

During a median follow-up of 58 (29–88) months, 32 (13.0%) patients experienced GC recurrence, with no difference in recurrence rates between the transplantation and control groups (Fig. 3a, $P = 0.351$). Among seven recurrences in the transplantation group (five kidney and two liver transplantation), six (85.7%) were abdominal recurrences and one (14.3%) was a distant metastasis. Among 25 recurrences in the control group, four (16.0%) were local recurrences, 12 (48.0%) were abdominal recurrences, and nine (36.0%) were distant metastases. In patients with stage 1 GC, no recurrence was observed in the transplantation group, which was not significantly different from the risk of recurrence in the control group (Fig. 3b, $P = 0.142$). In contrast, in patients with stage 2/3 GC, the risk of recurrence was significantly higher in the transplantation group than in the controls (Fig. 3c, $P = 0.049$). In case of recurrence, palliative chemotherapy was applied. The responses were very poor that most of the patients died within 1 year after recurrence.

Mortality

Median survivals were 42 (18–96) months in the transplantation group and 58 (33–86) months in the control group. Thirty-one (12.6%) patients died during the follow-up period, with a higher risk of all-cause death in the transplantation group than in the control group ($P < 0.001$, Fig. 3d). Five- and Ten-year overall survivals were 74.9% and 54.4% in the transplantation group and 91.5% and 84.3% in the control group. The higher mortality rate in transplantation group was observed among patients with stage 1 GC (Fig. 3e, $P = 0.005$), as well as those with stage 2/3 GC (Fig. 3f, $P = 0.015$). Analyzing the cause of death by cancer stage, among patients with stage 1 GC, the incidence of non-GC-related deaths was significantly higher in the transplantation group than in the controls (19.2% [5/26] vs. 1.4% [2/144], $P = 0.001$), but the incidence of GC-related deaths did not differ between groups (0% [0/26] vs. 2.8% [3/144], $P = 0.999$, Fig. 4a). The causes of non–GC-related deaths among patients with stage 1 GC were sigmoid colon diverticular perforation (n = 1), lung cancer (n = 1), cardiovascular disease (n = 1), pneumonia (n = 1), and unknown benign cause (n = 1, data from statistics Korea [24]) in the transplantation group; unknown benign causes (n = 2, statistics Korea) in the control group.

Among patients with stage 2/3 GC, the incidence of GC-related deaths was higher in the transplantation group than in the controls, although the difference did not reach statistical significance (40.0% [6/15] vs. 18.0% [11/61], $P = 0.087$, Fig. 4b). The incidence of non-GC-related deaths was similar between the two groups (6.7% [1/15] vs. 4.9% [3/61], $P = 0.898$), and the causes were peritonitis (n = 1) in the transplantation group; pneumonia (n = 1), idiopathic pulmonary fibrosis (n = 1), and unknown benign cause (n = 1) in the control group.

Prognosis of transplanted organs after gastric cancer surgery

After GC surgery, three kidney recipients experienced death-censored graft failure during a median follow-up of 42 (18–96) months (Supplementary Fig. 5). All of these patients had stage 1 GC and did not experience cancer recurrence or death. The cause of allograft failure was chronic rejection in all three patients. Hemodialysis was offered for these patients. No recipient who had received adjuvant chemotherapy had graft failure.

Discussion

Surgery is the best treatment method for resectable GC in

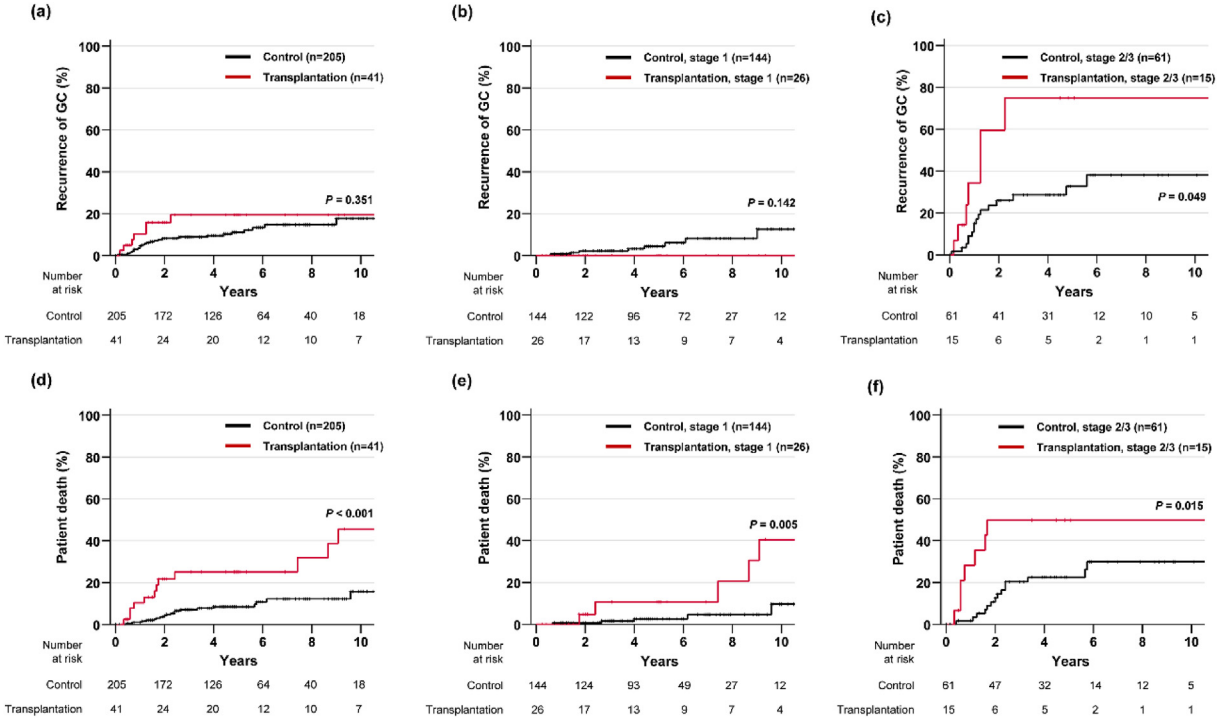

Fig. 3. Recurrence of gastric cancer and patient mortality.
Patients with (a,d) all cancer stages, (b,e) stage 1 cancer, and (c,f) stage 2/3 cancer. GC, gastric cancer.

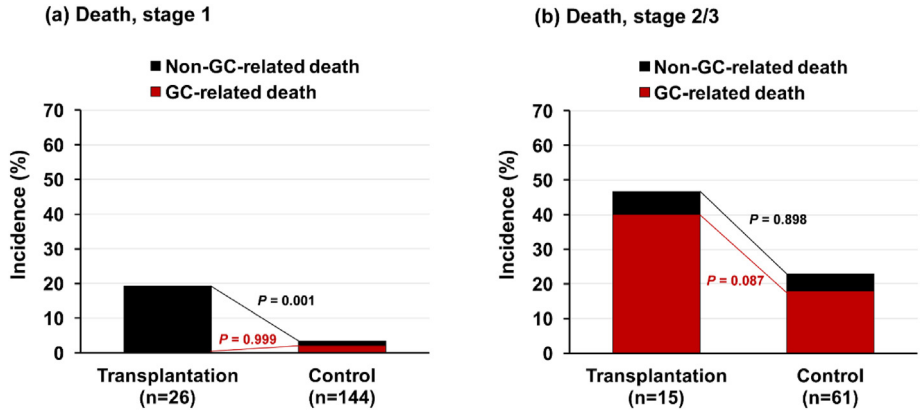

Fig. 4. Differences in the cause of death according to cancer stage
(a) Stage 1 cancer and (b) stage 2/3 cancer. GC, gastric cancer.

patients with prior solid organ transplantation, as it is for patients who have not undergone transplantation surgery. However, several comorbidities and immunosuppressive drugs used for organ recipients have raised concerns that the patients may experience worse postoperative outcomes. In the short-term, we found no differences in recovery or surgical complications between patients who were or were not solid organ recipients. Although blood transfusions were more common and the times to first soft diet and hospital discharge were longer in transplant recipients, these differences likely reflected their lower baseline hemoglobin and a more cautious postoperative care, rather than a more complicated perioperative course. In the long-term, the risk of GC recurrence was higher in transplant recipients than in non-transplant recipients, only when GC was at an advanced-stage (stage 2/3). The risk of all-cause death was higher in transplant recipients than in non-transplant recipients, regardless of GC stage. The cause of death in transplant recipients differed distinctly according to the cancer stage. Most of the deaths in patients with stage 2/3 GC were GC-related, whereas none of the deaths in patients with stage 1 disease were GC-related.

Major intraoperative concerns of gastrectomy in transplant recipients include excessive bleeding and tissue friability, resulting in longer operation times and subsequent complications. However, operation times and blood loss were similar between the transplantation and control groups in this study. Furthermore, detailed analysis of complication data revealed no difference in the incidence or characteristics of surgical complications.

Potential effects of chronic and concurrent use of immunosuppressants on perioperative surgical outcomes are another concern. CNIs, MMF, and corticosteroids are commonly used immunosuppressive drugs [25]. At present, lifelong administration of some of these drugs seems inevitable, although they have several adverse effects. The most important adverse effect is infection, which is a major contributor to patient outcomes after solid organ transplantation [26]. Surgical infection is likewise an important clinical issue after GC surgery [27]. Therefore, surgeons may be concerned about the possibility of increased risk of infectious complications after gastrectomy in solid organ recipients. In this study, infections, including intraabdominal fluid collection, wound infection, and pulmonary infection, were not different between the transplantation and control groups, although the transplantation recipients continued their immunosuppressive agents around the time of gastrectomy.

Another well-known side effect of CNI and MMF is gastrointestinal disturbance [11]. Among the transplantation recipients in this study, all were receiving a CNI and approximately half of them were taking MMF at the time of gastrectomy. However, the transplantation group did not experience more gastrointestinal complications during the immediate postoperative period. Days of first gas expulsion and first sips of water were also similar between groups. Although the initiation of soft diet and hospital discharge were delayed in the transplantation group, these delays were observed not only in the entire group but also in the subgroup without complications. This observation suggests that the delay was likely caused by the surgeons' concerns regarding the possible adverse effects of immunosuppressants, and not by the actual surgical complication in the transplantation group. Interestingly, grade 3 and 4 complications did not occur in the transplantation group, whereas they occurred in 4.9% of the control group patients. One possible explanation relates to the anti-inflammatory effects of perioperative corticosteroids in the transplant recipients. Prior studies reported protective effects of perioperative corticosteroids with respect to infectious complications after pancreaticoduodenectomy [28,29]. However, these results should be interpreted with caution, due to the relatively small size of the transplantation group and variations in types of bowel surgery used in this study.

The most important finding of our study was that transplant recipients with early-stage GC had a significantly higher rate of non–GC-related deaths compared to non-transplant recipients. In general, transplant recipients have a high risk of death, not only from their malignancy but also from other causes, such as cardiovascular disease, infection, suicide, and kidney or liver disease unrelated to the transplantation [30–34]. In this study, no one in the transplantation group with early GC experienced a GC-related death. Instead, two patients died from infection, and one died from cardiovascular disease (other two died from lung cancer and unknown benign cause). Therefore, we suggest focusing on post-transplantation care rather than oncologic care for transplant recipients with early-stage GC. General recommendations about post-transplant surveillance for non-GC-related death are well-demonstrated in the Kidney Disease: Improving Global Outcomes (KDIGO) guideline [35], although there is no established guideline for recipients of liver and heart transplantation.

Conversely, in patients with advanced-stage GC, transplant recipients exhibited a higher (although not quite significant) rate of GC-related death ($P = 0.087$) and a higher risk of GC recurrence ($P = 0.049$) compared to the controls. These findings may have been due to the use of immunosuppressants and a lower proportion of patients undergoing adjuvant chemotherapy in the transplantation group compared to the control group. Only 4 patients among 15 (26.7%) stage 2/3 GC received adjuvant chemotherapy in the

transplantation group. Furthermore, among those who received chemotherapy, the planned schedule was completed in only 50% of patients in the transplantation group, in contrast to 65.5% of those in the control group. The reason why adjuvant CTx was not appropriately administered in the recipient group cannot be clarified by retrospective searching for medical record, which was a limitation of this study. However, we considered two factors that may have contributed to these chemotherapy differences: 1) transplant recipients may have been assumed to be more susceptible to the adverse effects of chemotherapy due to their immunosuppressant usage, and 2) there may have been concerns that chemotherapy would adversely affect the graft survival. However, our results showed that graft failure did not occur in any patient who received adjuvant chemotherapy, while it did occur in three patients with stage 1 GC who did not undergo chemotherapy. This finding supports that strict adjuvant chemotherapy should be considered in patients with advanced-stage GC, including solid organ recipients.

The limitations of this study included the relatively small number of patients in the transplantation group, which limited its statistical power and led to heterogeneity for the types of transplanted organ and immunosuppressants. Second, since this was a single-center study with an observational (cohort) design for an extensive experience of GC surgery, generalizing the postoperative outcomes would be limited. Lastly, the majority of our study population had early GC; therefore, our results cannot fully reflect the usual situation in other countries where GC is generally diagnosed at advanced stage. However, to our knowledge, this is the first and largest comprehensive report to investigate the short- and long-term outcomes after gastrectomy of solid organ transplant recipients.

Conclusion

Transplant recipients exhibited similar short-term surgical outcomes and complications after GC surgery compared to non-transplant recipients. Active surveillance of non-GC-related deaths in patients with early GC and strict oncologic care in those with advanced GC should be the highest priorities during long-term postoperative care of transplant recipients after gastrectomy.

Role of the funding source

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CRediT authorship contribution statement

Deok Gie Kim: Conceptualization, Formal analysis, Data curation, Writing – original draft, Writing – review & editing. **Won Jun Seo:** Formal analysis. **Minah Cho:** Investigation, Resources. **Yoo-Min Kim:** Investigation, Resources. **Kyu Ha Huh:** Investigation, Resources. **Jae-Ho Cheong:** Investigation, Resources. **Woo Jin Hyung:** Investigation, Resources. **Myoung Soo Kim:** Investigation, Resources. **Hyoung-Il Kim:** Conceptualization, Investigation, Resources, Data curation, Supervision.

Declaration of competing interest

The authors declare no conflict of interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2021.04.017.

References

[1] Hart A, Smith JM, Skeans MA, et al. OPTN/SRTR 2017 annual data report: kidney. Am J Transplant 2019;19(Suppl 2):19–123. https://doi.org/10.1111/ajt.15274.
[2] Kwong A, Kim WR, Lake JR, et al. OPTN/SRTR 2018 annual data report: liver. Am J Transplant 2020;20(Suppl s1):193–299. https://doi.org/10.1111/ajt.15674.
[3] Engels EA, Pfeiffer RM, Fraumeni Jr JF, et al. Spectrum of cancer risk among US solid organ transplant recipients. J Am Med Assoc 2011;306:1891–901. https://doi.org/10.1001/jama.2011.1592.
[4] Collett D, Mumford L, Banner NR, Neuberger J, Watson C. Comparison of the incidence of malignancy in recipients of different types of organ: a UK Registry audit. Am J Transplant 2010;10:1889–96. https://doi.org/10.1111/j.1600-6143.2010.03181.x.
[5] Park B, Yoon J, Choi D, et al. De novo cancer incidence after kidney and liver transplantation: results from a nationwide population based data. Sci Rep 2019;9:17202. https://doi.org/10.1038/s41598-019-53163-9.
[6] Park JM, Choi MG, Yang CW, et al. Increased incidence of gastric cancer in renal transplant recipients. J Clin Gastroenterol 2012;46:e87–91. https://doi.org/10.1097/MCG.0b013e31825c0b3a.
[7] Lee IS, Kim TH, Kim YH, Yook JH, Kim BS, Han DJ. Clinical significance of gastric cancer surveillance in renal transplant recipients. World J Surg 2012;36:1806–10. https://doi.org/10.1007/s00268-012-1605-1.
[8] Chen J, Cheong JH, Hyung WJ, et al. Gastric adenocarcinoma after renal transplantation. Hepato-Gastroenterology 2004;51:895–9.
[9] Gong CS, Yoo MW, Kim BS, et al. De novo gastric cancer after liver transplantation. Ann Transplant 2016;21:386–91.
[10] D'Arcy ME, Coghill AE, Lynch CF, et al. Survival after a cancer diagnosis among solid organ transplant recipients in the United States. Cancer 2019;125:933–42. https://doi.org/10.1002/cncr.31782.
[11] Bunnapradist S, Neri L, Wong W, et al. Incidence and risk factors for diarrhea following kidney transplantation and association with graft loss and mortality. Am J Kidney Dis 2008;51:478–86. https://doi.org/10.1053/j.ajkd.2007.11.013.
[12] Ekberg H, Tedesco-Silva H, Demirbas A, et al. Reduced exposure to calcineurin inhibitors in renal transplantation. N Engl J Med 2007;357:2562–75. https://doi.org/10.1056/NEJMoa067411.
[13] Kleif J, Kirkegaard A, Vilandt J, Gogenur I. Randomized clinical trial of preoperative dexamethasone on postoperative nausea and vomiting after laparoscopy for suspected appendicitis. Br J Surg 2017;104:384–92. https://doi.org/10.1002/bjs.10418.
[14] Zou Z, Jiang Y, Xiao M, Zhou R. The impact of prophylactic dexamethasone on nausea and vomiting after thyroidectomy: a systematic review and meta-analysis. PloS One 2014;9:e109582. https://doi.org/10.1371/journal.pone.0109582.
[15] Waldron NH, Jones CA, Gan TJ, Allen TK, Habib AS. Impact of perioperative dexamethasone on postoperative analgesia and side-effects: systematic review and meta-analysis. Br J Anaesth 2013;110:191–200. https://doi.org/10.1093/bja/aes431.
[16] Lunn TH, Andersen LO, Kristensen BB, et al. Effect of high-dose preoperative methylprednisolone on recovery after total hip arthroplasty: a randomized, double-blind, placebo-controlled trial. Br J Anaesth 2013;110:66–73. https://doi.org/10.1093/bja/aes345.
[17] Chen CC, Siddiqui FJ, Chen TL, Chan ES, Tam KW. Dexamethasone for prevention of postoperative nausea and vomiting in patients undergoing thyroidectomy: meta-analysis of randomized controlled trials. World J Surg 2012;36:61–8. https://doi.org/10.1007/s00268-011-1343-9.
[18] Zargar-Shoshtari K, Sammour T, Kahokehr A, Connolly AB, Hill AG. Randomized clinical trial of the effect of glucocorticoids on peritoneal inflammation and postoperative recovery after colectomy. Br J Surg 2009;96:1253–61. https://doi.org/10.1002/bjs.6744.
[19] Fukami Y, Terasaki M, Okamoto Y, et al. Efficacy of preoperative dexamethasone in patients with laparoscopic cholecystectomy: a prospective randomized double-blind study. J Hepatobiliary Pancreat Surg 2009;16:367–71. https://doi.org/10.1007/s00534-009-0079-5.
[20] Ho DE, Imai K, King G, Stuart EA. Matching as nonparametric preprocessing for reducing model dependence in parametric causal inference. Polit Anal 2017;15:199–236. https://doi.org/10.1093/pan/mpl013.
[21] Williamson A, Hoggart B. Pain: a review of three commonly used pain rating scales. J Clin Nurs 2005;14:798–804. https://doi.org/10.1111/j.1365-

2702.2005.01121.x.
[22] Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205–13. https://doi.org/10.1097/01.sla.0000133083.54934.ae [pii].
[23] Lee JY, Kim HI, Kim YN, et al. Clinical significance of the prognostic nutritional index for predicting short-and long-term surgical outcomes after gastrectomy: a retrospective analysis of 7781 gastric cancer patients. Medicine (Baltim) 2016;95:e3539. https://doi.org/10.1097/md.0000000000003539.
[24] Statistics Korea. Mortality data. Available from: http://kostat.go.kr/portal/eng/index.action.
[25] Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Transplant 2009;9(Suppl 3):S1–155. https://doi.org/10.1111/j.1600-6143.2009.02834.x.
[26] Fishman JA. Infection in organ transplantation. Am J Transplant 2017;17:856–79. https://doi.org/10.1111/ajt.14208.
[27] Kosuga T, Ichikawa D, Komatsu S, et al. Clinical and surgical factors associated with organ/space surgical site infection after laparoscopic gastrectomy for gastric cancer. Surg Endosc 2017;31:1667–74. https://doi.org/10.1007/s00464-016-5156-7.
[28] Laaninen M, Sand J, Nordback I, Vasama K, Laukkarinen J. Perioperative hydrocortisone reduces major complications after pancreaticoduodenectomy: a randomized controlled trial. Ann Surg 2016;264:696–702. https://doi.org/10.1097/sla.0000000000001883.
[29] Sandini M, Ruscic KJ, Ferrone CR, et al. Intraoperative dexamethasone decreases infectious complications after pancreaticoduodenectomy and is associated with long-term survival in pancreatic cancer. Ann Surg Oncol 2018;25:4020–6. https://doi.org/10.1245/s10434-018-6827-5.
[30] Rana A, Ackah RL, Webb GJ, et al. No gains in long-term survival after liver transplantation over the past three decades. Ann Surg 2019;269:20–7. https://doi.org/10.1097/SLA.0000000000002650.
[31] Saran R, Robinson B, Abbott KC, et al. USRDS annual data report, Vol 2 - ESRD in the United States, Chapter 5: Mortality. Am J Kidney Dis 2018;73:S411–26. https://doi.org/10.1053/j.ajkd.2018.12.016. 2019.
[32] Aberg F, Gissler M, Karlsen TH, et al. Differences in long-term survival among liver transplant recipients and the general population: a population-based Nordic study. Hepatology (Baltimore, Md 2015;61:668–77. https://doi.org/10.1002/hep.27538.
[33] Kahwaji J, Bunnapradist S, Hsu JW, Idroos ML, Dudek R. Cause of death with graft function among renal transplant recipients in an integrated healthcare system. Transplantation 2011;91:225–30. https://doi.org/10.1097/TP.0b013e3181ff8754.
[34] Sarnak MJ, Levey AS, Schoolwerth AC, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American heart association councils on kidney in cardiovascular disease, high blood pressure research, clinical cardiology, and epidemiology and prevention. Circulation 2003;108:2154–69. https://doi.org/10.1161/01.CIR.0000095676.90936.80.
[35] KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Transplant 2009;9(Suppl 3):S1–155. https://doi.org/10.1111/j.1600-6143.2009.02834.x.