ORIGINAL ARTICLE

Postoperative outcomes of cancer surgery in patients with and without kidney failure with dialysis therapy: a matched-pair cohort study

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ABSTRACT

Background. The difference in outcomes of cancer surgery between patients with and without kidney failure with dialysis therapy (KFDT) remains uncertain.

Methods. Using 2010–18 data in a national inpatient database in Japan, we identified patients who had undergone resection of colorectal, lung, gastric or breast cancer. We matched selected patient characteristics, type of cancer, surgical procedure and hospital of up to four patients without KFDT to each patient with KFDT. We assessed 30-day mortality and postoperative complications.

Results. Through matching, we identified 2248 patients with KFDT (807 with colorectal, 579 with lung, 500 with gastric and 362 with breast cancer) and 8210 patients without KFDT (2851 with colorectal, 2216 with lung, 1756 with gastric and 1387 with breast cancer). Postoperative complications occurred in a higher proportion of patients with KFDT than of those without KFDT after colorectal [20.3% versus 14.6%; risk difference (RD): 5.7% [95% confidence interval (95% CI) 2.6%–8.8%]], lung [18.0% versus 12.9%; RD: 5.1% (95% CI 1.6%–8.4%)], gastric [25.0% versus 13.2%; RD: 11.8% (95% CI 7.6%–16.2%)] and breast cancer surgery [7.5% versus 3.5%; RD: 3.9% (95% CI 1.1%–6.9%)]. Patients with KFDT had a higher 30-day mortality than those without KFDT after gastric cancer surgery [1.6% versus 0.3%; RD: 1.3% (95% CI 0.1%–2.3%)]. Heart failure and ischemic heart disease occurred more frequently in patients with KFDT.

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Conclusions. Patients with KFDT had higher rates of postoperative complications and 30-day mortality; however, RDs varied between cancer types. The higher rates of postoperative complications in patients with KFDT were mainly attributable to cardiovascular complications.

Keywords: cancer, kidney failure with dialysis therapy (KFDT), mortality, postoperative complication, surgery

INTRODUCTION

Kidney failure with dialysis therapy (KFDT) is strongly associated with all-cause death [1, 2]. The high risk of death in patients with KFDT partly attributable to malignancy, which occurs more frequently in patients with KFDT. Various studies have reported standardized incidence ratios of 1.18–1.44 for malignancy among patients with KFDT compared with the general population [3–7]. However, the mechanisms underlying excess mortality in patients with KFDT have not yet been fully elucidated.

Resection is the cornerstone of curative therapy for most patients with solid malignancies without metastasis. One previous study showed that patients on dialysis are more likely to have perioperative comorbidities, such as respiratory failure, after general surgical procedures, including procedures other than cancer surgery [8]. The more frequent postoperative complications after cancer resection may contribute to the excess mortality in patients with KFDT; however, there has been little research on this topic. Postoperative complications may also have negative impacts on eligibility for subsequent treatment, such as adjuvant chemotherapy. Therefore, it is crucial to further investigate the probability of postoperative outcomes in patients with KFDT after cancer surgery.

To further explore postoperative complications, including (i) which types of complications differ between patients with and without KFDT and (ii) whether these differences are dependent on the primary cancer site, we conducted a retrospective cohort study in patients who had undergone cancer surgery and were stratified by KFDT status.

MATERIALS AND METHODS

Data source

In this matched-pair cohort study, we used the Diagnosis Procedure Combination database, a national inpatient database in Japan [9]. This database includes administrative claims and discharge abstract data and covers over 50% of all inpatient admissions to acute care hospitals in Japan. The database includes the following information: patient age and sex; discharge status; primary diagnosis on admission; comorbidities on admission; post-admission complications encoded in accordance with the International Classification of Diseases, 10th revision (ICD-10) codes; and tumor node metastasis (TNM) classification of malignant tumors and surgical and anesthetic procedures encoded with original codes in Japan. Details of this database have been provided previously [9]. The Institutional Review Board of the University of Tokyo approved the present study. Because the data were anonymized, the requirement for informed consent from individual patients was waived.

Study participants and study period

We identified patients who had been admitted for planned surgery for colorectal, lung, gastric or breast cancer. We focused on these cancers because they are the most common types of cancer in Japan. We applied the following exclusion criteria: (i) multiple cancer surgeries during the index admission; (ii) age <18 years; (iii) clinical cancer stage 4 or missing data on cancer stage; and (iv) missing data on smoking status.

We defined KFDT patients as those with a recorded diagnosis of kidney failure (ICD-10 code, N18.0) on admission and those with procedure codes for chronic hemodialysis or peritoneal dialysis before the index planned surgery.

Study outcomes and definitions of variables

The primary outcomes comprised 30-day mortality after the index operation date and postoperative complications during hospitalization. Postoperative complications were defined as follows: heart failure, ischemic heart disease, pulmonary embolism, heart rhythm abnormalities, respiratory failure, surgical site infection, anastomotic leakage, ileus, pneumonia, cerebral infarction and postoperative drainage procedure. ICD-10 codes for defining these complications are provided in supplementary codes. Secondary outcomes included rates of the types of postoperative complications listed above and emergency re-admission within 30 days after discharge. We collected data on the following covariates: age, sex; fiscal year of discharge; primary cancer site; clinical cancer stage; type of surgical procedure.
procedure; anesthesia type (general anesthesia, general and epidural anesthesia and other); body mass index (BMI); smoking history (current smoker or not); and relevant medical history such as myocardial infarction, cerebral infarction, diabetes and chronic pulmonary diseases. We also documented the length of hospital stays after the index surgery.

**Matching**

We matched up to four eligible non-KFDT patients to each eligible patient with KFDT for age (within 5 years), sex, index fiscal year (within 3 years), primary cancer site, clinical cancer stage, surgical procedure and hospital to which the patient had been admitted [10].

**Statistical analysis**

For each primary cancer site, we estimated risk differences (RDs) in outcomes rather than relative risk as the main effect indicator, because RDs are better understood by physicians and patients than risk ratios or odds ratios [11]. The 95% confidence intervals (95% CI) in RDs were calculated using bootstrapping (1000-time resampling) in the matched cohort. For the secondary effect indicator, we used conditional logistic regression models stratified on matched sets to estimate the odds ratio with 95% CI for associations between KFDT and outcomes. We further used conditional logistic regression models to adjust for potential confounders, including anesthesia type, BMI, smoking history, history of myocardial infarction, cerebral infarction, diabetes and chronic pulmonary diseases. In Model 1, we only stratified within matched sets. In Model 2, we further adjusted for covariates in addition to stratification within matched sets. We performed sensitivity analyses as follows: (i) we estimated RD using a linear regression generalized estimating equation model in which we treated each hospital as a cluster [12], and (ii) we only included patients with KFDT for whom we had identified four matched patients without KFDT (i.e. we excluded matched pairs in ratios of 1:3 or less). We conducted all analyses with R, version 3.6.3 and Stata 16 SE (Stata, College Station, TX, USA).

**RESULTS**

During the study period, 371960 patients fulfilled the inclusion criteria. After the exclusion of 41521 of these patients, we identified 2338 patients with KFDT and 328,101 without KFDT. Through matching, we identified 2248 patients with KFDT (807, 579, 500 and 362 with colorectal, lung, gastric and breast cancer, respectively) and 8210 without KFDT (2851, 2216, 1756 and 1387 with colorectal, lung, gastric and breast cancer, respectively)
FIGURE 2: Differences in risks of primary outcomes between matched cohorts of patients with and without KFDT. Matched for age (within 5 years), sex, index fiscal year (within 3 years), primary cancer site, clinical cancer stage, surgical procedure and hospital to which admitted.

Overall, 64.1% of the matched cohort was male, 45.5% were aged 65–74 years and 29.0% were aged 75–84 years. Patients with KFDT had lower BMIs and were less likely to have undergone general and epidural anesthesia (Table 1). In addition, patients with KFDT were more likely to have histories of comorbidities other than chronic pulmonary disease. Details of surgical procedures are shown in Supplementary data, Table S1.

The 30-day mortalities in all patients with and without KFDT were 0.7% and 0.1%, respectively (RD: 0.5%; 95% CI 0.2–0.9); 0.5% and 0.1%, respectively, for those with colorectal cancer (RD: 0.4%; 95% CI −0.2 to 0.9); 0.7% versus 0.2%, respectively, for lung cancer (RD: 0.5%; 95% CI −0.2 to 1.2); 1.6% and 0.3%, respectively, for gastric cancer (RD: 1.3%; 95% CI 0.1–2.3); and 0% and 0%, respectively, for breast cancer (RD: 0%), (Figure 2).

Overall, there was a greater proportion of postoperative complications in patients with KFDT than in those without KFDT (18.7% versus 12.0%; RD: 6.7%; 95% CI 5.0–8.4). A higher proportion of patients with KFDT than those without KFDT had heart failure (3.7% versus 1.1%; RD: 2.6%; 95% CI 1.3–4.0), lung cancer (2.8% versus 1.1%; RD: 1.6%; 95% CI 0.2–3.0), gastric cancer (4.0% versus 1.3%; RD: 2.7%; 95% CI 0.9–4.5) and breast cancer surgery (1.4% versus 0.1%; RD: 1.3%; 95% CI 0.2–2.5) (Table 2). Additionally, compared with patients without KFDT, those with KFDT had more frequent ischemic heart disease after colorectal cancer (3.3% versus 1.0%; RD: 2.4%; 95% CI 1.1–3.7), lung cancer (3.5% versus 0.9%; RD: 2.6%; 95% CI 1.0–4.1) and gastric cancer (4.0% versus 1.3%; RD: 2.7%; 95% CI 0.9–4.5). After colorectal cancer surgery, emergency readmission was required more frequently by patients with KFDT than by those without KFDT (Fig. 2, Table 2).

We observed a longer length of hospital stay after the surgery in those with KFDT compared with those without KFDT (Table 3).

In the conditional logistic regression models, odds ratios in Model 1 were similar to those in Model 2 (Supplementary data, Figure S1). Sensitivity analysis (i) excluding matched pairs in ratios of 1:3 or less and (ii) using a linear regression generalized estimating equation model yielded similar results (Supplementary data, Figure S2).

DISCUSSION

Using a national inpatient database in Japan, we compared postoperative outcomes after surgery for four common types of cancer between patients with and without KFDT. Matched-pair cohort analyses showed that patients with KFDT had a higher 30-day mortality and incidence of postoperative complications than those without KFDT. The RDs in outcomes differed between the different types of cancer. The higher rates of postoperative complications in patients with KFRT were mainly attributable to cardiovascular complications.

The present findings are consistent with those of a previous study of patients undergoing non-emergency general surgery other than cancer resection [8]. In that study, patients undergoing dialysis had a higher risk of vascular complications (adjusted odds ratio 1.69; 95% CI 1.04–2.75) and postoperative death (adjusted odds ratio 2.57; 95% CI 2.15–3.08). In our study, the differences in proportions of postoperative complications between patients with and without KFDT appear to be mainly attributable to heart failure and ischemic heart disease. Patients with KFDT have narrower safe ranges of fluid balance and increased risks of intra-dialytic hypotension and pulmonary congestion, especially perioperatively. Meticulous perioperative management of dialysis treatment times and ultrafiltration rates may improve outcomes in patients with KFDT [13–16]. In addition, optimizing perioperative fluid administration may contribute to better management. A multi-disciplinary approach involving surgeons, anesthesiologists and nephrologists is helpful in reducing the excess risk of perioperative complications in patients with KFDT [17,18].

We found that RDs varied between the different types of cancer studied. Several factors may explain this. First, patient characteristics, such as age, baseline comorbidities and smoking status, differed between the different cancer types, and these differences may have been reflected by differences
Postoperative outcomes of cancer surgery in patients with and without KFDT

| Outcomes                        | Colorectal cancer | Lung cancer | Gastric cancer | Breast cancer |
|---------------------------------|-------------------|-------------|----------------|---------------|
|                                 | Risk differences (95% CI) | Without KFDT, n (%) | With KFDT, n (%) | Without KFDT, n (%) | With KFDT, n (%) | Without KFDT, n (%) | With KFDT, n (%) | Without KFDT, n (%) | With KFDT, n (%) | Without KFDT, n (%) | With KFDT, n (%) | Without KFDT, n (%) | With KFDT, n (%) |
| Postoperative complications     |                   |             |                |                |                |                |                |                |                |                |                |                |                |
| Heart failure                   | 2.6 (1.3–4.0)     | 32 (1.1)    | 30 (3.7)       | 1.6 (0.2–3.0)  | 25 (1.1)       | 16 (2.8)       | 2.7 (0.9–4.5)  | 22 (1.3)       | 20 (4.0)       | 1.3 (0.1–2.5)  | 1 (0.1)         | 5 (1.4)         |
| Ischemic heart disease          | 2.4 (1.1–3.7)     | 28 (1.0)    | 27 (3.3)       | 2.6 (1.0–4.1)  | 20 (0.9)       | 20 (3.5)       | 2.7 (1.0–4.5)  | 22 (1.3)       | 20 (4.0)       | 1.3 (0.1–2.7)  | 5 (0.4)         | 6 (1.7)         |
| Pulmonary embolism              | -0.1 (–0.2 to 0.0) | 2 (0.1)    | 0 (0.0)        | 0.1 (–0.3 to 0.4) | 2 (0.1)       | 1 (0.2)       | -0.1 (–0.3 to 0.1) | 2 (0.1)       | 0 (0.0)        | 0.0 (0.0–0.0)  | 0 (0)           | 0 (0)           |
| Heart rhythm abnormalities      | 1.6 (0.1–3.1)     | 74 (2.6)    | 34 (4.2)       | 0.1 (–2.1 to 2.3) | 124 (5.6)     | 33 (5.7)       | 2.0 (0.0–4.2)  | 52 (3.0)       | 25 (5.0)       | 2.1 (0.1–4.0)  | 17 (1.2)        | 12 (3.3)        |
| Respiratory failure             | 0.5 (–0.3 to 1.2) | 15 (0.5)    | 8 (1.0)        | -0.3 (–1.2 to 0.5) | 26 (1.2)     | 5 (0.9)        | 2.2 (0.7–3.8)  | 14 (0.8)       | 15 (3.0)       | 0.5 (–0.3 to 1.2) | 1 (0.1)       | 2 (0.6)        |
| Surgical site infection         | 0.8 (–0.9 to 2.5) | 118 (4.1)   | 40 (5.0)       | -0.5 (–1.1 to 0.4) | 35 (1.6)     | 6 (1.0)        | 1.8 (–0.4 to 3.9) | 60 (3.4)       | 26 (5.2)     | -0.6 (–1.9 to 0.7) | 24 (1.7)       | 4 (1.1)        |
| Anastomotic leakage             | 0.5 (–1.0 to 2.0) | 95 (3.3)    | 31 (3.8)       | 0.3 (–0.3 to 0.7) | 2 (0.1)       | 2 (0.3)        | 2.7 (0.7–4.7)  | 37 (2.1)       | 24 (4.8)       | 0.0 (0.0–0.0)  | 0 (0)           | 0 (0)           |
| Ileus                           | -2.0 (–3.4 to –0.7) | 136 (4.8)  | 22 (2.7)       | 0.0 (0.0–0.0) | 0 (0) | 0 (0) | -0.2 (–1.4 to 1.0) | 32 (1.8) | 8 (1.6) | 0.0 (0.0–0.0) | 0 (0) | 0 (0) |
| Pneumonia                       | 0.4 (–0.4 to 1.1) | 18 (0.6)    | 8 (1.0)        | 1.3 (–1.6 to 3.3) | 82 (3.7)     | 29 (5.0)       | 1.1 (–0.4 to 2.6) | 27 (1.5)       | 13 (2.6)       | 0.2 (–0.4 to 0.8) | 1 (0.1)       | 1 (0.3) |
| Cerebral infarction             | 0.3 (–0.2 to 0.9) | 8 (0.3)    | 5 (0.6)        | 0.7 (–0.1 to 1.6) | 7 (0.3) | 6 (1.0) | 1.4 (0.3–2.5) | 4 (0.2) | 8 (1.6) | 0.3 (–0.3 to 0.8) | 0 (0) | 1 (0.3) |
| Postoperative drainage          | 0.3 (–0.6 to 1.3) | 36 (1.3) | 13 (1.6)       | 0.0 (0.0–0.0) | 0 (0) | 0 (0) | 0.8 (–0.5 to 2.2) | 24 (1.4) | 11 (2.2) | 0.0 (0.0–0.0) | 0 (0) | 0 (0) |
| Emergent readmission            | 2.2 (0.5–4.0)     | 109 (3.8)   | 49 (6.1)       | 1.4 (–0.6 to 3.4) | 87 (3.9) | 31 (5.4) | 2.0 (–0.3 to 4.3) | 70 (4.0) | 30 (6.0) | 0.1 (–0.9 to 1.1) | 10 (0.7) | 3 (0.8) |
in shared risk factors for cancer and cardiovascular disease, including kidney failure, according to cancer site [19]. Second, it is plausible that the invasiveness of curative resections differed between cancer sites; however, it is not possible to objectively evaluate such differences. Our data provide useful information for physicians and patients regarding perioperative risks and may be helpful in shared decision-making with patients with KFRT and various types of cancer [20].

One strength of our study is the large cohort of KFDT patients who had undergone curative cancer surgery, despite our finding that patients with KFDT comprised only 0.7% of patients in the database who had undergone such surgery. The size of our patient cohort enabled us to collect abundant data on KFDT patients undergoing cancer surgery. Our findings could provide useful information to assist decision-making on surgery by KFDT patients and their surgeons and nephrologists, and shed light on one of the as yet unanswered issues in the field of onco-nephrology [21,22]. Furthermore, we adjusted for potential differences in practice patterns between hospitals by matching the hospitals to which patients with and without KFDT were admitted. This matching would have eliminated the influences of both these hospitals’ functions and their experience (patient volumes), enabling fairer comparisons between patients with and without KFDT.

We need to acknowledge two limitations of the study. First, coding of postoperative complications using ICD-10 codes was likely short of completely accurate; however, the procedure codes for cancer surgery in the database are accurate [23]. Second, our study cohort did not include patients whose anticipated high operative risk prevented them from undergoing surgery.

CONCLUSIONS
Patients with KFDT have a higher risk of 30-day mortality and a greater incidence of postoperative complications than those without KFDT. Cardiovascular complications were the most frequently occurring type of postoperative complication in patients with KFRT, the incidence differing between different types of cancer. Surgeons, anesthesiologists and nephrologists should provide patients with KFDT with multidisciplinary perioperative care to decrease their excess risk of postoperative complications.

SUPPLEMENTARY DATA
Supplementary data are available at cks online.

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The authors declare that the results presented in this paper have not been published previously in whole or part, except in abstract format.

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AUTHORS’ CONTRIBUTIONS
Y.M., M.I., S.A. and H.Y. designed the study. Y.M., S.A., K.U., K.F. and H.Y. were involved in data acquisition. Y.M., M.I. and S.A. were responsible for the statistical analysis. Y.M., M.I. and S.A. interpreted the data and wrote the first draft of the manuscript. Y.H., M.N., K.D. and H.Y. revised the manuscript critically for important intellectual content. All authors approved the final version of the manuscript. The corresponding author had full access to the data in the study and took final responsibility for the decision to submit it for publication.

CONFLICT OF INTEREST STATEMENT
M.N. reports personal fees from Akebia, grants and personal fees from Astellas, personal fees from AstraZeneca, grants and personal fees from Bayer, grants and personal fees from Boehringer Ingelheim, personal fees from GSK, grants and personal fees from JT, grants and personal fees from Kyowa Kirin, grants and personal fees from Mitsubishi Tanabe, grants and personal fees from Ono, grants and personal fees from Chugai, grants and personal fees from Daiichi Sankyo, and grants from Takeda, outside the submitted work.

Authors other than M.N. do not have conflicts of interest.

DATA AVAILABILITY STATEMENT
Data may be obtained from a third party and are not publicly available.

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