Diabetes Mellitus with Obesity is a Predictor of Recurrence in Patients with Non-metastatic Renal Cell Carcinoma

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Objective: To investigate the associations of diabetes mellitus with recurrence and prognosis after surgery for non-metastatic renal cell carcinoma and the effect modification of obesity on the above relationships.

Methods: We retrospectively evaluated 543 patients with non-metastatic renal cell carcinoma (pT1-4N0M0) who underwent radical or partial nephrectomy. The association of diabetes mellitus with recurrence was analyzed using the Kaplan–Meier method and the Cox regression model. We also examined whether the above relationships were modified by obesity using subgroup analysis and tests of interaction. For subgroup analysis, the body mass index was categorized as non-obese (<25 kg/m²) and obese (≥25 kg/m²).

Results: Eighty-two patients (15.1%) had a history of diabetes mellitus. During the mean follow-up of 66.7 months, 68 patients (12.5%) developed recurrence. Although the body mass index was not associated with recurrence, diabetes mellitus was an independent predictor of recurrence in multivariate analysis (hazard ratio 2.43, \( P = 0.003 \)), along with tumor diameter, grade and pathological T stage. In further subgroup analysis, the same relationship between diabetes mellitus and recurrence was clearly shown in the obese group (hazard ratio 4.07, \( P = 0.010 \)), but not in the non-obese group (hazard ratio 1.95, \( P = 0.125 \)). At the same time, obesity modified the effect of diabetes mellitus on recurrence with a trend (\( P_{interaction} = 0.086 \)). In the obese group, 5-year recurrence-free survival rates were 75.3 and 91.9% for diabetes mellitus and non-diabetes mellitus patients, respectively (\( P < 0.001 \)). Restricting analyses to patients with clear cell type histology did not materially change these results.

Conclusions: Diabetes mellitus is a predictor of recurrence following surgery for non-metastatic renal cell carcinoma, especially in obese patients.

Key words: diabetes mellitus – obesity – renal cell carcinoma – recurrence

INTRODUCTION

Renal cell carcinoma (RCC) accounts for 2–3% of all cancers and is increasing worldwide (1). Although most RCC patients present with localized disease, due to the recent widespread prevalence of screening with abdominal ultrasonography and computed tomography, ~30% of these patients eventually experience recurrence during the course of the disease (2). The prognosis after recurrence is poor, and new prognosticators are thus required to predict recurrence preoperatively in patients with non-metastatic RCC and to solicit their participation in clinical trials.

Diabetes mellitus (DM), a metabolic disease, is increasing substantially worldwide (3). Recently, several cohort studies have shown that DM is a risk factor for several cancers, including breast, endometrial, pancreatic and colorectal...
cancers (4—7). This is the case with RCC—a large multicenter study reported that a history of DM increased the relative risk of RCC by 40% (8). Also, considering that several RCC genes, such as VHL, MET, FLCN and FH, relate to metabolic pathways that are influenced by metabolic stress or nutrient stimulation, DM could be biologically associated with RCC (9). However, a paucity of data exists regarding the prognostic significance of DM in RCC patients (10—12).

The association between obesity and malignant diseases, including RCC, has been extensively investigated. In RCC, obese patients have a higher risk of developing RCC; but several studies reported that their prognosis was better (13). Also, obesity is strongly linked to type 2 DM through insulin resistance and metabolic syndrome (14). Recently, the interaction between obesity and DM has been studied in several cancers (6,7,15—18). These findings suggest the possible role of DM with obesity in cancer development. Thus, the effect of obesity could be considered in the analysis of the prognostic role of DM.

In the current study, we determined whether DM was an independent predictor of recurrence after curative surgery in patients with non-metastatic RCC. We also investigated the effect modification of obesity on the association between DM and recurrence.

PATIENTS AND METHODS

After obtaining institutional review board approval, we retrospectively reviewed data on 563 Japanese patients with non-metastatic RCC (pT1—4N0M0) who underwent radical or partial nephrectomy between January 2001 and May 2011 at our institution. Twenty patients were excluded due to missing data, leaving 543 patients for analysis. All tumors were clinically staged by radiological examination, including computed tomography, and in selected cases, bone scintigraphy. A systematic lymph node dissection was not routinely performed. The lymph nodes were dissected for pathological examination only when lymphadenopathy was detected radiologically or during surgery. Patients with pathological lymph node involvement were excluded from analysis. All specimens were pathologically examined for histological subtype, grade and pathological stage. Pathological stage was determined according to the 2009 TNM classification (19). Grade was determined according to the Union Internationale Contre le Cancer and the American Joint Committee on Cancer in 1997 (20).

History of DM was determined by reported physician diagnosis and the results of preoperative laboratory tests. All patients with DM in our cohort had type 2 DM. In the current study, the following clinicopathological variables were evaluated: history of DM, age, gender, laterality, body mass index (BMI), history of hypertension, history of cardiovascular disease, Charlson—Romano index, type of surgery, tumor diameter, histological subtype, grade, and pathological T stage. The BMI was calculated as weight divided by height squared (kg/m²).

After surgery, follow-up examinations, including physical examination, laboratory tests, ultrasonography, X-ray, computed tomography, and, in selected cases, bone scintigraphy, were performed every 3—6 months during the first 2 years and every 6—12 months thereafter. The primary endpoint of the current study was recurrence-free survival (RFS). RFS was calculated from the date of surgery to the date at which recurrence was confirmed, the date of death of any cause, or the date of the last follow-up examination. The secondary endpoint was cancer-specific survival (CSS) and overall survival (OS). CSS/OS was calculated from the date of surgery to the date of death due to RCC/any other cause, or the date of the last follow-up examination.

Patients were classified into two groups according to their DM history: DM and non-DM. Bivariate comparisons of patient characteristics and cancer features between DM and non-DM patients were carried out using the chi-square test for categorical variables and Student’s t-test for continuous variables. Univariate and multivariate Cox regression model analysis was performed to identify prognostic factors. All variables were included in the full model, irrespective of statistical significance in the univariate analysis. From a full model, a reduced model was obtained using a backward selection procedure. Survival was evaluated using the Kaplan—Meier method and the log-rank test. The effect modification by obesity was explored by stratifying subjects into non-obese and obese categories (BMI <25 and ≥25 kg/m², respectively) according to obesity criteria specific to Asia-Pacific populations (21) and testing for interaction by including DM, BMI and the cross product of these in our models. All statistical analyses were performed using the Kaplan—Meier method and the log-rank test. The effect modification by obesity was explored by stratifying subjects into non-obese and obese categories (BMI <25 and ≥25 kg/m², respectively) according to obesity criteria specific to Asia-Pacific populations (21) and testing for interaction by including DM, BMI and the cross product of these in our models. All statistical analyses were performed using the Kaplan—Meier method and the log-rank test. The effect modification by obesity was explored by stratifying subjects into non-obese and obese categories (BMI <25 and ≥25 kg/m², respectively) according to obesity criteria specific to Asia-Pacific populations (21) and testing for interaction by including DM, BMI and the cross product of these in our models. All statistical analyses were performed using the Kaplan—Meier method and the log-rank test.
During the mean follow-up of 66.7 months (median: 52.8 months), 28 (5.2%) or 45 (8.3%) patients died of RCC or any other cause, respectively. Sixty-eight patients (12.5%) developed recurrence (19 patients in the obese group and 49 patients in the non-obese group). DM was an independent predictor of recurrence in the reduced multivariate model \[ \text{HR (hazard ratio) 2.43, } P = 0.003; \text{ Table 2}\], along with tumor diameter, grade and pathological T stage. BMI was not associated with recurrence \[ P = 0.991\]. The 5-year RFS rates of DM patients were significantly lower than those of non-DM patients (77.9 vs 89.3%; log-rank \( P = 0.003\); Fig. 1A).

Next, we investigated the effect modification of obesity on the association between DM and recurrence after surgery. After stratification by obese status, we found a strong association between DM and recurrence in the obese group \( \text{HR 4.07, } P = 0.010; \text{ Table 3}\), but not in the non-obese group \( \text{HR 1.95, } P = 0.125\); Table 3) in the full multivariate model. Similar results were obtained in the reduced multivariate model (data not shown). The formal test for interaction between DM and BMI indicated that obesity modified the effect of DM on recurrence with a trend but did not reach significance \( P\text{-interaction} = 0.086\). In the obese group, the 5-year RFS

### Table 1. Clinical and pathological characteristics of total subjects, stratified by history of DM

| Variables                                      | All patients No. (%) | History of DM | P     |
|------------------------------------------------|----------------------|---------------|-------|
|                                                | DM                  | Non-DM       |       |
| Total number of patients                       | 543                 | 82 (15.1)     | 461 (84.9)         |       |
| Mean age (SD), years                           | 61.0 (11.9)         | 64.3 (10.2)   | 60.4 (12.1)         | 0.006 |
| Gender                                         |                      |               |       |
| Male                                           | 389 (71.6)          | 64 (78.0)     | 325 (70.5)          |       |
| Female                                         | 154 (28.4)          | 18 (22.0)     | 136 (29.5)          |       |
| Laterality                                     |                      |               |       |
| Right                                          | 289 (53.2)          | 45 (54.9)     | 244 (52.9)          |       |
| Left                                           | 254 (46.8)          | 37 (45.1)     | 217 (47.1)          |       |
| Mean BMI (SD), kg/m²                            | 23.6 (3.5)          | 24.3 (3.4)    | 23.4 (3.5)          | 0.045 |
| History of hypertension (%)                    | 197 (36.3)          | 42 (51.2)     | 155 (33.6)          | 0.003 |
| History of cardiovascular disease (%)          | 77 (14.2)           | 21 (25.6)     | 56 (12.1)           | 0.003 |
| Charlson–Romano index                           | <0.001              |               |       |
| 0–1                                            | 375 (69.1)          | 41 (50.0)     | 334 (72.5)          |       |
| ≥2                                             | 168 (30.9)          | 41 (50.0)     | 127 (27.5)          |       |
| Type of surgery (%)                             |                      |               |       |
| RN                                             | 418 (77.0)          | 66 (80.5)     | 352 (76.4)          |       |
| PN                                             | 125 (23.0)          | 16 (19.5)     | 109 (23.6)          |       |
| Mean tumor diameter (SD), cm                   | 4.1 (2.4)           | 4.5 (2.7)     | 4.0 (2.4)           | 0.094 |
| Histological subtype (%)                       |                      |               |       |
| Clear                                          | 482 (88.8)          | 78 (95.1)     | 404 (87.6)          |       |
| Non-clear                                      | 61 (11.2)           | 4 (4.9)       | 57 (12.4)           |       |
| Grade (%)                                      |                      |               |       |
| G1                                             | 60 (11.1)           | 4 (4.9)       | 56 (12.1)           |       |
| G2                                             | 383 (70.5)          | 62 (75.6)     | 321 (69.6)          |       |
| G3                                             | 100 (18.4)          | 16 (19.5)     | 84 (18.2)           |       |
| Pathological T stage (%)                       |                      |               |       |
| T1a                                            | 315 (58.0)          | 41 (50.0)     | 274 (59.4)          |       |
| T1b                                            | 113 (20.8)          | 18 (22.0)     | 95 (20.6)           |       |
| T2                                             | 56 (4.6)            | 4 (4.9)       | 51 (4.6)            |       |
| T3–4                                           | 90 (16.6)           | 19 (23.2)     | 71 (15.4)           |       |

DM, diabetes mellitus; SD, standard deviation; BMI, body mass index; RN, radical nephrectomy; PN, partial nephrectomy.
rates of DM patients were significantly lower than those of non-DM patients (75.3 vs 91.9%; log-rank $P < 0.001$; Fig. 1B).

The prognostic significance of DM might be caused by the difference in histology subtype since both DM and clear cell type histology were more common in older patients (Table 1). Therefore, we further analyzed the association of DM with recurrence in the subgroup of patients with clear cell type histology. In this subgroup, DM was an independent predictor of recurrence in the reduced multivariate model (HR 2.15, $P = 0.015$), as it was in the total cohort. The 5-year RFS rates of DM patients were significantly lower than those of non-DM patients (79.6 vs 88.5%; log-rank $P = 0.657$).

Moreover, after stratification by obese status, a strong association between DM and recurrence was found in the obese group (HR 3.89, $P = 0.016$), but not in the non-obese group (HR 1.77, $P = 0.217$; Table 3) in the full multivariate model. The formal test for interaction showed that obesity modified the effect of DM on recurrence with a trend using a test of interaction. These findings were replicated in the subgroup of patients with clear cell type histology.

Finally, we analyzed the association of DM with CSS and OS as the secondary endpoint. No statistical difference was found in CSS (95.4 vs. 96.4%; log-rank $P = 0.949$) and OS (93.8 vs. 94.1%; log-rank $P = 0.325$) between DM and non-DM patients. Similarly, in the subgroup of patients with clear cell type histology, CSS and OS were not statistically different between DM and non-DM patients (data not shown).

### DISCUSSION

In the current study, we demonstrated that DM is an independent predictor of recurrence following curative surgery in patients with non-metastatic RCC after adjustment of other clinicopathological factors. Moreover, in the subgroup analysis based on obesity, this significance was more evident in the obese group than in the non-obese group. We also showed that obesity modifies the effect of DM on recurrence with a trend using a test of interaction. These findings were replicated in the subgroup of patients with clear cell type histology. These results indicated that a combination of DM and obesity may play an important role in the progression of RCC following curative surgery.

Few studies assessed the association between DM and the prognosis of RCC with inconsistent results. Although published only as a congress abstract, one study from Italy reported that DM was associated with poor prognosis (10). In another Italian study on a surgical series, however, DM was reported to have no influence on the prognosis in RCC patients.
A recent study from Korea showed that DM was a predictor of OS, but not CSS, in patients with localized RCC (11). For the first time, we evaluated the association of DM with recurrence after curative surgery for non-metastatic RCC. We revealed that DM is an independent predictor of recurrence. The current study, however, showed no association between DM and CSS and OS. In our cohort, a small number of patients died of RCC (5.2%) or any other cause (8.3%), possibly as a result of the relatively short follow-up and racial characteristics. Thus, our findings are preliminary and not yet conclusive. Further follow-up should be performed to clarify the association of DM with CSS and OS in RCC patients.
Interestingly, we found a strong association between DM and recurrence in the obese group but not in the non-obese group, indicating that DM with obesity could potentiate the progression of RCC following surgery. Similar findings have been published for other malignant diseases. Patients with DM and obesity were reported to have a high risk of breast cancer and endometrial cancer in several cohort studies (6,7). Moreover, we have previously reported that DM is significantly associated with high-grade prostate cancer detection via extended biopsy in obese patients, but not in non-obese patients (15). In addition, DM was associated with an increased risk of biochemical recurrence after radical prostatectomy in obese patients, but not in non-obese patients (16).

In the current study, patients were stratified by BMI using a cutoff for Asian populations that is recommended by the World Health Organization (WHO) but is lower than the cutoff used in the aforementioned studies on people of other ethnicities (21). Although Asians have a lower BMI than other ethnicities (21), accumulating evidence has suggested that Asians have relatively high body fat deposits at a lower BMI (22). Thus, the above data could be supportive of our finding despite the ethnic variations of the definition of obesity. Taken together, DM with obesity may be involved in carcinogenesis and cancer development.

Considering the sequence of the development of obesity and insulin resistance, our finding could be biologically explained by the timing and order of the development of DM and cancer. Patients in the early phase of type 2 DM are usually obese and have hyperglycemia and hyperinsulinemia, which increases the bioavailability of insulin-like growth factor (IGF)-1 and creates an environment that favors cancer growth (14,23). Subsequently, as pancreatic β-cells become depleted over decades of living with DM, the patients tend to become thinner and develop hypoinsulinemia, which decreases the bioavailability of IGF-1 and eventually creates a harsh environment for cancer growth (14,23). Indeed, insulin secretory capacity was found to be higher in obese DM patients than in non-obese DM patients (24). In the current study, when using a cutoff age of 65 years, a strong association between DM and recurrence was observed in the younger group (HR 3.56, \( P = 0.004 \)), but not in the older group (HR 1.44, \( P = 0.458 \)) in multivariate analysis (data not shown). Moreover, age significantly modified the effect of DM on recurrence (\( P \)-interaction = 0.045; data not shown). Therefore, considering that younger age reflects the short duration of DM to some extent, patients with the early phase of DM tend to be obese and may therefore have a high risk of RCC progression.

The role of insulin–IGF axis in cancer growth has been investigated in RCC. RCC cell lines express IGF-1 receptor and exhibit in vitro cell proliferation mediated through IGF-1 receptor (25). In an in vivo xenograft tumor model, the systemic administration of IGF-1 stimulates the growth of RCC (26). Moreover, IGF-1 receptor expression is positively associated with poor prognosis in clear cell RCC patients (27). All of the above data indicate the importance of insulin–IGF axis in the development of RCC, which is supportive of our findings.

The current study has several limitations. First, it may be limited by its retrospective nature. Second, we could not analyze the levels of testosterone, insulin or IGFs, which may be considered relevant, nor lifestyle variables relating to glucose metabolism, such as physical activity and diet. DM is a complicated disease that is characterized not only by hyperglycemia but also by other metabolic impairments. Thus, the prognostic significance of DM may be affected by various metabolic factors. Also, the association between the duration and severity of DM and the prognosis of RCC was not assessed in the current study. Finally, the prevalence of DM in our cohort (15.1%) was much higher than the prevalence in the previous Italian and Korean studies (8.6 and 11.4%) (11,12). In Japan, ~13.5% of the population have type 2 DM or impaired glucose tolerance, which reflects a relatively high prevalence of DM in Japanese population (28). Thus, racial, genetic and environmental differences in the pathophysiology of DM may affect the prognostic role of DM in RCC patients.

In conclusion, DM was a predictor of recurrence following surgery for non-metastatic RCC, especially in obese patients. This finding indicates the prognostic significance of DM with obesity for RCC patients. The current study is preliminary and our findings need to be confirmed in prospective cohorts of various ethnicities. More detailed investigations into DM case history, including the age at onset, duration, severity, therapy and other factors, will clarify the role of DM in RCC progression and prognosis.

Conflict of interest statement
None declared.

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