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Relationships of obesity and diabetes mellitus to other primary cancers in surgically treated gastric cancer patients

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ABSTRACT

Background: Other primary cancers (OPC) have been reported in gastric cancer (GC) patients. Recent studies have shown relationships of obesity and diabetes mellitus to cancer development in several organs. The purpose of this study was to investigate the relationships of obesity and diabetes mellitus (DM) to the prevalence of OPC in GC patients.

Methods: We reviewed 435 GC patients who were treated surgically and followed their outcomes after surgery. Patients with body mass index (BMI) $\geq$ 25 kg/m^2 were defined as obese. Fasting plasma glucose (FPG) and HbA1c levels were examined before surgery.

Results: OPC was observed in 109 GC patients (25.1%): 40 (9.2%) with synchronous OPC and 76 (18.2%) with metachronous OPC. The most common OPC was colorectal cancer (22.8%). OPC was frequently observed in patients with DM ($p = 0.0022$), and DM was an independent risk factor for the occurrence of OPC (odds ratio, 2.215; 95% confidence interval, 1.2007–4.0850; $p = 0.011$). Synchronous OPC was frequently observed in patients with obesity ($p = 0.025$), and obesity was an independent risk factor for the occurrence of synchronous OPC (odds ratio, 2.354; 95% confidence interval, 1.1246–4.9279; $p = 0.023$). Metachronous OPC was frequently observed in patients with DM ($p = 0.0071$), and DM was an independent risk factor for the occurrence of OPC (odds ratio, 2.680; 95% confidence interval, 1.0291–6.9780; $p = 0.044$).

Conclusion: There is a need to be aware of the possibility of OPC in GC patients with DM/obesity. They should undergo intensive screening for OPC before and after gastrectomy.

1. Introduction

Cancer screening using endoscopy and radical gastric resection with regional node dissection have improved the clinical outcomes of patients with gastric cancer (GC) [1,2]. However, several issues remain for further improvement of the prognosis of GC patients. One of these major issues is synchronously and/or metachronously associated or secondary cancers in several organs. In 1932, Warren and Gates [3] described the concept of multiple primary malignant tumors, and such associations have been well investigated in all organs. Other primary cancers (OPC) in GC patients have previously been reported in many series [4–8], and these studies reported an OPC incidence of 2.0–4.2 percent in GC patients [4,6–8]. However, it is well known that cancer incidence has gradually increased in many organs. "Synchronous cancers are detected more often than metachronous cancers. In pre-metachronous or post-metachronous cancer, the most common type was colorectal cancer, and in synchronous cancer, the most common type was liver cancer" [8].

Obesity is an emerging risk factor for several cancers worldwide, and the relationships between obesity and cancers have been well investigated in many organs [9–11]. Increased body weight is associated with increased death rates for all cancers combined and for cancers at multiple specific sites [9]. Regarding cancers of the gastrointestinal tract, the relationship in colon cancer patients has been well investigated [12–14]. In addition, excess body weight has been associated with an increased risk of cardia gastric cancer, but this association is not found in non-cardia gastric cancer [15–17]. Furthermore, patients with obesity sometimes have diabetes mellitus (DM). DM is also a risk factor for several cancers, and the relationship between DM and colorectal cancers has been well investigated [18,19]. DM patients also have a higher risk of GC [20,21] and DM is associated with GC mortality [21]. However,

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there has been very little information regarding the relationship between multiple cancers/OPC and obesity/DM, and this relationship has yet to be investigated in GC patients.

The purpose of this study was to undertake a retrospective investigation of the relationships of obesity evaluated by body mass index (BMI) and DM to the prevalence of OPC in patients with surgically treated GC.

2. Patients and methods

2.1. Patients

A total of 435 consecutive patients with GC, who were treated between 2002 and 2010 in Shinshu University Hospital, were enrolled in the present study. According to the National Institutes of Health criteria, a BMI of 25.0–29.9 kg/m^2 is classified as overweight, and a BMI of 30.0 or greater is classified as obesity [22]. Usually, overweight patients with a BMI higher than 25.0 kg/m^2 are assessed as obese in Japan, as determined by the Japan Society for the Study of Obesity; 75 patients (17.2%) with a BMI higher than 25 kg/m^2 had obesity, and 360 patients (82.8%) with a BMI less than 25 kg/m^2 had normal body weight. The BMI was calculated from body weight and height at the time of diagnosis of gastric cancer. All patients were checked regarding DM; 47 patients had been treated previously for DM, and DM was newly diagnosed before surgery in 5 patients. In these 52 patients, DM was routinely controlled by physicians until elective surgery for GC, and there were no patients with type I DM. In GC patients, fasting plasma glucose (FPG) and hemoglobin A1c (HbA1c) levels were examined at the time before medical control of DM. Background data of GC patients with and without obesity are shown in Table 1, and those with and without DM are shown in Table 2. The operative method including distal gastrectomy, proximal gastrectomy, and total gastrectomy was determined according to the site of gastric cancer. In Stage II or III patients, S-1 was administered as adjuvant chemotherapy, but patients with severe comorbidity or aged 80 and more were excluded. In this series, there was no postoperative and hospital mortality in GC patients treated surgically.

Primary cancer arising from other organs was defined according to the criteria of Warren and Gates [3]. When two primary cancers were detected within one year, they were considered synchronous. When two primary cancers were not detected within one year, they were considered metachronous. Metachronous OPC included antecedent cancers before surgery for GC and subsequent cancers after surgery for GC. All OPC were evaluated histopathologically by taking a biopsy or resection. If the histopathological findings were similar, we used the immunostaining method. The patients with OPC consulted an expert in each field and were treated as appropriate.

The histopathologic findings of GC were obtained using resected specimens. The clinicopathologic features of GC were described according to the TNM classification (7th edition).

2.2. Other primary cancer screening before surgery

Before surgery for GC, we performed total colonoscopy when GC patients could have a meal, and we performed computed tomography (CT) of the whole body. Since 2005, ^{18}F-fluorodeoxyglucose positron-emission tomography (FDG-PET) of the whole body has been performed to stage gastric cancer and detect synchronous OPC.

2.3. Clinical outcome after surgery

After surgery, the gastric cancer patients were followed in the outpatient clinic of Shinshu University Hospital in order to check for the recurrence and metastasis of gastric cancer by esophagogastroduodenoscopy and CT of the whole body. Six months after operation, the patients were routinely checked by CT. One year after operation, CT and esophagogastroduodenoscopy were performed, and then CT and esophagogastroduodenoscopy were continued annually. Colonoscopy was performed 1 year after operation, and then every year in patients with colon neoplasm detected before and after surgery, and every 1–2 years in patients without colon neoplasm. From 2005, FDG-PET was performed to detect advanced gastric cancer preoperatively and once a year after operation to check for metastasis and to detect new tumors. Ninety-two (21.1%) patients underwent FDG-PET. If abnormalities were detected, the interval was reduced. All patients except for the terminally ill and those refusing the examinations underwent our surveillance program. These programs were continued until 5 years after operation. The median follow-up period was 39 months.

Table 1
Background data of gastric cancer patients with and without obese.

Variable	With obese ($n = 75$)	Without obese ($n = 360$)	p-value
Gender			0.71
men	50	248	
women	25	112	
Age (years old: mean ± SD)	66.7 ± 10.9	67.7 ± 10.5	0.5
Drinking			0.16
with	36	141	
without	39	219	
Smoking			0.76
with	27	123	
without	48	237	
Tumor location			
upper-third	23	105	
middle-third	33	128	
lower-third	19	127	
Tumor size (mm: mean ± SD)	43.2 ± 30.4	48.5 ± 32.8	0.19
Histologic type			0.25
tub/pap	46	197	
por/sig/muc	29	153	
special type[a]	0	10	
Depth of invasion			0.1
pT1	45	178	
pT2 or more	30	182	
Node metastasis			0.17
pN0	48	199	
pN1 or more	27	161	
Distant metastasis			0.36
M0	75	356	
M1	0	4	
Stage			0.58
I	46	191	
II	11	60	
III	14	79	
IV	4	30	
Postoperative complication			0.76
with	31	142	
without	44	218	
Diabetes mellitus			0.018
with	15	37	
without	60	323	
BMI (kg/m^2: mean ± SD)	27.5 ± 3.0	21.3 ± 2.3	<0.0001
FPG (mg/dl: mean ± SD)	112.8 ± 36.5	106.9 ± 25.5	0.09
HbA1c (%: mean ± SD)	6.20 ± 0.95	5.98 ± 0.76	0.036

With obese, BMI ≧ 25 kg/m^2; Without obese, BMI<25 kg/m^2; SD, standard deviation; BMI, body mass index; FPG, fasting plasma glucose; tub/pap, well and moderately differentiated adenocarcinoma (tubular and papillary adenocarcinoma); por/sig/muc, poorly differentiated adenocarcinoma, signet ring cell carcinoma and mucinous adenocarcinoma.

[a] Including neuroendocrine carcinoma and hepatoid carcinoma.

2.4. Statistical analysis

Data are shown as prevalence or mean and ordinal data were compared by the Mann–Whitney test, and the Chi-square test or

Table 2
Background data of gastric cancer patients with and without diabetes mellitus.

Variable	With diabetes mellitus ($n = 52$)	Without diabetes mellitus ($n = 383$)	p-value
Gender			0.043
men	42	256	
women	10	127	
Age (years old: mean ± SD)	71.6 ± 7.9	67.0 ± 10.8	0.0003
Drinking			0.04
with	28	149	
without	24	234	
Smoking			0.028
with	25	125	
without	27	258	
Tumor location			0.85
upper-third	17	111	
middle-third	18	143	
lower-third	17	129	
Tumor size (mm: mean ± SD)	42.1 ± 30.0	48.3 ± 32.7	0.19
Histologic type			0.28
tub/pap	24	219	
por/sig/muc	26	182	
special type[a]	2	10	
Depth of invasion			0.32
T1	30	193	
T2 or more	22	190	
Node metastasis			0.88
N0	29	218	
N1or more	23	165	
Distant metastasis			0.97
M0	51	380	
M1	1	3	
Stage			0.95
I	29	208	
II	9	62	
III	11	82	
IV	3	31	
Postoperative complication			0.69
with	22	151	
without	30	232	
Obese			0.0489
with	14	61	
without	38	322	
BMI (kg/m^2: mean ± SD)	23.3 ± 3.2	22.3 ± 3.4	0.035
FPG (mg/dl: mean ± SD)	144.9 ± 52.0	102.8 ± 17.3	<0.0001
HbA1c (%: mean ± SD)	7.26 ± 1.09	5.82 ± 0.53	<0.0001

With obese, BMI ≥ 25 kg/m^2; L-group, BMI < 25 kg/m^2; SD, standard deviation; BMI, body mass index; FPG, fasting plasma glucose; tub/pap, well and moderately differentiated adenocarcinoma (tubular and papillary adenocarcinoma); por/sig/muc, poorly differentiated adenocarcinoma, signet ring cell carcinoma and mucinous adenocarcinoma.
[a] Including neuroendocrine carcinoma and hepatoid carcinoma.

Fisher's exact probability test. Multivariate analysis of independent risk factors was carried out by multiple logistic regression tests. Survival rates after gastrectomy were calculated by the Kaplan–Meier method. $P < 0.05$ was considered significant.

3. Results

3.1. Occurrence of OPC

Of 435 patients with GC, 109 patients (25.1%) had one or more OPC, giving a total of 127 OPC (Table 3). Forty GC patients (9.2%) had synchronous OPC, and 76 GC patients (17.5%) had metachronous OPC: 60 patients with antecedent OPC, 15 with subsequent OPC, and one with both types of metachronous OPC. The median interval between GC surgery and diagnosis of subsequent cancer was 24.5 months. OPC in the gastrointestinal tract was frequently observed, namely, in 34.9% of the patients with OPC. Additionally, adenomas in the colorectum were identified in 133 (30.6%) of the GC patients. Synchronous OPC was most frequently observed in the colorectum, while metachronous OPC was most frequently observed in the urogenital organs.

3.2. Comparison of patients with and without OPC

Regarding the clinicopathologic features of GC patients with and without OPC (Table 4), OPC was frequently observed in elderly patients ($p = 0.001$), patients with distant metastasis ($p = 0.02$), and patients with DM ($p = 0.0022$). We next analyzed age, distant metastasis, and DM, which had a significant impact on the occurrence of OPC, using multiple logistic regression tests. DM was an independent risk factor for the occurrence of OPC in GC patients (Table 5).

3.3. Comparison of patients with and without synchronous OPC

Regarding the clinicopathologic features of GC patients with and without synchronous OPC (Table 4), synchronous OPC was frequently observed in men ($p = 0.0067$) and obese patients ($p = 0.025$). We next analyzed sex and obesity, which had a significant impact on the occurrence of synchronous OPC, using multiple logistic regression tests. Obesity was an independent risk factor for the occurrence of synchronous OPC in GC patients (Table 5).

3.4. Comparison of patients with and without metachronous OPC

Regarding the clinicopathologic features of GC patients with and without metachronous OPC (Table 4), metachronous OPC was frequently observed in elderly patients ($p = 0.038$), patients with habitual drinking ($p = 0.04$), and patients with DM ($p = 0.0071$). HbA1c level was significantly higher in patients with metachronous OPC than in those without it ($p = 0.0496$). We next analyzed age, drinking, DM, and HbA1c, which had a significant impact on the

Table 3
Gastric cancer patients with other primary cancer.

Organs	Synchronous	Metachronous			Total (%)
		Antecedent	Subsequent	Total	
Head and neck					13 (11.9)
Laryngopharynx	3	2	1	3	6
Thyroid	2	1	3	4	7
Chest					23 (21.1)
Lung	3	6	4	10	13
Thymus			1	1	1
Breast		9		9	9
Gastrointestinal tract					38 (34.9)
Esophagus	3	4		4	7
Duodenum	1	1		1	2
Colorectum	19	7	3	10	29
Hepatobiliary system					7 (6.4)
Liver	1	5		5	6
Pancreas			1	1	1
Urogenital system					25 (22.9)
Kidney	1	1	1	2	3
Bladder	2	7	2	9	11
Prostate	2	6	1	7	9
Testis		2		2	2
Gynecologic organs					9 (8.3)
Uterus		8		7	7
Ovary		2		2	2
Retroperitoneum		2		2	2 (1.8)
Skin	1		1	1	2 (1.8)
Hematopoietic system	3	5		5	8 (7.3)
Number of patients (%)	40 (9.2)	60 (13.8)	16 (3.7)	76	109 (25.1)
Number of cancers	41	68	18	86	127

Table 4
Clinicopathologic features of gastric cancer patients with and without OPC.

	OPC			Synchronous OPC			Metachronous OPC		
	With ($n = 109$)	Without ($n = 326$)	p-value	With ($n = 40$)	Without ($n = 395$)	p-value	With ($n = 76$)	Without ($n = 359$)	p-value
Gender									
men	76	222		35	263		46	252	
women	33	104		5	132		30	107	
Age (years old: mean ± SD)	70.0 ± 8.1	66.7 ± 11.1	0.001	69.9 ± 8.4	67.3 ± 10.7	0.07	69.8 ± 8.2	67.0 ± 10.9	0.038
Drinking			0.45			0.11			0.04
with	41	136		21	156		23	154	
without	68	190		19	239		53	205	
Smoking			0.29			0.26			0.06
with	33	117		17	133		19	131	
without	76	209		23	262		57	228	
Tumor location			0.66			0.47			0.79
upper-third	35	93		15	113		23	105	
middle-third	41	120		14	147		30	131	
lower-third	33	113		11	135		23	123	
Tumor size (mm: mean ± SD)	45.0 ± 31.3	48.4 ± 32.8	0.35	44.4 ± 31.7	47.9 ± 32.5	0.54	44.9 ± 30.2	48.1 ± 32.9	0.44
Histologic type			0.22			0.17			0.96
tub/pap	66	177		26	217		43	200	
por/sig/muc	39	143		12	170		31	151	
special type[a]	4	6		2	8		2	8	
Depth of invasion			0.49			0.62			0.6
pT1	59	164		22	201		41	182	
pT2 or more	50	162		18	194		35	177	
Node metastasis			0.36			0.44			0.83
pN0	66	181		25	222		44	203	
pN1 or more	43	145		15	173		32	156	
Distant metastasis			0.02			0.27			0.29
M0	106	325		39	392		74	357	
M1	3	1		1	3		2	2	
Stage			0.13			0.16			0.7
I	67	170		26	211		44	193	
II	17	54		5	66		14	57	
III	15	78		4	89		13	80	
IV	10	24		5	29		5	29	
Postoperative complication			0.051			0.016			0.47
with	52	121		23	150		33	140	
without	57	205		17	245		43	219	
Obese			0.35			0.025			0.76
with	22	53		12	63		14	61	
without	87	273		28	332		62	298	
BMI (kg/m^2: mean ± SD)	22.5 ± 3.0	22.3 ± 3.5	0.7	23.3 ± 3.1	22.3 ± 3.4	0.077	22.4 ± 3.0	22.4 ± 3.5	0.88
Diabetes mellitus			0.0022			0.1			0.0071
with	22	30		8	44		16	36	
without	87	296		32	351		60	323	
FPG (mg/dl: mean ± SD)	112.5 ± 36.3	106.4 ± 24.1	0.1	108.9 ± 34.8	107.8 ± 27.0	0.86	114.1 ± 35.7	106.6 ± 25.7	0.09
HbA1c (%: mean ± SD)	6.15 ± 0.84	5.98 ± 0.79	0.08	6.00 ± 0.82	6.02 ± 0.81	0.94	6.20 ± 0.84	5.98 ± 0.79	0.0496

With obese, BMI ≧ 25 kg/m^2; Without obese, BMI<25 kg/m^2; SD, standard deviation; BMI, body mass index; FPG, fasting plasma glucose; tub/pap, well and moderately differentiated adenocarcinoma (tubular and papillary adenocarcinoma); por/sig/muc, poorly differentiated adenocarcinoma, signet ring cell carcinoma and mucinous adenocarcinoma.

[a] Including neuroendocrine carcinoma and hepatoid carcinoma.

Table 5
Multiple logistic regression analysis for OPC.

	Odds ratio	95% Confidence interval	p-value
OPC			
Age	1.0283	1.0052–1.0520	0.016
Distant metastasis	8.4381	0.8316–85.6194	0.0712
Diabetes mellitus	2.2147	1.2007–4.0850	0.0109
Synchronous OPC			
Sex	3.6153	1.3780–9.4847	0.009
Obese	2.3541	1.1246–4.9279	0.0231
Metachronous OPC			
Age	1.0174	0.9884–1.0471	0.2422
Drinking	0.4587	0.2437–0.8635	0.0157
Diabetes mellitus	2.6798	1.0291–6.9780	0.0435
HbA1c	1.0038	0.6577–1.5321	0.9859

occurrence of metachronous OPC, using multiple logistic regression tests. DM was an independent risk factor for the occurrence of metachronous OPC in GC patients (Table 5). Among 60 patients with antecedent metachronous cancers, 14 patients had diabetes. All of them had been diagnosed with diabetes prior to the detection of antecedent metachronous cancer. The median period between the onset of diabetes and the detection of antecedent cancers was 24 months. There were no patients in whom diabetes was diagnosed after the detection of antecedent cancers.

3.5. Clinical outcome after surgery

There were no differences in overall survival after gastrectomy between GC patients with and without OPC (Fig. 1A). The overall survival after gastrectomy in GC patients with synchronous OPC was significantly better than in those without it ($p = 0.04$; Fig. 1B),

while there was no difference in the overall survival after gastrectomy between GC patients with and without metachronous OPC (Fig. 1C). Furthermore, there was no difference in the overall survival after gastrectomy between GC patients with and without obesity (5-year survival rate, 74.0% vs. 72.6%; $p = 0.54$), or with and without DM (5-year survival rate, 67.1% vs. 73.7%; $p = 0.57$).

4. Discussion

Regarding OPC in GC patients, the incidence has previously been reported to be less than 5% [4,6]; however, a recent report showed an incidence of 20% [7]. We also detected an incidence of 25% in surgically treated GC patients. Therefore, intensive screening and follow-up are important for GC patients to detect OPC clinically. Colorectal cancer synchronously and metachronously associated with GC should be attended to in the management before and after gastric surgery because of its high frequency. Ikeda et al. [23] reported that colorectal cancer was detected most frequently after surgery in GC patients. We also demonstrated that colorectal cancers were observed in 6.7% of GC patients, and we suggest that colonoscopic examination may be useful for the detection of colorectal neoplasm in such patients. Our previous research [24] demonstrated a high incidence of colorectal adenoma in GC patients, so they should be surveyed for colon neoplasm more thoroughly than usual. Moreover, previous gastrectomy makes it difficult to perform surgery for colon cancer because of intra-abdominal adhesion. Therefore, we performed colonoscopy for GC patients even without colon neoplasm at least every 2 years to avoid surgery caused by tumor progression. As metachronous OPC, cancers in the urogenital tract, including bladder and prostate cancers, should be attended to, given these results. However, other researchers did not demonstrate a high incidence of metachronous OPC in the urogenital tract in surgically treated GC patients. In Japan, recently, the incidence of prostate cancer has gradually increased [25]. The fact that the present study was performed in the last decade may have caused the results to differ from previous reports in terms of the incidence of OPC associated with GC. Although GC patients with OPC may have several issues, including in terms of postoperative outcomes, the long-term outcome after gastrectomy in GC patients with OPC was similar to that without OPC. The intensive check-up and follow-up for OPC, such as in the present study, may have influenced their similar outcomes in surgically treated GC patients.

Excess body weight is considered to be one of the risk factors of cancer incidence in several organs [16]. In the present study, obesity evaluated by BMI was an independent risk factor of synchronous OPC in GC patients. Furthermore, synchronous colorectal cancer was frequently associated with GC. It is well known that overweight or metabolic syndrome is related to the development of colorectal cancer [12,13,26,27], and DM is a risk factor of colorectal cancer [18,19]. Hyperglycemia associated with insulin resistance also promotes the development of colorectal cancer [28,29]. In other organs, an association between obesity and cancer development has been well investigated, and it has been found that many studies on the association between DM and cancer development have been influenced by the high prevalence of obesity in DM patients. In the present study, synchronous OPC was frequently observed in GC patients with obesity. Because many GC patients

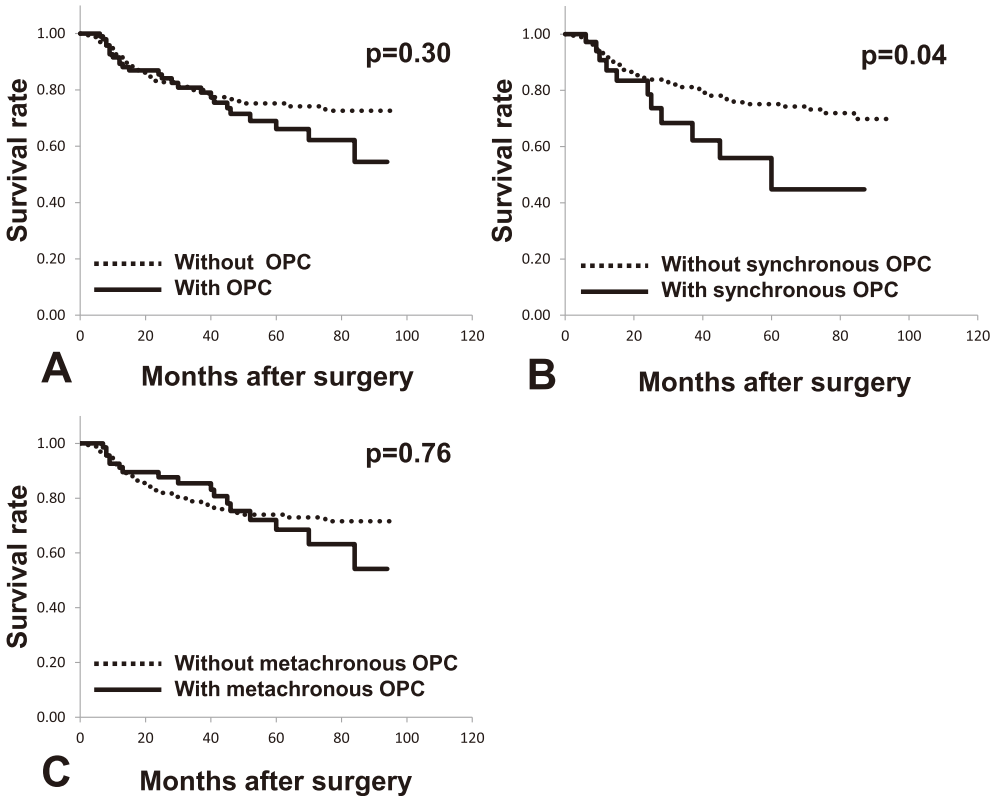

Fig. 1. Overall survival curves. **A.** Between gastric cancer (GC) patients with and without other primary cancer (OPC), there was no difference in overall survival ($p = 0.3$). The 5-year survival rates in GC patients with and without OPC were 66.1% and 75.2%, respectively. **B.** Between GC patients with and without synchronous OPC, there was a significant difference in overall survival. The 5-year survival rate in GC patients with synchronous OPC was poorer than in those without it (44.8% vs. 75.1%). **C.** Between GC patients with and without metachronous OPC, there was no difference in overall survival ($p = 0.76$). The 5-year survival rates in GC patients with and without metachronous OPC were 68.5% and 74.0%, respectively.

with obesity may exhibit these metabolic conditions, the possibility of synchronous OPC, especially colorectal cancer, may warrant intensive investigation before gastric surgery. However, metachronous (probably subsequent) OPC was not associated with obesity because many of the GC patients may improve in terms of excess body weight after gastrectomy.

Type 2-DM is not a single disease, but a group of metabolic disorders characterized by hyperglycemia. This metabolic disease group was an independent risk factor for the occurrence of OPC in GC patients, and GC patients with DM frequently showed obesity. FPG and HbA1c showed high levels in GC patients with DM before surgery, and these data were taken before sufficient control of DM for gastric surgery or treatment for newly detected DM. Although FPG and HbA1c levels were high in GC patients with OPC, the differences were not significant. This may have been due to the fact that this study population included GC patients with DM who had already been treated. Furthermore, there was no difference in HbA1c level in GC patients with and without synchronous OPC, while this level was higher in GC patients with metachronous OPC than in those without it. From these results, we suggest that metachronous OPC may frequently arise in GC patients with DM. It is considered that obesity and/or DM may be insufficiently controlled after treatment for antecedent OPC, and these conditions may also result from insufficient control of the metabolic situation after gastric surgery. However, we failed to demonstrate a high BMI in GC patients with OPC because DM had already been treated in some of the GC patients or BMI had decreased with the progression of DM status. Furthermore, many of the patients with type 2-DM are obese, and an association between DM and cancer incidence may be influenced by the high prevalence of obesity in DM patients. Not only DM but also obesity may be characterized by hyperglycemia, hyperinsulinemia, and a high incidence of OPC in GC patients.

As metachronous OPC in GC patients, we should attend to the urogenital tract as well as the lower digestive tract. Obesity has shown a weak association with prostate cancer incidence [30], and the influence of obesity on bladder cancer has been poorly understood [31]. In contrast to the relationship of obesity to these cancers, Kasper et al. [32] reported a reduced risk of prostate cancer in men with DM, while Larsson et al. [33] reported an increased risk of bladder cancer in DM patients. DM is a multifactorial and chronic group of metabolic disorders characterized by hyperglycemia. Although DM is considered an increased risk for several cancers, organ-specific mechanisms may be important for cancer initiation or development. Regarding the association between GC and OPC in the urogenital tract, further investigation is necessary from the viewpoint of obesity and a hyperglycemic state.

Regarding the relationship between obesity and long-term outcome after surgery in GC patients, several researchers have demonstrated that obesity/overweight may correlate with the long-term outcome; however, this remains controversial. Some researchers reported that obesity was associated with a good prognosis in GC patients [34,35], while others reported that it was associated with a worse prognosis [36,37]. Other groups demonstrated that it may not correlate with the prognosis of GC patients [38,39]. Because, in the present study, neither obesity nor DM was correlated with the overall survival after gastrectomy for GC, these associations remain unresolved. Furthermore, the presence of OPC and metachronous OPC was not correlated with long-term outcome after surgery; however, GC patients with synchronous OPC had a worse outcome after surgery than those without it. Although obesity has been described as increasing the incidence of several complications after gastrectomy for GC in some reports [35,38,40], other researchers reported that such a correlation was not observed [41,42]. In the present study, GC patients with synchronous OPC frequently had obesity and postoperative complications. These factors may influence the long-term outcome after gastrectomy in GC patients with synchronous OPC. However, regardless of the presence of obesity and/or OPC, curative surgery may be appropriate for GC and/or OPC detected by intensive check-up because of a lack of mortality associated with gastrectomy and no difference in this regard between GC patients with OPC and metachronous OPC in this series.

Some reports described that there were significant differences in clinicopathological features such as tumor location between gastric cancer patients with and without OPC [43]. However, our results showed no differences in tumor location, depth of invasion, lymph node metastasis, and histologic type between cases with and without OPC, but they did indicate that diabetes was an independent risk factor of OPC, in addition to alcohol drinking. Smoking was associated with metachronous OPC in univariate analysis, although it was not significant in multivariate analysis. Diabetes management and lifestyle modification should be considered in gastric cancer patients.

There are several limitations of this study. First, the number of patients was small and this study was retrospective. Second, the OPCs had a wide variety in terms of malignant potential or type of treatment. This may be important for patient outcome. Third, our study period was insufficient to investigate subsequent cancer.

In conclusion, there is a need to be aware of the possibility of OPC in GC patients with DM/obesity. They should undergo intensive screening for OPC before and after gastrectomy.

Ethical approval

This study was retrospective, so we regarded Ethical Approval was not necessary.

Author contribution

Daisuke Takeuchi contributed to study design, data collection and writing.

Naohiko Koide contributed to study design.

Daisuke Komatsu contributed to data collection.

Shinichi Miyagawa contributed to writing.

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We have nothing to state about this.

Conflicts of interest

The authors declare that they have no conflict of interest.

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