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The Risk of Developing Multiple Primary Cancers among Long-Term Survivors Five Years or More after Stomach Carcinoma Resection

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Recently, the number of long-term survivors of ≥ 5 years after stomach carcinoma resection is increasing in Japan. The clinical courses of 4,883 patients who underwent stomach carcinoma resection were retrospectively reviewed to investigate the cause of death including multiple primary cancers (MPC) and delayed stomach carcinoma recurrence among long-term survivors of ≥ 5 years. Of 3,061 patients who survived for ≥ 5 years, 1,203 patients (39.3%) were dead after 5 years survival, including 299 patients (24.9%) who died of MPC. Of 84 patients (7.0%) who died of recurrent stomach carcinoma, 25 patients were newly diagnosed ≥ 5 years postoperative. The most common site of MPC was lung in 124 patients, and 347 patients (44.7%) had a smoking-related MPC, including 124 lung, 63 esophagus, 62 head and neck, and 98 other cancers. We examined the prognostic differences in 527 patients with MPC according to the diagnosis time. In 325 patients of long-term survivors in whom MPC was diagnosed ≥ 5 years postoperative, 5-year survival rate and the median survival time after diagnosis were 35.1% and 17.7 months, respectively. This outcome was significantly poorer than that of 160 patients in whom MPC was diagnosed within 5 years postoperative (58.5% and 62.7 months, $P < 0.0001$). In conclusion, MPC accounted for approximately a quarter of the cause of death in long-term survivors. Lifestyle instructions including smoking cessation are important. Periodical cancer screening allows the early asymptomatic diagnosis and may contribute to a decrease in cancer mortality of MPC in long-term cancer survivors.

Keywords: long-term cancer survivors; multiple primary cancers; periodical cancer screening; smoking-related cancers; stomach carcinoma
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Introduction

Recently, the treatment outcomes of patients with stomach carcinoma have improved in Japan, because of the development of the group medical screening system and the progress in diagnostic techniques, adjuvant chemotherapy and surgical procedures. The number of patients who survive ≥ 5 years after stomach resection is also increasing. According to the Foundation for Promotion of Cancer Research (2018), the number of cancer deaths in 2016 was 372,986, and the death rate per 100,000 people was 298.3, accounting for 28.5% of the total number of death. Stomach carcinoma mortality rate, which accounted for approximately 50% and 40% of all cancer mortality rate in 1960's for males and females, respectively, continuously decreased to 13.6% and 10.2% in 2016. According to data obtained from cancer registries of 21 prefectures, the 5-year relative survival rate for stomach carcinoma diagnosed during 2006-2008 was 64.6%.

With the development of cancer registration system in recent years, the statistics and survival rate of cancer have been analyzed in many countries (Corkum et al. 2013; Donin et al. 2016). Furthermore, the synchronous or the metachronous multiple primary cancer (MPC) was analyzed similarly. According to the definition of Warren and Gates (1932), the criteria for MPC are as follows: each tumor must present a definitive picture of malignancy, each tumor must be distinct, and the probability of one tumor being a metastasis of another must be excluded. MPC is classified in three groups according to the onset time as follows; MPC of the patients' medical history, MPC of synchronous onset, and postoperative metachronous MPC.

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The risk of second MPC in the cancer survivors was also examined. In the conventional reports (Youlden and Baade 2011; Tabuchi et al. 2012; Corkum et al. 2013; Coyte et al. 2014; Donin et al. 2016), to investigate the risk of cancer survivors developing second MPC, they conducted a retrospective cohort study using data from cancer registry. These investigations included the cancer of all sites diagnosed as an initial cancer. Their results showed that cancer survivors were at higher risk of MPC as compared with the general population. One of the reason was because the cancer survivors might undergo more MPC screening than a non-cancer control (Corkum et al. 2013). Another reason was because the risk of developing tobacco- or alcohol-related MPC was mainly related to the lifestyle of the patients before the onset of the initial cancer (Tabuchi et al. 2012).

According to the treatment guidelines for stomach carcinoma (Japanese Gastric Cancer Association 2017), a postoperative 5-year periodic medical examination is recommended. On the other hand, after 5 years patients should be referred to regional general physicians or should be encouraged to undergo cancer screening provided as a part of health care programs in their districts. Although cancer survivors may have a higher risk of MPC than non-cancer controls, there is not the appropriate cancer screening program recommended ≥ 5 years after stomach resection, and it is poor in the evidence that cancer screening actually reduces cancer mortality of MPC.

The efficacy of the MPC screening should be evaluated not by the improvement of the morbidity or the early diagnosis rate of MPC, but by the improvement of the cancer mortality rate of MPC. In the conventional reports, they examined the onset risk of MPC mainly by the investigation of the morbidity, but did not mention much about the cancer mortality rate of MPC so far. In their reports, the mean of the observation period after the cancer diagnosis in the cancer survivor was short with 3.9-7.1 years and 'cancer survivors' might include many patients who died of an initial cancer during the relatively early period within 5 years after the initial cancer diagnosis. Cancer survivors included the patients with the short follow-up time of 3 months at the minimum (Tabuchi et al. 2012) and also included the synchronous MPC, or the patients with metachronous MPC diagnosed within a short period after the initial cancer diagnosis (Coyte et al. 2014). These reports lack in the information about the risk of MPC in long-term survivors ≥ 5 years after the initial cancer diagnosis.

The aim of this study is to investigate the cause of death including the cancer mortality of MPC and delayed stomach carcinoma recurrence in long-term survivors of ≥ 5 years following stomach carcinoma resection, so that we can evaluate the risk of the MPC and create a database to enlighten the necessity of MPC screening in long-term survivors of ≥ 5 years after stomach carcinoma resection. We considered whether we could decrease cancer mortality by preventing such a cause of death in long-term survivors. The clinical courses of 4,883 patients who were surgically treated for stomach carcinoma were retrospectively reviewed to investigate MPC occurrence and stomach carcinoma recurrence by the method of the retrospective cohort study using the data from cancer registry.

Patients and Methods

Study population

We included 4,883 patients who were surgically treated for stomach carcinoma between November 1975 and December 2010, and registered at the cancer registry of Saitama Cancer Center. The clinical course of the patients was retrospectively reviewed for ≥ 5 years until December 2016 to investigate the outcomes, including stomach carcinoma recurrence and MPC occurrence.

Statement of Ethics

The present study was reviewed and approved by the Ethics Committee of the Saitama Cancer Center, Japan. Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

The follow-up and analysis of the clinical course after stomach resection

Clinical data was obtained from the patients' medical records. Most patients were regularly screened for carcinoma recurrence including contrast-enhanced computed tomography (CT) or ultrasonography (US) every 3-6 months. Gastroscopy were performed every year. The postoperative periodical surveillance was usually conducted for 5 years after surgery. After 5 years, most patients without diagnosis of cancer recurrence or MPC were transferred to other hospitals. After transfer to other hospitals, the medical history of patients was investigated by reviewing the questionnaires to the bereaved, the death certificates from local government offices near the patients' residence, and the reports from those hospitals, regarding the survival confirmation, MPC, and the cause of death.

We investigated clinical course of long-term survivors of ≥ 5 years following stomach carcinoma resection with respect to the cause of death, the occurrence of MPC, and the delayed recurrence of stomach carcinoma. We also analyzed the survival rates of the patients in whom MPC was diagnosed with postoperative MPC ≥ 5 years after stomach surgery in comparison to the patients, in whom MPC was diagnosed within 5 years.

Statistical analysis.

Possible associations between the diagnostic time and the site in MPC were assessed using the chi-squared test or Fisher's exact test for categorical variables. Overall survival rate (OS) was calculated from the date of surgery to the date of death by any cause or the last follow-up visit. OS were evaluated using the Kaplan-Meier method and the

statistical testing was based on the Mann-Whitney U or the log-rank test for continuous variables. *P* values of < 0.05 were considered to indicate statistical significance. All statistical analyses were performed using the JMP software program (v.11 SAS Institute Inc., Cary, North Carolina, USA).

Results

Number of the long-term survivor ≥ 5 years after surgery and cause of death

During the study periods, 3,061 patients (62.7%) survived for ≥ 5 years and 1,822 (37.3%) died within 5 years (Fig. 1). Among the 3,061 survivors, 1,858 patients (60.7%) are still alive at the time of investigation: 1,582 patients (85.1%) without malignant disease, 13 patients (0.7%) with recurrent stomach carcinoma, and 263 (14.2%) with MPC. Of the 1,203 patients (39.3%) who died after 5 years of survival, 383 patients (31.8%) died of malignant neoplasm; namely, 84 patients (7.0%) who died of recurrent stomach carcinoma and 299 patients (24.9%) who died of MPC. Moreover, 677 patients (56.3%) died of other causes including heart or brain disease, accidents and senility, while the cause of death was unknown in 143 patients (11.9%). By contrast, among 1,822 patients who died within 5 years, 1,472 patients (80.8%) died of recurrent stomach carcinoma, 80 patients (4.4%) died of MPC, 243 patients (13.3%) died of other causes, and 27 patients (1.5%) died of unknown cause of death. Overall, the number of patients of unknown cause of death was 170 (3.5%) of 4,883 total number of patients and was 5.6% of 3,025 deceased patients during the observation periods.

In all 4,883 patients of this study, the 5- and the 10-year survival rate, the mean and median observation period were 62.6%, 53.0%, 10.0 years, and 8.0 years, respectively. The mean and median observation period in the 3,061 survivors of ≥ 5 years after surgery were 15.1 years, and 13.6 years, respectively. The longest observation period was 39.2 years. The postoperative 5-year survival rate according to the stage by the UICC of all 4,883 patients are as follows; Stage IA: 98.6%, IB: 96.5%, IIA: 90.1%, IIB: 84.3%, IIIA: 73.6%, IIIB: 59.1%, IIIC: 31.6%, and IV: 22.2%.

As for the adjuvant chemotherapy, oral administration of S-1 was carried out during the 12 months after surgery in the patients with stage II, IIIA and IIIB of Union for International Cancer Control (UICC), excluding T1 population from stage II/III, after the efficacy of S-1 was proven in 2006 (Sakuramoto et al. 2007). Before S-1 introduction, oral administration of UFT was enforced as adjuvant chemotherapy.

Of the 84 patients who died of recurrent stomach carcinoma ≥ 5 years after surgery, 59 patients had a diagnosis of carcinoma recurrence within 5 years, and 25 patients had a diagnosis of delayed recurrence ≥ 5 years after surgery. Of the 13 patients who were alive with recurrent stomach carcinoma ≥ 5 years, two patients were diagnosed with

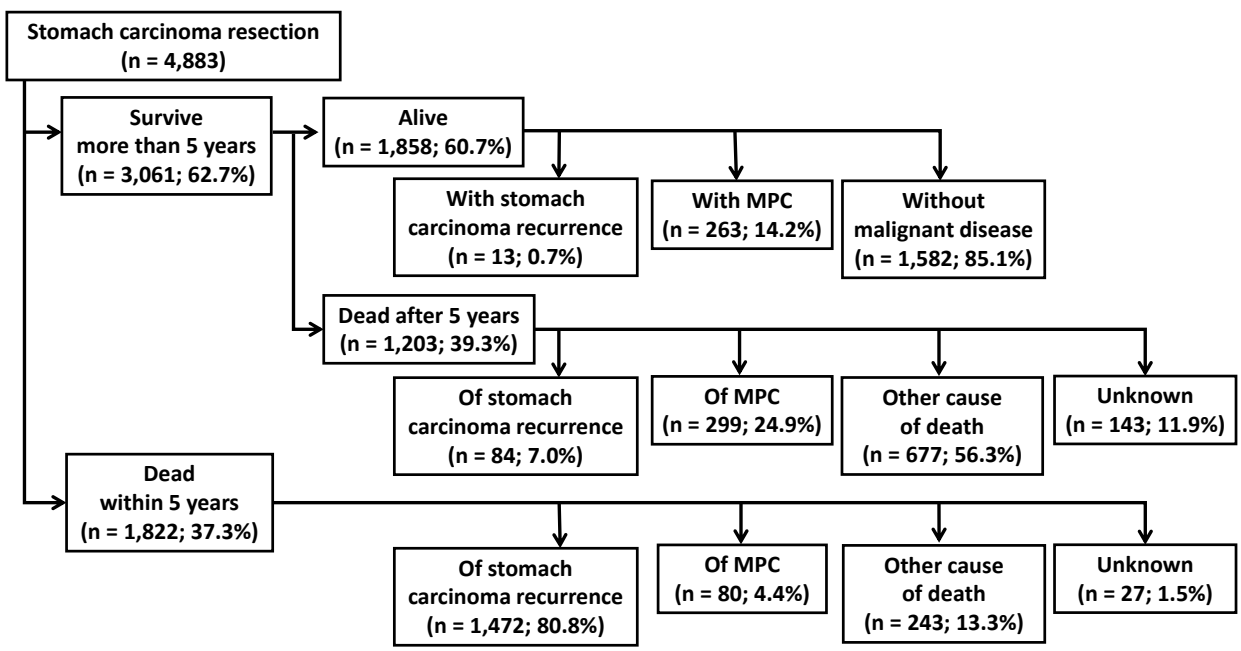

Fig. 1. Patients flow showing the outcomes of the patients who underwent stomach carcinoma resection.
We included 4,883 patients who were surgically treated for stomach carcinoma between November 1975 and December 2010, and registered at the cancer registry of Saitama Cancer Center. During the study periods, 3,061 patients (62.7%) survived for ≥ 5 years and 1,822 (37.3%) died within 5 years. Of the 1,203 patients (39.3%) who died after 5 years of survival, 383 patients (31.8%) died of malignant neoplasm, including 84 patients (7.0%) who died of recurrent stomach carcinoma and 299 patients (24.9%) who died of MPC.
677 patients (56.3%) died of other causes. The cause of death in 143 patients (11.9%) was unknown.

recurrence ≥ 5 years after surgery. Among 1,569 patients who had a diagnosis of stomach carcinoma recurrence during the observation periods, 13 patients were alive with recurrence, 84 patients were dead of stomach carcinoma recurrence after 5 years, and 1,472 patients were dead of stomach carcinoma recurrence within 5 years postoperative. In 27 (25; dead of recurrence, 2; alive with recurrence) of 1,569 patients (1.7%), the recurrence was newly diagnosed ≥ 5 years after surgery (Table 1, Fig. 1).

The histological types and conclusive stages of the tumor were diagnosed according to the Japanese classification of gastric carcinoma (Japanese Gastric Cancer Association 2011). Sixteen (59.3%) of 27 patients were examined to present with some symptoms, and had a diagnosis of cancer recurrence. The most common site of recurrence was peritoneal dissemination diagnosed in 15 patients, whereas the second site was lymph node metastasis in eight patients. In eight patients, carcinoma recurrence was confirmed based on histological findings in biopsy specimens obtained by surgery or endoscopy or by the cytological examination of ascites. In the other 19 patients, recurrence was diagnosed based on imaging. A patient had a diagnosis of recurrence with peritoneal dissemination 8 years and 9 months after total stomach resection, representing the latest diagnosis of cancer recurrence. No MPC was diagnosed elsewhere. The prognosis of the patients who were diagnosed with recurrence was poor. Their median duration of life was 8.7 months after the diagnosis of a cancer recurrence.

The sites of MPC and the prognostic difference according to the time of postoperative MPC diagnosis

Among 4,883 patients who were surgically treated for stomach carcinoma, 776 patients had MPC during the

Table 1. Characteristics of the 27 patients in whom stomach carcinoma recurrence was newly diagnosed ≥ 5 years after surgery.

		Histological Diagnosis	Pathological Stage	Symptom at recurrence diagnosis	Recurrence Site	Recurrence Diagnosis	Recurrence Time	OS after Recurrence	Outcome
1	64M	tub2	IIIA	(+)	Lymph-node	(CT)	5Y	3M	Dead
2	71F	por2/tub2	IA	(–)	Peritoneal dissemination, Liver, Lung	(CT)	5Y	1Y7M	Alive
3	48M	sig	IIA	(–)	Lymph-node	(CT)	5Y1M	10M	Dead
4	44M	por2/sig	IIB	(+)	Peritoneal dissemination	(CT)	5Y1M	2Y3M	Dead
5	54M	por2	IIIC	(–)	Lymph-node	(CT)	5Y1M	7M	Dead
6	44M	sig	IIIC	(+)	Peritoneal dissemination	(CT)	5Y3M	1Y1M	Dead
7	49M	por2	IIIC	(+)	Peritoneal dissemination	Surgery	5Y3M	2Y5M	Dead
8	50M	por2	IIIA	(+)	Brain	(CT)	5Y5M	4M	Dead
9	68M	por2/sig	IIIA	(–)	Peritoneal dissemination, Lung	(CT)	5Y5M	6M	Dead
10	58F	por2	IIB	(–)	Peritoneal dissemination	Surgery	5Y6M	4M	Dead
11	65F	por2/tub2	IIIB	(+)	Peritoneal dissemination	(CT)	5Y7M	1Y8M	Alive
12	63M	pap	IIIC	(–)	Peritoneal dissemination	(CT)	5Y7M	5M	Dead
13	60M	tub2	IIIC	(+)	Peritoneal dissemination	Surgery	5Y9M	2Y6M	Dead
14	70M	por2/sig	IIIB	(–)	Anastomotic region, Lymph-node	Endoscope	5Y10M	5M	Dead
15	46M	por2	IIIC	(+)	Peritoneal dissemination	Surgery	5Y11M	1Y4M	Dead
16	30M	por2/sig	IIIB	(+)	Pleural dissemination	(CT)	6Y2M	1M	Dead
17	68M	tub2	IIIA	(+)	Lymph-node, Lung Liver, Bone	(CT)	6Y7M	3M	Dead
18	30F	por2/sig	IIIB	(+)	Ovary	Surgery	6Y11M	9Y6M	Dead
19	62M	tub2/tub1	IIA	(+)	Peritoneal dissemination, Liver, Lung	(CT)	6Y11M	1M	Dead
20	73M	por2	IIIC	(+)	Peritoneal dissemination	Endoscope	6Y11M	4M	Dead
21	61M	tub2	IB	(–)	Lymph-node, Liver	(CT)	7Y5M	7M	Dead
22	47F	por2	IIB	(+)	Peritoneal dissemination	(CT)	7Y6M	8M	Dead
23	42M	por2	IIIA	(–)	Lymph-node	(CT)	8Y1M	1Y1M	Dead
24	51M	sig	IIIB	(+)	Peritoneal dissemination	(CT)	8Y4M	9M	Dead
25	55F	por2/sig	IIIB	(–)	Lymph-node	(CT)	8Y5M	1Y5M	Dead
26	52F	por2/muc	IB	(+)	Pleural dissemination, Bone, Ovary	Cytology	8Y5M	2M	Dead
27	39M	por2	IIIB	(–)	Peritoneal dissemination	(CT)	8Y9M	11M	Dead

The histological types and conclusive stages of the tumor were diagnosed according to the Japanese classification of gastric carcinoma (Japanese Gastric Cancer Association 2011).
Histological classification: por2, non-solid type of poorly differentiated adenocarcinoma; sig, signet-ring cell carcinoma; muc, mucinous adenocarcinoma; tub1, well-differentiated tubular adenocarcinoma; tub2, moderately differentiated tubular adenocarcinoma; pap, papillary adenocarcinoma.

observation periods. The list of MPC sites in 776 patients is shown in Table 2. 106 patients had MPC in their preoperative medical history. MPC was diagnosed synchronously and postoperative metachronously with stomach carcinoma in 141 and 529 patients, respectively. The most common site of MPC was lung in 124 patients. The site of MPC was listed as follows in order; colon and rectum in 123, urologic organ in 106, remnant stomach in 68, esophagus in 63, and head and neck in 62. At the time of investigation, 263 patients were still alive. Among the 513 patients (66.1%) who died during an observation period, the cause of death was MPC in 379 patients (48.8%), recurrent stomach carcinoma in 49, other cause of death in 80, and unknown in five. 347 patients (44.7%) had a smoking-related MPC (Vineis et al. 2004), including 62 patients in head and neck, 124 in lung, 63 in esophagus, 50 in urinary-tract (except 56 prostate from 106 urologic organ), 43 in pancreas, and 5 in uterine-cervix (except 11 uterine corpus and 6 ovary from 22 gynecologic organ). 187 patients (53.9%) of those died of MPC (Table 2).

Among the 529 patients with postoperative metachronous MPC, we examined the prognostic differences according to the time of MPC diagnosis after stomach resection. Two patients died of recurrent stomach carcinoma after MPC diagnosis, of which one patient had esophageal carcinoma and the other had uterine carcinoma; they were excluded. Therefore, we analyzed the difference of the survival rate in 527 patients.

The list of postoperative MPC sites in 527 patients is shown in Table 3. The patients were classified in two groups according to the time of MPC diagnosis after stomach resection. In 160 patients MPC was diagnosed within 5 years and in 325 patients MPC was diagnosed ≥ 5 years after stomach resection. In 42 patients, the time of MPC diagnosis was unknown. These 325 patients were long-term survivors ≥ 5 years postoperative. Of 325 patients in whom MPC was diagnosed ≥ 5 years postoperative, 204 (62.8%) patients died of MPC. Whereas, of 160 patients in whom MPC was diagnosed within 5 years postoperative, 85 (53.1%) patients died of MPC during an observation period. Mortality of MPC in the patients in whom MPC was diagnosed within 5 years postoperative was significantly better than that of the patients in whom MPC was diagnosed ≥ 5 years postoperative ($P = 0.0425$). In 325 patients in whom MPC was diagnosed ≥ 5 years postoperative, the 5-year survival rate and the median survival time after diagnosis were 35.1% and 17.7 months, respectively. This outcome was significantly poorer than that of 160 patients in whom MPC was diagnosed within 5 years postoperative (58.5% and 62.7 months, $P < 0.0001$; Fig. 2).

In the patients in whom MPC was diagnosed within 5 years postoperative, the average age of patients at the time

Table 2. A list of the organs affected by Multiple Primary Cancers (MPC)

Site of MPC	Past History	Syn-chronous	Meta-chronous	Total	Alive	Dead	Cause of death			
							MPC	Recurrence of Stomach cancer	Other Cause	Un-known
Head & Neck	26	12	24	62	21	41	19	11	11	0
Lung	12	7	105	124	35	89	77	4	8	0
Esophagus	2	33	28	63	19	44	31	5	8	0
Remnant Stomach	*	*	68	68	27	41	35	0	6	0
Brain	2	0	7	9	1	8	7	1	0	0
Mammary Gland	16	3	18	37	22	15	3	6	6	0
Pancreas	0	6	37	43	5	38	37	0	1	0
Bile Duct	0	5	26	31	1	30	26	1	2	1
Liver	1	9	28	38	2	36	33	0	3	0
Colon & Rectum	12	41	70	123	45	78	50	6	20	2
Urologic organ	16	13	77	106	56	50	32	6	11	1
Gynecologic organ	11	4	7	22	10	12	5	7	0	0
Hematology	5	3	21	29	12	17	15	1	1	0
Skin	2	2	4	8	3	5	1	1	2	1
Duodenum	1	2	0	3	2	1	0	0	1	0
Retro-peritoneum	0	1	0	1	1	0	0	0	0	0
Unknown Origin	0	0	9	9	1	8	8	0	0	0
Total	106	141	529	776	263	513	379	49	80	5

The list of MPC in 776 patients is shown. 106 patients had MPC in their preoperative medical history. MPC was diagnosed synchronously and metachronously with stomach carcinoma in 141 and 529 patients, respectively, during the observation period in the patients who underwent stomach carcinoma resection.

Table 3. The list of postoperative MPC sites.

Site of MPC	Total	Diagnosis time of postoperative MPC								
		Within 5-years				After 5-years				Unknown Time of MPC diagnosis
			Dead				Dead			
			Total	MPC	Other Cause		Total	MPC	Other Cause	
Total	527	160	103	85	18	325	219	204	15	42
Head & Neck	24	13	8	6	2	10	6	4	2	1
Lung	105	37	25	23	2	62	47	47	0	6
Esophagus	27	13	10	8	2	12	7	7	0	2
Remnant Stomach	68	16	8	6	2	52	33	29	4	0
Brain	7	2	2	2	0	4	4	4	0	1
Mammary Gland	18	8	2	1	1	10	1	0	1	0
Pancreas	37	7	7	7	0	24	21	21	0	6
Bile Duct	26	4	4	4	0	14	13	13	0	8
Liver	28	6	6	5	1	18	17	17	0	4
Colon & Rectum	70	22	17	12	5	43	27	25	2	5
Urologic organ	77	22	8	7	1	49	22	17	5	6
Gynecologic organ	6	2	1	1	0	4	2	2	0	0
Hematology	21	7	4	3	1	12	10	10	0	2
Skin	4	1	1	0	1	3	2	1	1	0
Duodenum	0	0	0	0	0	0	0	0	0	0
Retroperitoneum	0	0	0	0	0	0	0	0	0	0
Unknown Origin	9	0	0	0	0	8	7	7	0	1

In 160 patients, postoperative MPC was diagnosed within 5 years after stomach resection. In 325 patients, postoperative MPC was diagnosed ≥ 5 years after stomach resection. In 42 patients, the time of postoperative MPC diagnosis was unknown.

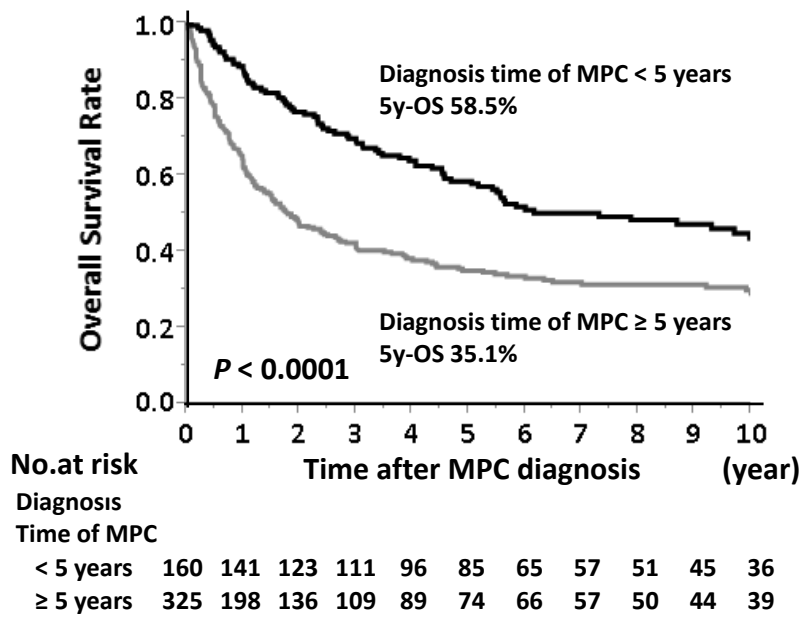

Fig. 2. The difference in overall survival rate based on the diagnosis time of postoperative MPC.
We examined the prognostic differences in 527 patients with MPC according to the diagnosis time. In 325 patients in whom MPC was diagnosed ≥ 5 years postoperative, 5 years survival rate and the median survival time (MST) after diagnosis were 35.1% and 17.7 months, respectively (Grey line). This outcome was significantly poorer than that of 160 patients in whom MPC was diagnosed within 5 years postoperative (58.5% and 62.7 months; Black line) ($P < 0.0001$).

of MPC diagnosis was 68.2 years old (range, 34-86 years old) and 9 of 160 patients (5.6%) were 80 years or older, which was significantly younger as compared with the patients in whom MPC was diagnosed ≥ 5 years postoperative, in which the average age was 72.4 years old (range, 38-95 years old) and 71 of 325 patients (21.9%) were 80 years or older ($P < 0.0001$). In the elderly patients 80 years or older, the mortality of MPC, the 5-year survival rate and the MST after MPC diagnosis were 81.3 %, 18.8%, 11.5 months respectively, which were significantly worse than those in younger patients (55.3%, 47.9%, and 78.1 months respectively, $P < 0.0001$).

After excluding the patients 80 years or older, the number of the patients in whom MPC was diagnosed within 5 years postoperative was counted with 151, and the number of the patients in whom MPC was diagnosed ≥ 5 years postoperative was counted with 254. In 151 patients in whom MPC was diagnosed within 5 years postoperative, the 5-year survival rate and the MST after MPC diagnosis were 60.7% and 65.0 months respectively, which were also significantly better than those in 254 patients in whom MPC was diagnosed ≥ 5 years postoperative (39.7% and 20.8 months, $P = 0.0002$). However, the significant difference was not recognized about the mortality of MPC between both groups (77 of 151 patients, 51.0%, vs. 147 of 254 patients, 57.9%, $P = 0.1784$).

Discussion

The number of long-term survivors of ≥ 5 years following stomach resection is increasing. In long-term survivors, the roles of the postoperative periodic surveillance are as follows; an early detection of asymptomatic cancer recurrence or postoperative MPC, monitoring of the nutritional status, prevention of bowel obstruction, the provision of psychological support, and the management of symptoms such as a reflux of digestive juice.

The surgeon often has a question how many years it takes until the final diagnosis of delayed stomach cancer recurrence after curative resection. Some case reports of the patients in whom recurrent stomach carcinoma was diagnosed ≥ 10 years after stomach resection were reported (Okugawa et al. 2010; Blanchette et al. 2013). In this study, among the 3,061 five-year survivors, recurrent stomach carcinoma was newly diagnosed in only 27 patients (0.9%), representing 1.7% of the 1,569 patients with a diagnosis of recurrent stomach carcinoma. The rate of the late recurrence of ≥ 5 years and of ≥ 10 years diagnosed after surgery was reported to be 7.1%-8.6% and 1.1%-1.4% respectively, among all patients with a recurrent stomach carcinoma (Lee et al. 2016; Shin et al. 2016).

The number of patients of unknown cause of death was 170 (5.6%) of 3,025 deceased patients during the observation periods. The dropout bias is caused by inability to patient follow-up, but should be less than 10% for a reliable range. In the past cohort studies regarding the efficacy of the stomach cancer screening (Lee et al. 2016; Miyamoto et al. 2007), the rate of the patients who were lost to follow-up during an observation period was 6.8%, and 10.7%, respectively.

There is no evidence that strict follow-up after curative stomach resection benefits survival, because the early detection of asymptomatic recurrence did not improve overall survival in patients with recurrence (Kodera et al. 2003; Eom et al. 2011). Even if an asymptomatic recurrence was diagnosed earlier than a symptomatic recurrence and the survival time from recurrence diagnosis to final outcomes was significantly extended more than that in the patients with a symptomatic recurrence, the overall survival is not significantly affected by the presence or absence of symptoms.

On the other hand, it was reported that early detection of stomach carcinoma recurrence may be associated with improved survival because it may provide an opportunity for the treatment to be initiated while the patient's condition is sufficiently stable to receive effective therapy, including resection of recurrence site and chemotherapy (D'Ugo et al. 2013). The detection of non-peritoneal recurrence before the appearance of symptoms may provide survival benefit, because additional surgery at the site of recurrence can be performed (Fujiya et al. 2017). Clinically resectable cases of liver metastasis from stomach carcinoma are rare, but in the 256 patients undergoing hepatic resection, the 5-year overall survival rate was 31.1% (Kinoshita et al. 2015). Forty-five patients (17.6%) survived for ≥ 5 years without recurrence after hepatic resection and might have been cured from recurrence with liver metastases. When symptomatic recurrence is diagnosed, the patient's performance status may be insufficient to undergo chemotherapy. Due to the developments in chemotherapy for stomach carcinoma, the overall response rate was improved up to 46.0%, and some patients could achieve the complete remission from carcinoma (Ohtsu et al. 2011).

The periodical screening may help the early detection of postoperative MPC rather than a diagnosis of the carcinoma recurrence in long-term survivor ≥ 5 years after surgery. In 2016, the number of cancer-related deaths accounted for 28.5% of total number of death in Japan (Foundation for Promotion of Cancer Research 2018). In this study, among 1,203 patients who died ≥ 5 years after stomach resection, 299 patients (24.9%) died of MPC, which was similar to the cancer-related mortality of the general populations. In approximately a quarter of long-term survivors of ≥ 5 years following stomach carcinoma resection, the cause of death was MPC. The number of patients who were newly diagnosed as a malignant neoplasm ≥ 5 years postoperative and died were counted with 229 (19.0% of 1,203 patients who died after ≥ 5 years), including 204 patients with postoperative MPC (Table 3) and 25 with delayed stomach cancer recurrence (Table 1). Along with extension of the observation period, the morbidity and the mortality of postoperative MPC newly diagnosed may increase in long-term survivors.

In this study, the overall survival rate after postoperative MPC diagnosis and the mortality of MPC in whom MPC was diagnosed within 5 years after stomach resection was significantly better than those in whom MPC was diagnosed ≥ 5 years postoperative. In other words, MPC diagnosed in long-term survivor ≥ 5 years after stomach resection may result in a poorer prognosis as compared with MPC diagnosed within 5 years postoperative. One of the reasons is because the patients in whom MPC was diagnosed ≥ 5 years after stomach resection included more elderly patients 80 years or older as compared with the patients in whom MPC was diagnosed within 5 years postoperative. Many of them were too old to undergo chemotherapy or surgery. Older patients are prone to develop complications such as cardiopulmonary disease, renal dysfunction, and diabetes. Because many of them are suffering from malnutrition after stomach resection, their performance status may be insufficient to be candidates for appropriate cancer treatment. In the elderly patients 80 years or older, the mortality and the survival rate after MPC diagnosis were significantly worse than those in younger patients. The survival rate of the patients in whom MPC was diagnosed within 5 years after stomach resection was also significantly better than that of the patients in whom MPC was diagnosed ≥ 5 years postoperative, even after excluding the patients 80 years or older. Against our expectation, the significant difference was not recognized about the mortality of MPC between both groups in the analysis excluding elderly patients.

As for the site of MPC in long-term cancer survivors, the particularly more frequent site was not found as compared with a general population (Kaneko and Yamaguchi 1999; Tabuchi et al. 2012). Therefore, in a cancer survivor the periodical cancer screening is recommended as well as general population.

The second reason is because the survival time after the MPC diagnosis might be affected by a screening bias. The patients in whom MPC was diagnosed within 5 years after surgery tend to receive cancer screening more frequently, as compared with the patients in whom MPC was diagnosed ≥ 5 years postoperative. Since most of patients attend a hospital for periodical surveillance for 5 years after surgery, postoperative MPC was diagnosed in a relatively early and asymptomatic stage. Conversely, long-term survivors who lived ≥ 5 years after carcinoma resection tend to neglect periodical medical screening, because they do not aware of the risk of MPC. As for the survival rate, they might lead to the detection of tumors with more favorable biology, such as relatively slower-growing or asymptomatic pre-clinical tumors compared with symptomatic cases diagnosed without screening (Kaneko and Yamaguchi 1999; Mahnken et al. 2008). The patients in whom MPC was diagnosed within 5 years postoperative seems to include early and curable cancer more as compared with the patients in whom MPC was diagnosed ≥ 5 years postoperative.

It remains unclear whether screening of the postoperative MPC results in the improvement of cancer-related mortality in long-term survivors. The early detection of asymptomatic MPC by cancer screening does not necessarily contribute to the improvement of cancer-related mortality. Therefore, the efficacy of the cancer screening is not evaluated by increasing early diagnosis or overall survival rate of MPC, but is evaluated whether it can reduce cancer-related mortality. The evidence implying that cancer screening contributes to the reduction of the cancer-related mortality has been proven by randomized control trial (RCT), studying in lung cancer (National Lung Screening Trial Research Team et al. 2011), colorectal cancer (Atkin et al. 2010), breast cancer (Ohuchi et al. 2016), and cervical cancer (Ronco et al. 2010). As for stomach carcinoma screening, the evaluation of efficacy has been assessed only by cohort study and case-control study so far (Miyamoto et al. 2007; Jun et al. 2017).

Furthermore, similar to early diagnosis of cancer recurrence, the early asymptomatic diagnosis of MPC may be associated with a decrease in cancer mortality, because it may provide an opportunity for the patients to undergo effective cancer treatment while the patients' performance status is sufficiently stable. On the other hand, when a symptomatic MPC is diagnosed, it is often more advanced stage of cancer as compared with an asymptomatic MPC and the patients' performance status may be insufficient to undergo appropriate cancer therapy. This may be the third reason that a survival rate of MPC decreases in long-term survivors. Therefore, it is important to educate them about the necessity of the cancer screening. If a long-term survivor has adequate performance status to undergo treatment, we recommend to undergo a periodical cancer screening.

Periodic endoscopic surveillance after distal stomach resection was reported to be useful in detecting remnant stomach cancer at an early stage, which offers a chance for the patient to undergo endoscopic treatment or laparoscopic surgery and leads to an improved prognosis in patients with remnant stomach cancer (Ohira et al. 2016).

In the conventional reports regarding the risk of developing MPC in the cancer survivors, they examined the onset risk of MPC mainly by the investigation of the morbidity, but did not mention much about the cancer mortality rate of MPC so far. The observation period was relatively short and the reports included many patients who died of an initial cancer during the early period within 5 years after the initial cancer diagnosis. A study from U.S.A. (Donin et al. 2016) reported about the cancer death in cancer survivors. In their study, the patients who died of an initial cancer accounted for 46.5% of all deaths of cancer survivors, and the mortality due to MPC was only 7.0%. In our study, we could clarify the risk of MPC mortality. Therefore, we can do more impressive and effective enlightenment about the necessity of MPC screening in long-term cancer survivors of ≥ 5 years after stomach carcinoma resection, as compared with the conventional reports.

Because the carcinogenic risk in the cancer survivors is similar to that in general population, it is necessary to remove a carcinogenic risk factor to prevent development of MPC. Active tobacco smoking is carcinogenic and causes cancers not only of the lungs, but also in the multiple regions and organs including the head and neck, esophagus, stomach, pancreas, kidneys, urinary tract, and uterine cervix (Vineis et al. 2004). The risk of developing stomach carcinoma is 50-60% higher on an average in smokers than in non-smokers according to cohort and case-controlled studies, demonstrating positive dose-response relationships with the number of cigarettes smoked and the duration of smoking. The risk of developing a smoking-related second MPC is also higher by continuation of smoking postoperative, because many of the patients with stomach carcinoma have the lifestyle of the smoking before the initial stomach resection (Youlden and Baade 2011; Tabuchi et al. 2012). Although the beneficial effects of smoking cessation were first observed in relation with lung cancer, it has also been reported that smoking cessation may exert similar risk-reducing effects for other tobacco-related cancers (Bosetti et al. 2006; Nishihara et al. 2013).

It was also reported by prospective cohort study that smokers may lose at least 10 years of lifespan. The excess mortality among smokers was mainly induced by the increased risk of disease such as chronic obstructive pulmonary disease, ischemic heart disease, and the ischemic stroke as well as lung cancer, as compared with non-smokers (Pirie et al. 2013; Chen et al. 2015). These smoking-related mortality may also decrease by smoking cessation.

In this study, among the 3,061 patients who were long-term survivors for ≥ 5 years, 325 (10.6%) patients developed postoperative MPC during the observation period. 126 patients (38.8%) had smoking-related MPC, including 62 patients in lung, 17 in urinary-tract (except 32 prostate among 49 urologic organ), 10 in head and neck, 12 in esophagus, 24 in pancreas, and one in uterine cervix (Table 3). 90 patients (71.4%) of those died of MPC. The carcinogenic risk in these patients may be decreased by early smoking cessation.

A limitation of this study was relatively small number of patients by the single-center experience. Therefore, we attempted to overcome this limitation by a long observation period following a surgery, which was necessary to investigate the more number of the mortality of MPC in long-term survivors of ≥ 5 years after surgery. The cohort study to investigate the smoking-related mortality required study period ten years or more (Pirie et al. 2013; Chen et al. 2015). Our investigation also had some other limitations. One of the reasons is because it becomes difficult recently that the government office near the patients' residence provides the information about the cause of death according to the protection rule of the personal information, even if the information of the life and death of the patients is obtained. The other reason is because it was difficult to obtain the answer of the questionnaires from the bereaved regarding the cause of death of the patients who transferred to the other hospital more than ten years ago.

In conclusion, about a quarter (24.9%) of long-term survivors following stomach carcinoma resection is at risk of dying of MPC, which was similar to the cancer-related mortality of the general populations (28.5%). In 19.0% of the patients who died ≥ 5 years, MPC and the delayed stomach carcinoma recurrence was newly diagnosed ≥ 5 years after stomach resection. The survival rate and the mortality of the patients in whom MPC was diagnosed ≥ 5 years after stomach carcinoma resection was significantly poorer than that of the patients in whom MPC was diagnosed within 5 years. Periodical cancer screening allows the early asymptomatic diagnosis of MPC and may contribute to a decrease in cancer mortality, because it may provide an opportunity for the patients to undergo effective cancer treatment while the patients' performance status is sufficiently stable.

According to the results of this study, we are able to clarify the risk of MPC mortality in long-term cancer survivors of ≥ 5 years after stomach cancer resection. We, therefore, can create the guidelines about the surveillance for the long-term cancer survivors, including the periodical cancer screening and the education for lifestyle improvements such as smoking cessation, which are important for long-term survivors of ≥ 5 years after stomach carcinoma resection, as well as general population.

Author Contributions

Amikura, K. participated in manuscript writing, study concept and design, acquisition of data, analysis and interpretation of data, the sequence alignment, drafted the manuscript and revising it critically for important intellectual content.

Ehara, K. and Kawashima, Y. participated in the acquisition, analysis, or interpretation of clinical data and critical revision.

All authors helped to perform the research, read and approved the final version of manuscript to be published. And also, all authors had agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest

The authors declare no conflict of interest.

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