

Short Communication

Patients with Multiple Primary Gastric Cancers Tend to Develop Second Primaries in Organs Other Than the Stomach

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Abstract: The multiple occurrence of a single cancer tends to result in the increased vulnerability of some other organs to another malignancy. In the present study, we examined a total of 1,606 patients with gastric cancer to ascertain whether the frequency of second primaries in organs other than the stomach is higher in patients with multiple gastric cancers than in those with a single gastric cancer. Primary cancers of other organs were present in 87 (5.9%) of 1,474 patients with single gastric cancer and in 16 (12.1%) of 132 patients with multiple gastric cancers. The difference was statistically significant. The most frequent site of the occurrence of a second primary was the colo-rectum, followed by the urogenital organs, uterus, breast, and lung in descending order of frequency. We therefore assume that the occurrence of multiple cancers in the stomach is not merely a chance phenomenon but is related to both genetic predisposition and environmental factors.

Key Words: multiple gastric cancers, single gastric cancer, second primary malignancy

It is not uncommon for two or more distinct types of cancer to develop in the same stomach. The incidence of multiple primary gastric cancers in the general patient population with gastric cancer is reported to be 5–9%.^{1–3} Detection is one of the major clinical problems associated with multiple primary gastric cancers, and emphasis has been placed on the necessity of ensuring that multiple lesions are not overlooked during the diagnostic examination of the stomach. To this end, the clinical and pathological features of multiple gastric cancers have been defined in contradistinction to those of single gastric cancer, and they can be summarized as follows:

1. the occurrence of multiple gastric cancers is more frequent in males than in females,
2. the incidence of multiple gastric cancers increases with advancing age,
3. a large proportion of cases are cases of early cancer, and
4. well-differentiated adenocarcinoma accounts for a greater proportion of cases than it does in cases with a single primary gastric cancer.

Another important point in this issue is the postulation that patients with multiple gastric cancers tend to develop second primaries in organs other than the stomach. This report is the first to provide convincing evidence in support of the contention that primary cancers of organs other than the stomach are more frequent among patients with multiple gastric cancers than among those with a single gastric cancer.

During the past 19 years, from 1970 through 1988, a total of 1,606 patients with primary gastric cancer (excluding cases with residual stomach cancer) underwent gastrectomy at the First Department of Surgery at Tottori University. Of these patients, 1,474 had a single gastric cancer and 132 had multiple gastric cancers. Of the 1,606 patients with gastric cancer, primary cancers of organs other than the stomach were noted in 103 cases (6.4%), with 34 being cases of synchronous multiple cancers and 69 being metachronous. Multiple cancers were regarded as synchronous when the time interval between detection of the first and the second cancer was less than 1 year, otherwise they were regarded as metachronous. These cases were analyzed to determine whether or not the frequency with which primary cancer occurs in organs other than the stomach is higher in patients with multiple gastric cancers than in those with single gastric cancer. None of the patients were lost during the follow-up study.

As a result, primary cancers of organs other than the stomach were present in 87 (5.9%) of 1,474 cases of

Table 1. Incidence of primary cancers in organs other than the stomach in patients with gastric cancer

Gastric cancer	Synchronous	Metachronous ^a		Total
		Group A	Group B	
Single cancer (<i>n</i> = 1,474)	28 (1.9%)	32 (2.2%)	27 (1.8%)	87 (5.9%)
Multiple cancers (<i>n</i> = 132)	6 (4.5%)	6 (4.5%)	4 (3.0%)	16 (12.1%)*

^a Group A: cases in which second primaries developed after gastrectomy. Group B: cases in which first primaries developed before gastrectomy

* $P < 0.05$, χ^2 -text

Table 2. Distribution of sites with primary cancers in organs other than the stomach in patients with either single or multiple gastric cancers

Sites	Single gastric cancer		Multiple gastric cancers	
	Synchronous primaries	Metachronous primaries	Synchronous primaries	Metachronous primaries
Oropharynx	2	4	0	2
Esophagus	3	0	1	0
Colorectum	7	11	2	1
Liver	3	7	0	0
Pancreas	1	3	2	0
Lung	2	5	0	2
Thyroid	1	2	0	0
Breast	1	8	0	1
Uterus	0	9	0	1
Kidney, bladder, prostate	4	6	0	1
Hematopoietic tissue	3	3	0	1
Others	1	1	1	1
Total	28	59	6	10

single gastric cancer and in 16 (12.1%) of 132 cases of multiple gastric cancers. Thus, the incidence of primary cancers in other organs was significantly higher in the latter group (Table 1). With regard to the relative time of detection of primary cancers in organs other than the stomach, primary cancers of other organs were synchronous with gastric cancer in 28 (1.9%) patients with single gastric cancer and in 6 (4.5%) patients with multiple gastric cancers, while the second primary cancers were metachronous in 59 (4.0%) patients with single gastric cancer and in 10 (7.5%) patients with multiple gastric cancers. Thus, the frequency of incidence for cancers in other organs, irrespective of whether they were synchronous or metachronous, was higher in the cases of multiple gastric cancers.

Among the organs other than the stomach of patients with gastric cancer in which a second primary cancer was found, the most frequent was the colo-rectum, followed by the urogenital organs, uterus, breast, and lung in descending order of frequency (Table 2).

When cancer occurs in one organ, there is a tendency towards an increased vulnerability of some other

organs to the development of a second primary cancer. Studies on the occurrence of multiple cancers in different organs have provided some clues to the elucidation of carcinogenic factors and the mechanism(s) of the development of malignancies. Genetic predisposition, common environmental factors, and iatrogenic factors have been implicated as possible causes of concurrent cancers of multicentric origin.⁴ According to a genetic study of breast cancer, if a mother has breast cancer, her daughters also have a high risk of developing the same malignancy.⁵ It is known that, in some types of colo-rectal cancer, genetic predisposition plays an etiologic role as suggested by the existence of hereditary cancer syndromes. Gastric and colo-rectal cancers, gastric and esophageal cancers,^{6,7} and cancer of the upper alimentary tract and lung cancer^{8,9} are known to be common combinations, and the existence of such pairs suggests that environmental factors, such as dietary habits and smoking, may also be involved in the mechanisms of development of the various pairs of cancers. Radiotherapy and chemotherapy are known to be followed quite fre-

quently by the occurrence of a second cancer, a fact that implicates iatrogenic chemical factors in multiple carcinogenesis.^{10,11}

In Japan, since gastric cancer is a common malignancy, the occurrence of gastric cancer and cancer of other organs is by no means infrequent. The incidence of such a combination is 2.0–4.0% when based on clinical diagnosis^{7,12} and 13.4% when calculated from diagnosis at autopsy.⁶ In our hospital, as discussed above, 6.4% of patients with gastric cancer had a second cancer in some other organs. If patients who had a previously diagnosed cancer before the diagnosis of gastric cancer in a certain hospital were included in the cases of multiple primary cancers, the number of cases would become artificially increased, because of the bias that results from the tendency of patients to be directed towards specialized hospitals for better treatment. Therefore, when such cases of metachronous cancers of organs other than the stomach, in which the metachronous cancers have been treated before gastrectomy, were excluded from the calculations, the incidence of concurrent cancers of the stomach and other organs proved to be 4.6% (72/1,575) at our clinic.

It is of particular interest that a second cancer occurs more frequently in cases of multiple gastric cancers than in those of a single gastric cancer. This observation implies that the occurrence of multiple cancers in the stomach is not merely a chance phenomenon, pointing to the likely possibility that both genetic predisposition and environmental factors are related not only to gastric carcinogenesis but also to the development of a second cancer in some other susceptible organ.

Reported evidence indicates that, among the organs of patients with gastric cancer in which a second cancer is likely to occur, the most frequent is the colo-rectum, followed by the uterus, esophagus, mammary gland, oro-pharynx, lung, and liver in descending order of frequency.⁶ A similar tendency was observed in our clinic. One of the possible reasons why the combination of gastric and colo-rectal cancers is more frequent might be that some alimentary carcinogen(s) acts on both organs. Another possible reason is that gastrectomy-related alterations of intestinal microflora and bile metabolism may favor colo-rectal carcinogenesis.^{13,14} Caygill et al.¹⁵ determined the mortality risk from cancer of the large intestine after gastric surgery using a "years at risk" calculation in 5-year bands. They found that there was a significantly higher risk of cancer of the large bowel from 20 years after operation onwards. Accordingly, it seems reasonable

to suggest that colo-rectal cancer, which occurs in surgically treated patients with gastric cancer, is not a chance phenomenon but is often the result of a process that involves genetic predisposition, environmental factors, and/or some iatrogenic factors.

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