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Risk factors for double primary malignancies and their clinical implications in patients with sporadic gastric cancer

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Abstract

Aims: We carried out a large scale study to identify the risk factors for double primary malignancy (DPM) development in gastric cancer patients and to evaluate the clinical implications for these patients.
Methods: A total of 2593 patients who underwent gastrectomy for primary gastric cancer from January 2005 to November 2010 were reviewed with regard to DPM. We compared the clinicopathological characteristics, risk factors for developing DPM, and prognosis between the DPM(+) group and the DPM(−) group.
Results: Of the 2593 patients, 152 (5.9%) were diagnosed with DPM. The most common accompanying malignancies were colorectal, lung and thyroid. Multivariate analysis indicated that age ($p = 0.016$) and MSI status ($p = 0.002$) were associated with a higher frequency of DPM. 30.3% of patients were diagnosed with DPM within 1 year around perioperative period and 53.3% of patients had DPM detected during 5 years of post-operative follow up periods. Although there was no significant difference in overall survival between the DPM(+) and DPM(−) group, DPM(+) patients had a worse prognosis than DPM(−) patients in stage I gastric cancer.
Conclusions: Gastric cancer patients over the age of 60 or with a MSI-high status had an increased risk for developing DPM. Further, in stage I gastric cancer, the presence of DPM was associated with a worse prognosis. Therefore, careful pre- and postoperative surveillance is especially important in these patients.

Keywords: Double primary malignancy; Microsatellite instability; Gastric cancer; Prognosis

Introduction

With the extension of lifespan in humans, cancer prevalence and mortality are increased throughout a lifetime.[1–3] Among the various cancers, gastric cancer is one of the major cancer because it is the fourth most common type of cancer and the second leading cause of cancer-related deaths worldwide.[4] As results of the advances in surveillance programs, improved surgical techniques, perioperative management, and adjuvant treatment, the overall survival of gastric cancer patients has significantly improved.[5–7] With this prolonged survival, the chance of second primary malignancy has also increased in gastric cancer patients.[8–10]

Since Billroth first documented multiple primary malignant neoplasms in 1889,[11] numerous reports have been published on the subject and the overall prevalence of multiple primary malignancies is reported between 0.73% and 11.7%.[10,12–16] In a study that focused on gastric cancer, 4.2% of patients were found to have a second primary cancer, which was frequently colorectal or lung cancer.[10] In a separate report, differentiated tumor histology was the only independent risk factor for developing synchronous cancer in gastric cancer patients.[15]

Until now, only a few studies have focused on the risk factors for double primary malignancies (DPM) in gastric cancer patients. Therefore, we carried out a large scale study to identify the risk factors for DPM development in

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gastric cancer patients and to evaluate the clinical implications for these patients.

Materials and methods

We reviewed data of 2593 gastric cancer patients who underwent curative gastrectomy with lymph node dissection at Yonsei University College of Medicine between January 2005 and November 2010 with regard to double primary cancers. All of the patients had histologically confirmed adenocarcinoma and the surgical specimens underwent microsatellite instability (MSI) testing. DPM was defined as a malignancy that was confirmed elsewhere in addition to stomach. This study was reviewed and approved by the Institutional Review Board of Severance Hospital, Yonsei University College of Medicine (4-2012-0839).

The clinicopathological characteristics including MSI status, the sites of DPM, the interval from first cancer to second primary malignancy, and survival were evaluated based on medical records. MSI analysis and interpretation was followed the previous report of our institute.[17] Tumors were staged according to the 6th edition of the International Union Against Cancer classification.[18] Histological type was classified into two groups: 1) differentiated type, which included papillary, well-, or moderately-differentiated adenocarcinoma and 2) undifferentiated type, which included poorly differentiated or undifferentiated adenocarcinoma, signet ring cell carcinoma, and mucinous carcinoma.

For statistical analysis, the SPSS (version 18.0; SPSS Inc., Chicago, IL, USA) program was used. Categorical variables were analyzed using the chi-square test, and continuous data were analyzed using the Mann–Whitney test. For multivariate analysis, logistic regression was used. Overall survival was calculated from date of surgery to date of death from any cause. Patients alive or lost to follow-up were censored at the date last known to be alive. Differences in survival between groups were compared using Kaplan–Meier curves and tested using log-rank test. All P-values < 0.05 were considered statistically significant.

Results

Clinicopathological characteristics based on double primary status

As shown in Table 1, patients were divided into two groups according to the presence or absence of DPM. Among the 2593 gastric cancer patients, 152 had DPM. The clinicopathological characteristics including gender, age, BMI, lesion number, tumor size, Lauren classification, histological type, MSI status, and TNM stage were compared between DPM(+) and DPM(−) group. The mean age of patients was 63.7 ± 10.8 years in the DPM(+) group and 57.3 ± 12.1 years in the DPM(−) group ($p < 0.001$). The incidence of patients over the age of 60 was 43.6% in the DPM(−) group, which was significantly different ($p < 0.001$) from the 65.8% observed in the DPM(+) group. The DPM(+) group had a higher incidence of intestinal type (57.2% vs 47.4%, $p = 0.005$) and more histologically differentiated tumors (50.0% vs 41.5%, $p = 0.042$) than the DPM(−) group. In the sub-analysis of histological type for each stage, the proportions of differentiated tumors in stage I patients were, respectively, 50.6% and 56.1% in DPM(−) and DPM(+) groups ($p = 0.364$); those in stage II, III, and IV patients were 41.1% and 42.9% ($p = 1.000$), 27.7% and 45.0%

Table 1
Clinicopathological characteristics of gastric cancer patients according to the presence of double primary malignancy.

	DPM(−) ($n = 2441$)	DPM(+) ($n = 152$)	P-value[a]
Gender			
Male	1632	109	0.247
Female	809	43	
Age (years)			
≤40	233	7	<0.001[b]
41–60	1144	45	
>60	1064	100	
Body mass index (Kg/m^2)			
<27	2203	133	0.264
≥27	238	19	
Number of GC			
1	2373	147	0.615
2 or more	68	5	
Tumor size (cm),			
≤2	590	32	0.723[b]
2<,≤5	1188	81	
5<,≤10	577	34	
>10	86	5	
Lauren classification			
Intestinal	1158	87	0.005
Diffuse	1136	51	
Mixed	147 (6.0)	14	
Histology			
Differentiated	1012	76	0.042
Undifferentiated	1429	76	
MSI			
MSS/MSI-L	2256	126	<0.001
MSI-H	185	26	
T category			
T1	1104	65	0.927
T2	635	40	
T3	668	45	
T4	34	2	
N category			
N0	1359	82	0.440
N1	595	43	
N2	303	20	
N3	184	7	
Stage			
I	1354	82	0.135
II	367	21	
III	481	40	
IV	239	9	
EGC/AGC			
EGC	1104	65	0.614
AGC	1337	87	

[a] Chi-square.
[b] Mann-Whitney test. DPM; double primary malignancy.