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• *CLINICAL RESEARCH* •

Clinical analysis of multiple primary malignancies in the digestive system: A hospital-based study

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Abstract

AIM: To analyze the characteristics of multiple primary malignancies (MPMs) of digestive system; including incidence, types of tumor combinations, time intervals between development of multiple tumors, clinical course, and prognostic factors affecting survival and mortality.

METHODS: Data from a total of 129 patients treated from January 1991 to December 2000 for pathologically proved MPMs, including at least one originating from the digestive system, were reviewed retrospectively.

RESULTS: Among 129 patients, 120 (93.02%) had two primary cancers and 9 (6.98%) had three primary cancers. The major sites of MPMs of the digestive system were large intestine, stomach, and liver. Associated non-digestive cancers included 40 cases of gynecological cancers, of which 31 were carcinoma of cervix and 10 cases of genitourinary cancers, of which 5 were bladder cancers. Other cancers originated from the lung, breast, nasopharynx, larynx, thyroid, brain, muscle, and skin. Reproductive tract cancers, especially cervical, ovarian, bladder, and prostate cancers were the most commonly associated non-GI cancers, followed by cancer of the lung and breasts. Forty-three cases were synchronous, while the rest (86 cases) were metachronous cancers. Staging of MPMs and treatment regimes correlated with the prognosis between survival and non-survival groups.

CONCLUSION: As advances in cancer therapy bring about a progressively larger percentage of long-term survivors, the proportion of patients with subsequent primary lesions will increase. Early diagnosis of these lesions, based on an awareness of the possibility of second and third cancers, and multidisciplinary treatment strategies will substantially increase the survival of these patients.

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Key words: Multiple primary malignancies; Digestive system

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INTRODUCTION

Many types of cancer, when treated early and aggressively, can be cured. The potential, however, for cancer to occur independently a second time, or more often, in the same patients remains an ever present risk. Interest in multiple primary malignancies (MPMs) is long-standing since Warren and Gates in 1932. He proposed that each suspected primary tumor (1) must be clearly malignant as determined by histological evaluation; (2) must be geographically separate and distinct. The lesion should be separated by normal appearing mucosa. If a secondary neoplasm is contiguous to the initial primary tumor or is separated by mucosa with intraepithelial neoplastic changes, the two should be considered as confluent growth rather than multi-centric carcinomas; and (3) the possibility that the second neoplasm represents a metastasis should be excluded. The observation that the invasive carcinoma arises from an overlying epithelium, which demonstrates a transition from carcinoma *in situ* to invasive carcinoma, is helpful, and when the separate foci have significant differences in histology, the diagnosis of separate primary cancers is appropriate[1,2].

Multiple primary cancers may be synchronous or metachronous depending on the interval between their diagnosis. Synchronous cancers are diagnosed simultaneously or within an interval of about 6 mo, and metachronous cancers are secondary cancers that developed more than 6 mo after the diagnosis of primary cancers usually after treatment of primary lesions[2].

MPMs were classified into four types: (1) multicentric, if the two distinct carcinomata arise in the same organ or tissue; (2) systemic, if they arise on anatomically or

functionally allied organs of the same system (colon and rectum cancers), (3) paired organs, as in the breasts, and (4) random, if they occur as a co-incidental or accidental association in unrelated sites[3].

The development of more sophisticated invasive and non-invasive diagnostic tools has made it possible to detect cancer at an early stage. Furthermore, it has contributed to the detection of synchronous occult tumors, which were formerly overlooked.

An individual developing more than one primary tumor in anatomically and functionally unrelated organs may be considered as cancer-prone. People with a family history of cancer will inherit genetic cancer susceptibility as a risk factor for cancer. Gene mutations influence cancer susceptibility through changes of metabolism and catabolism of carcinogens. Tumor suppressor genes, such as *p53* and *FHIT*, may be candidates for target genes of these risk factors[4]. Genetic instability is also considered as a driving force behind carcinogenesis and the alterations of the length of single repetitive genomic sequences or microsatellite instability, implicating impaired DNA repair mechanism[5]. People with newly diagnosed cancers and survivors of earlier cancers who have genetic cancer susceptibility, therefore, have an increased risk of MPMs.

This study has analyzed the incidence of MPMs in digestive system, as well as the different tumor combinations, time interval between occurrence of tumors, staging, clinical course, and prognostic features of survival and non-survival groups.

The purpose of this study is to determine whether certain organs or systems are particularly susceptible to second or third primary cancers and, by clarifying this tendency, to aid in the early diagnosis of these lesions.

MATERIALS AND METHODS

Retrospective data from a total of 9 807 patients treated at the Mackay Memorial Hospital from January 1991 to December 2000 for pathologically proven cancer were reviewed from the Cancer Registry. Of these, 246 patients had multiple primary cancers, among which 129 (58 males and 71 females) had MPMs in the digestive system and were included in this study.

The histological criteria described by Warren and Gates[1] and Moertel *et al*.[3], were used for diagnosing multiple separate primary malignancies.

Clinical histories, diagnostic methods, histology, staging, and clinical course of each tumor were reviewed in all patients. The age at the onset of the primary cancer and the time intervals between two or more cancers were recorded. The distribution of the digestive and associated non-digestive cancers in these 129 patients was also investigated. Fifty-two patients had received previous radiotherapy or chemotherapy for their first cancers, and interval between the first and second cancers were recorded. All tumors had been staged according to the American Joint Committee on Cancer TNM staging system[6]. The prognostic factors between survival and non-survival groups were analyzed for double primary cancers.

The differences between groups were analyzed by Student's *t*-test for continuous variables and the χ^2 test for categorical data. A P value of <0.05 was considered as statistical significance.

RESULTS

Among the 9 807 pathologically proven cancer patients, 246 had MPMs, with an incidence of 2.5%. Among these, 129 (52.43%), including 58 males (44.96%) and 71 females (55.04%), had MPMs of the digestive system. One hundred and twenty patients (93.02%) had two primary malignancies, and nine (6.98%) had three primary malignancies. The age at onset of the primary cancers ranged from 29 to 89 years (mean 60.3±13.05 years) in double cancers, and 43 to 68 years (mean 50.22±7.9 years) in triple cancers. Forty-three patients (35.8%) were over 65 years of age. Fifty-two patients (40.3%) had received previous radiotherapy or chemotherapy for their first cancer. The interval between the first and second cancers was 0.5-28 years (mean 8.1±2.5 years) and 0.5-5 years (mean 3.2±3.7 years) in the 32 patients receiving radiotherapy and the 17 patients receiving chemotherapy respectively.

The distribution and incidence of MPMs of the digestive system are shown in Table 1. The major site for MPMs of the digestive system was the large intestine (colon, 23.17%; rectum, 25.82%), followed by the stomach (23.17%) and liver (15.23%).

Distributions of associated non-digestive cancers in patients with MPMs are shown in Table 2. There were

Table 1 Distribution of MPMs in digestive tract

Site	Number of MPMs	Total number	Incidence (%)	% in GI MPMs
Esophagus	8	374	2.14	5.29
Stomach	35	1 770	1.98	23.17
Small bowel	3	76	3.95	1.98
Ampulla Vater	3	76	3.95	1.98
Liver	23	2 081	1.11	15.23
Gall bladder	2	58	3.45	1.32
Pancreas	3	303	0.99	1.98
Colon	35	1 010	3.47	23.17
Rectum	39	1 059	3.68	25.82

From January 1991 to December 2000.

Table 2 Distribution of associated non-GI cancers in patients with MPMs in digestive system

Site	*n* (%)	%
Gynecological cancers	40	45.97
Cervix	31/40 (77.50)	
Endometrium	2/40 (5)	
Ovary	7/40 (17.50)	
Genitourinary cancers	10	11.49
Bladder	5/10 (50)	
Kidney	2/10 (20)	
Prostate	3/10 (30)	
Lung	10	11.49
NPC	5	5.74
Breast	10	11.49
Skin	4	4.59
Thyroid gland	2	2.29
Neuromuscular tumor	2	2.29
Tongue	2	2.29
Gum	1	1.14
Brain	1	1.14

40 cases (45.97%) with gynecological cancers, of which 31 cases (77.5%) were carcinoma of uterine cervix; 10 cases (11.49%) with genitourinary cancer, among which 5 (50%) had bladder cancers and 3 (30%) had prostate cancers.

The most common tumor combination in double primary malignancies (both cancers originating from the digestive tract) was colon and rectum (10 cases), as shown in Tables 5-8.

The most common tumor combination in double primary malignancies (at least one originating from the digestive system) was rectum and cervical cancer (14 cases) and shown in Table 4.

Nine patients had triple cancers (Table 9). Mean time interval between diagnosis of the first and second primary cancer was 7.2±3.86 years and for the second and third cancer was 5.24±3.85 years. Two out of these nine patients had initial squamous cell cancers of cervix and nasopharynx and developed synchronous adenocarcinoma of rectum and colon, with disease intervals of 9.4 and 5.9 years respectively.

Most of the tumors in double or triple primary malignancies were diagnosed at stages 3 or 4. Synchronous cancers were found in 43 cases, while 86 cases had metachronous cancers, among which 13 cases developed secondary cancers more than 10 years after diagnosis of primary malignancies (Tables 3 and 10).

There were no significant differences between the survival and non-survival groups in terms of age, gender, and time interval between first and second primary cancers. However, stage of tumor, especially stages 1-3 and radical treatment regimes correlated with prognosis in these two groups.

Table 3 Distribution of synchronous and metachronous MPMs in digestive system

Site	Synchronous (*n*)	Metachronous (*n*)	
		(1)	(2)
Colon[1]	13	10	19
Stomach[1]	8	3	11
Liver[1]	6	1	7
Esophagus[1]	0	1	1
Others[1]	0	2	1
Double GI	16	30	0
Total	43	47	39

[1]Exclude double GI cases. (1): Primary GI tract cancer, secondary cancers of other sites. (2): Primary cancers of other sites, secondary GI tract cancers.

Table 4 Distribution of MPMs in large intestine: 42 cases[1]

Subgroup	Large intestine	*n*	Non-GI cancers	*n*
(1)	Colon	5	Cervix	1
			Larynx	1
			Lung	1
			Uterus	1
			Left breast	1
	Rectum	5	Ovary	1
			Cervix	2
			Right breast	1
			Bladder	1
(2)	Colon	7	Cervix	2
			Ovary	1
			Thyroid	1
			Right thigh	1
			Bladder	1
			Nose	1
	Rectum	12	Cervix	9
			Right breast	1
			Thyroid	1
			Brain	1
(3)	Colon	7	Cervix	3
			Ovary	4
	Rectum	6	Cervix	3
			Left breast	1
			Lung	2

[1]Excluding double primary GI tract cancers (22 cases). (1): Primary GI tract cancer, secondary cancers of other sites. (2): Primary cancers of other sites, secondary GI tract cancers. (3): Synchronous.

Table 5 Distribution of MPMs in stomach: 22 cases[1]

Subgroup	Stomach	*n*	Non-GI cancers	*n*
(1)	Adenocarcinoma	3	Right breast	2
			NPC	1
(2)	Adenocarcinoma	11	Cervix	4
			Prostate	2
			Bladder	1
			Left kidney	1
			Tongue	1
			Larynx	1
			NPC	1
(3)	Adenocarcinoma	8	NPC	2
			Lung	3
			Prostate	1
			Bladder	1
			Skull	1

[1]Exclude double GI cases (12 cases). (1): Primary GI tract cancer, secondary cancers of other sites. (2): Primary cancers of other sites, secondary GI tract cancers. (3): Synchronous.

Table 6 Distribution of MPMs in liver: 14 cases[1]

Subgroup	Liver	*n*	Non-GI cancers	*n*
(1)	Hepatoma	1	Bladder	1
(2)	Hepatoma	7	Cervix	4
			Right breast	2
			Right leg	1
(3)	Hepatoma	6	Gum	1
			Skull	1
			Right kidney	1
			Lung	3

[1]Exclude double GI cases (10 cases). (1): Primary GI cancer, secondary cancers of other sites. (2): Primary cancers of other sites, secondary GI cancers. (3): Synchronous.

Table 7 Distribution of synchronous double GI MPMs: 16 cases

Site	*n*	Site	*n*
Esophagus	2	Stomach	1
		Gall bladder	1
Stomach	3	Rectum	1
		Gall bladder	1
		Sigmoid colon	1
Duodenum	1	Sigmoid colon	1
Sigmoid colon	3	Appendix	1
		Rectum	2
Rectum	3	Ascending colon	3
Liver	4	Hepatic flexure	1
		Stomach	3

Table 8 Distribution of metachronous double GI MPMs: 30 cases

1st cancer	*n*	2nd cancer	*n*
Esophagus	3	Stomach	1
		Liver	2
Stomach	4	Rectum	1
		Esophagus	1
		Liver	1
		Pancreatic head	1
GIST of ileum	1	Liver	1
Ampulla Vater	2	Liver	2
Appendix	2	Rectum	2
Cecum	2	Stomach	2
Colon	6	Liver	2
		Stomach	1
		Pancreatic head	3
Rectum	10	Stomach	1
		Liver	1
		Transverse colon	5
		Esophagus	3

Table 9 Sites and dates of diagnosis of triple primary cancers (nine cases)

Age (yr)/sex	First primary	Second primary	Third primary
68/Female	3/84 Cervix	6/93 Rectum	6/93 Sigmoid colon
46/Female	9/85 Cervix	8/88 Rectum	8/95 Ascending colon
49/Female	8/84 Ovary	10/86 Cervix	3/90 Rectum
47/Female	8/79 Breast	9/89 Cervix	10/97 Liver
50/Male	6/82 Stomach	5/85 Skin	4/91 Ascending colon
45/Male	8/84 Stomach	3/86 Prostate	1/92 Ascending colon
43/Male	3/89 Nasopharynx	2/95 Sigmoid colon	2/95 Rectum
46/Female	1/84 Larynx	4/88 Sigmoid colon	3/91 Esophagus
58/Female	3/71 Right breast	6/82 Sigmoid colon	6/92 Ascending colon

The age listed is that at the time of diagnosis of the first primary.

Table 10 Demographic and clinical data in survival and non-survival groups[1]

	Survival *n* = 40	Non-survival *n* = 80	*P*
Median age (yr)	61.50±13.60 (29–84)	60.00±14.78 (30–89)	0.46
Gender			
Male	16	39	0.18
Female	24	41	0.18
Time interval (mo)	32.78±27.07	32.98±18.58	0.49
Staging			
Stage 1	14	2	<0.01[b]
Stage 2	19	2	<0.01[b]
Stage 3	6	41	0.04[a]
Stage 4	1	35	0.16
Treatment regimes[2]			
Radical	36	16	<0.01[b]
Palliative	2	36	0.08
Supportive	2	28	0.08

[1]Excluding triple primary cancers nine cases. [2]Radical treatment includes radical surgery±radiotherapy±chemotherapy. Palliative treatment includes palliative surgery±radiotherapy±chemotherapy. [a]$P<0.05$, [b]$P<0.01$ *vs* others.

DISCUSSION

The presence of a single tumor does not offer immunity against the development of second, third, or additional primary malignant lesions in the same patient. Multiple primary malignant tumors in the same individual are experienced more frequently as advances in cancer treatment prolong life. Improved survival rates for patients with neoplastic disease, largely due to early diagnosis, allow more patients to survive long enough to develop subsequent primary tumors.

The incidence of MPMs has been carried out by the review of cancer registries in several countries, and ranged from 0.7 to 11%[7-10]. In our study, the incidence of MPMs was 2.21%, which was similar to the 2.6% as reported by Okamoto *et al*.[11].

In our study, the major site of MPMs in the digestive system was the large intestine, followed by stomach and liver. Cancers of the large intestine, particularly hereditary nonpolyposis colorectal cancers, were associated with increased frequencies of endometrial and ovarian cancers[12]. However, MPMs of large intestine in our study were most commonly associated with carcinoma of cervix (17 cases) and stomach (8 cases), while only two were associated with carcinoma of endometrium and six were with ovarian cancers. The significance of these differences may be due to the fact that carcinoma of cervix is much more common than endometrial cancer in our country. Unfortunately, no genetic evaluation was performed in our patients.

The predilection of MPMs for the large intestine is noted in numerous reports in the literatures[13-15]. In our series, 49 of 129 patients (37.98%) had colorectal malignancy as the first primary lesion. Of these, seven (14.28%) had a second primary cancer in the colon or rectum and four (8.16%) had a second primary cancer in the stomach. The interval between the diagnosis of the first primary colorectal cancer and the development of the second colorectal carcinoma averaged 7 years, and ranged from 1½ to 14 years. This suggests that patients without evidence of disease for 5 years after operation of colorectal cancers still require careful follow-up studies of gastrointestinal tract.

Genitourinary cancers, especially cervical and ovarian cancers, bladder and prostate cancers were the common associated non-GI cancers, followed by cancers of lung and breast. Thus, attention should be paid to these sites during the period of post-operative follow-up of the first primary cancer.

The majority of MPMs may occur as a result of random chance[16]. Nonetheless, different mechanisms have been considered to be involved in MPMs, such as intense exposure to carcinogens, the effects of chemo- and/or radiotherapy and the influence of genetic predisposition.

Both the chemo- and radiotherapy have been shown to be carcinogenic in several reports[17,18]. In our study, 52 patients (40.3%) had received previous radiotherapy or chemotherapy for their first cancer, and the interval between the first and second cancers was 0.5-28 years (mean 8.1 years) and 0.5-5 years (mean 3.2 years) in the 32 patients receiving radiotherapy and the 20 patients receiving chemotherapy respectively. This suggests that radiotherapy and/or chemotherapy may play an important role in the development of MPMs.

The main problem in proving a correlation between antineoplastic therapies and secondary cancer may be

attributable to detection bias rather than to carcinogenic therapy[19]. Beyond an increased zeal in searching, diagnostic agents and methods have improved such that the detection of cancer today is enhanced by improvements in technology, cytogenetics, and surveillance.

Based on a pooled analysis involving 316 relatives of 12 families, Lynch *et al*.[20], have demonstrated a 21.5% incidence of MPMs, a consistent 3% risk for a second primary cancer in each year of survival following the first onset, and a significantly higher 6.9% risk per year for the development of a third primary cancer following the second neoplasm.

In our study, there were no significant differences between the survival and non-survival groups in terms of age, gender, and time intervals between first and second primary cancers. Only stage of tumors, especially stages 1-3, and radical treatment regimes correlated with prognosis in these two groups.

Two important inferences can be obtained from our analysis: (1) the early diagnosis of a second primary lesion may alter survival rate. Hence more intensive surveillance and appropriate cytogenetic and molecular studies should be developed in order to improve strategies to detect MPMs, and (2) multidisciplinary treatment strategies are important to ameliorate quality of life and survival rates in patients with MPMs.

It is fundamental that patients who have been treated for cancers require careful follow-up studies. When symptoms and signs of tumor develop in a patient who has been treated for an initial cancer, they should not be assumed to represent metastases. The possibility of a localized and curable second primary cancer should be considered and evaluated. As advances in cancer therapy bring about a progressively large percentage of long-term survivors, the proportion of patients with subsequent primary lesions will increase. Early diagnosis of these lesions, based on an awareness of the possibility of second and third cancers, and multidisciplinary treatment will substantially increase the survival of these patients.

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