

Incidence and Significance of Multiple Primary Malignant Neoplasms

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To know the three questions about multiple primary cancers: 1) what are the characteristics of persons having multiple primary cancer? 2) Does the presence of a single primary cancer after the susceptibility to multiple primary cancers? 3) Does the location of one multiple primary cancer influence the site of others?, we analysed 121 cases of multiple primary malignant neoplasms registered in Seoul National University Hospital during 8 years from July 1978 to August 1986.

Of 121 cases, double primary malignant neoplasms were 119 cases and triples were 2 cases. The incidence of multiple primary malignant neoplasms was 0.7%.

The metachronous tumor (> 6 months) was found in 70 cases and the median time between the first and the second was 32 months. The most commonly associated tumors were stomach and primary liver carcinoma. Cervix and Lung cancer, Stomach and Rectal cancer, Stomach and Esophagus cancer were also commonly associated.

Key Words: multiple primary neoplasms, incidence, significance.

INTRODUCTION

The phenomenon of multiple primary malignant tumor in one patient simultaneously or metachronously is no more of medical curiosity. As further advances in cancer therapy bring about a progressively larger percentage of long term survivors, the proportion of patients with subsequent primary lesions will increase. But the treatment plan for multiple primary malignant tumors is still not established.

So, it might be hoped that such factors as genetic predisposition, etiology, and pathogenesis, that are obscure in patients with single lesion, may be brought out in bolder relief in patients with multiple cancers.

We analysed 121 cases of multiple primary malignant tumors registered in Seoul National University Hospital during 8 years from July 1978 to August 1986.

MATERIAL AND METHOD

The material for this study was derived from the clinical and pathologic observation of all patients with malignant neoplasms, who were seen out at the Seoul National University Hospital during 8-year period. Cases were included only if a pathologic examination of each lesion had been made. All clinical, surgical and pathological records for each patient were studied and where there was any doubt that one lesion was metastatic from the other, the pathologic material was reexamined. If a reasonable doubt still existed, the case was discarded.

The following criteria established by Warren and Gates are practical and realistic and we applied them in selecting cases for our study.

First, each tumor must present a definite picture of malignancy. This means that such neoplasm as the low grade in-situ carcinoma in an adenomatous polyp would be excluded. Second, each tumor must be distinct. This would exclude so called colliding tumors and carcinosarcomas.

Third, the probability that one lesion is metastatic from the other must be excluded. So that 121 cases were studied by age, sex, temporal relationship, classification and common association.

RESULT

Of 121 cases double primary malignant neoplasms were 119 cases and triples were 2 cases. The incidence of multiple primary malignant tumor was 0.7%. This group was composed of 71 male patients. The median age and range of ages of the patients in this series are presented in table 1. The youngest patient in this series was 24 year old female. The synchronous tumor (less than 6 months) was found in 51 cases and the metachronous tumor (more than 6 months) was found in 70 cases. In the metachronous tumor, the median interval between the first and the second was 30 months with range of from 7 months to 25 years.

The multiple lesions were diagnosed simultaneously in almost half of the patients in this series

and, as can be seen in Fig. 1, the number of patients with interval cancers decreased in a logarithmic fashion with the passage of time after the diagnosis of the initial lesion.

Multiple primary malignant tumors were classified by Moertel's classification. We found multiple cancers of multicentric origin in 14 of the 121 cases (11.6%) we collected and the different tissue or origin in 106 of the 121 cases (87.6%) (Table 2).

The multiple primary malignant neoplasm of multicentric origin was subclassified. The first was same tissue and organ. The second was the common, contiguous tissue, and the third was bilaterally paired organ were all breast cancers in our studies (Table 3)

The most commonly associated tumors were stomach and liver cancer. Cervix and lung cancer, stomach and rectal cancer, stomach and esophagus cancer were also commonly associated (Table 4).

Triple primary malignant neoplasms were 2 cases. The one case was larynx and stomach and lung cancer, the other case was stomach and renal pelvis and bladder cancer.

Table 1. Age at the Diagnosis

	Male (N=71) range (mean)	Female (N=50) range (mean)
Synchronous	38 – 76 (59)	32 – 61 (54)
Metachronous		
First	33 – 72 (53)	27 – 79 (51)
Second	39 – 74 (59)	30 – 80 (55)
Third	55 – 64 (60)	

DISCUSSION

Although a few poorly documented reports of cases of multiple primary malignant neoplasms may be found in the earlier literature, the most clearly documented cases of multiple primary malignant neoplasm were presented by Billroth in the late nineteenth century¹¹. In the early years of this century, patients with multiple cancers were

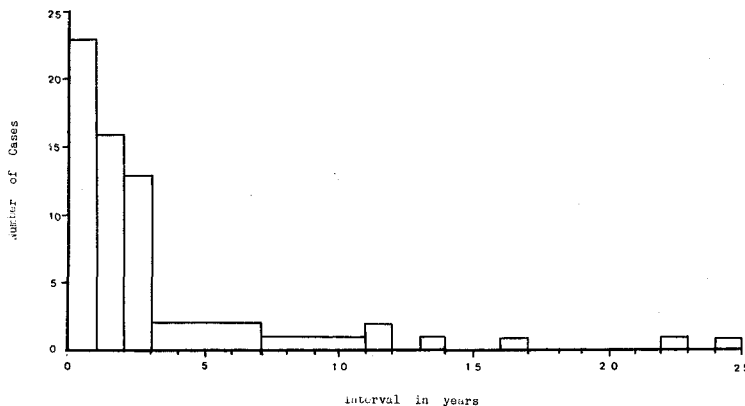


Fig. 1. Time interval in patients with metachronous multiple primary malignant neoplasms.

Table 2. Classification by Moertel

	No. of cases (%)
1. Multicentric origin	14 (11.6%)
a. same tissue and organ	3
b. common contiguous tissue shared by different organs	6
c. bilaterally paired organs	5
2. Different tissue of organ	106 (87.6%)
3. Multicentric origin plus different tissue or organ	1 (0.8%)

Table 3. Multicentric Origin

1. Same tissue and organ	
colon and rectum	3
2. Common, contiguous tissue	
mouth and pharynx	1
pharynx and esophagus	2
larynx and esophagus	2
kidney and bladder	1
3. Bilaterally paired organs	
breast	5

Table 4. Different Tissue or Organ

Stomach & liver	6	Stomach & rectum	6
Stomach & lung	5	Cervix & lung	5
Lung & larynx	5	Stomach & cervix	4
Stomach & esophagus	4	Stomach & larynx	4
Cervix & rectum	4	Cervix & thyroid	4
Stomach & breast	3	Stomach & nasopharynx	3
Stomach & mouth	3	Stomach & bladder	3
Lung & breast	3	Lung & bladder	3

Table 5. Multiple Primary Cancers of Different Tissues or Organs Reported Significant Tumor Associations

Bladder + cervix	Cervix + colorectal	Leukemia + lung
Bladder + colorectal	Cervix + lung	Leukemia + melanoma
Bladder + pharynx	Cervix + oral cavity	Leukemia + skin
Bladder + prostate	Cervix + skin	Leukemia + thyroid
Breast + colorectal	Cervix + thyroid	Lip + lung
Breast + larynx	Colorectal + kidney	Lung + oral cavity
Breast + lymphangiosarcoma	Colorectal + larynx	Lung + pancreas
Breast + osteogenic sarcoma	Colorectal + oral cavity	Lung + salivary gland
Breast + ovaries	Colorectal + ovary	Lymphoma + melanoma
Breast + salivary gland	Colorectal + uterus	Lymphoma + skin
Breast + thyroid	Larynx + lung	Multiple myeloma + stomach
Breast + uterus	Larynx + pancreas	Oral cavity + skin
Lymphoma + sarcoma, kaposi	Ovary + thyroid	Oral cavity + uterus
Ovary + uterus	Pharynx + prostate	Uterus + skin
Pheochromocytoma + thyroid	Prostate + salivary gland	

only infrequently reported. By 1932 Warren and Gates were able to collect 1259 cases from the world literature²⁾. From that date to the present the number of reported cases has increased in an almost exponential fashion.

We have developed some criteria for diagnosis. Billroth did first, but he made them far too rigid, insisting that each tumor have a distinct micro-

scopic morphology and that each give rise to its own metastasis. The criteria later enunciated by Warren and Gates now generally accepted. The criteria seems quite reasonable and we selected the patients by this criteria.

Moertel have developed the classification of patients with multiple primary cancers. Table 2 shows the rather simple but functional classifica-

tion that our study has employed.

The incidence of multiple primary malignant neoplasm has seems to increase. Moertel³⁾ reported 2.8% of all patients with malignant neoplasms. Mersheiner⁴⁾ reported 3.2%.

Using necropsy cases, Warren and his associates^{5,6)} found that 3.7% of all patients with malignant neoplasms seen from 1926 through 1931 had multiple primary lesions, and 6.8% of the patients seen from 1932 through 1943. In Korea, 0.3% was reported by Yonsei university⁷⁾. In our study the incidence of multiple primary malignant neoplasms was 0.7%.

The median interval between the first and second cancer was 32 months with a range of from 7 months to 25 years. Berrett reported 3.2 years, and Cleary reported 7 years⁸⁾. When Slaughter⁹⁾ reviewed the literature in 1944, he found multiple cancer of the same or paired organs in 1018 (54%) of the 1868 cases he collected. In 631 (also 54%) of the 1171 cases in the single series of the Watson¹⁰⁾ the same or paired organ were affected. Almost all authors have agreed that multiple cancers of the same organ of paired organ occur far more frequently than would be expected by chance alone. But in our study multicentric lesions were only 14 cases (11.6%). In our case selection we missed many cases of multicentric lesions. So that the incidence of our report may underestimate the incidence because of incomplete tumor registry and short follow-up period.

All of the tumor combination listed in table 5 have been reported to occur in a significantly greater frequency than chance alone would allow¹⁾.

In our study, the most commonly associated tumors were stomach and primary liver cancer. Some difference were shown in our report from the other reports.

Now it becomes apparent that the presence of a single malignant tumor does not offer immunity against the development of another primary malignant tumor in the same patient and that most cancer patients have excess risk for specific later cancers, depending on the original cancer type and the knowledge of these risk is of true clinical importance. So, careful follow-up study and early diagnosis of those lesions, based on awareness of the possibility of the second cancer, will substantially increase the survival of these patients.

CONCLUSION

We analysed 121 cases of multiple primary malignant tumors registered in Seoul National University Hospital during 8 years from July 1978 to August 1986.

The results were as follow:

- 1) Of 121 cases, double primary malignant neoplasms were 119 cases and triples were 2 cases.
- 2) The incidence of multiple primary malignant tumor was 0.7%.
- 3) Th emetachronous tumor (>6 months) was found in 70 cases and the median time between first and seond was 32 months.
- 4) The most commonly associated tumors were Stomach & Liver, Cervix & Lung, Stomach & Rectal, Stomach & Esophagus were also commonly associated.

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다발성 원발성 악성 종양

—121 예의 임상적 분석—

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한 환자에서 두개 이상의 중복암이 발생하는 경우는 매우 드물게 알려져 왔으나 근래에 들어와 치료법의 발달로 환자의 수명이 연장되고 진단법이 발달되면서 그 보고가 증가되고 또한 관심도 높아지고 있는 상태이다. 따라서 이런 중복암을 가진 환자의 특성을 분석함으로써 발생할 수 있는 2차 3차 암의 조기 발견 및 나아가서는 발암 물질과 유전적 요인 등을 찾아 암의 치료 및 예방에 이용 할 수 있겠다. 이에 1978. 7~1986. 8까지 8년간 서울 대학교 병원에서 중복암으로 진단되어 치료 받은 121예를 대상으로 하여 다음과 같은 결과를 얻었다. 전체 발생율은 0.7%이었으며 이중 2중복암이 119례, 3중복암이 2례 있었다. 동시성은 (6개월 이내) 51례, 속발성은 (6개월 이상) 70례이었으며 속발성의 경우 70%이상에서 3년내에 2차 암이 발생했다. Moertel 분류에 의한 mvlticentriz은 11.6%로 다소 낮은 빈도를 보였으며 다른 장기에 발생한 중복암 중에서는 위암과 간암, 위암과 직장암의 빈도가 가장 높았다.