Hiroshima Journal of Medical Sciences
Vol. 33, No. 3, 447~453, September, 1984
HIJM 33-60



# A Study of Multiple Primary Malignant Neoplasms associated with Lung Cancer*)

Masayuki NISHIKI, Tsuyoshi KATAOKA, Tsuneo OKUMICHI, Motoi YAMANE, Hirofumi NAKATSUKA and Haruo EZAKI

*The Second Department of Surgery, Hiroshima University School of Medicine, 1-2-3, Kasumi, Minami-ku, Hiroshima 734, Japan*

(Received June 23, 1984)

*Key words: Multiple primary molignant neoplasms, Lung cancer*

## ABSTRACT

At the Second Department of Surgery, Hiroshima University School of Medicine, we encountered 11 cases of multiple primary malignant neoplasm involving the lung and other organ. This figure represents 4.2% of 260 cases of lung cancer treated during the 18-year period from 1966 to 1983. The mean age at onset was 7.6 years older than that for all cases of lung cancer; a significant difference was found ($p<0.01$). Men outnumbered women, 1.6:1, without a significant difference. According to histological type, squamous cell carcinoma tended to be more frequent. The 5-year survival rate was lower among patients with multiple primary malignant neoplasm than among those with lung cancer only and a large majority of the former patients died in the early time. Possible predisposing factors for multiple primary malignant neoplasm are the history of smoking, family history of cancer, history of exposure to radioactive substances, radiotherapy, chemotherapy, etc. However, it is not beyond conjecture. The apparent incidence of multiple primary malignant neoplasm involving the lung and other organ is expected to increase in the future as the diagnosis and treatment of cancer are improved and the life spans of cancer patients are prolonged. Moreover, because of its malignancy, lung cancer tends to become the second cancer[4,14], cancer patients should be carefully followed up, with the lungs being included in the scope of observation.

## INTRODUCTION

The cases of multiple primary malignant neoplasm (MPMN) are increasing as the diagnostic and therapeutic techniques for cancer are improved and the survival times of cancer patients are prolonged. In this paper the author discusses the biological characteristics of 63 cases of multiple cancer treated at our department and especially in 11 cases of MPMN involving the lung and other organ together with review of literature.

## MATERIALS AND METHODS

The difinition of MPMN was essentially that of Waren, S. and Gates, O. (1932)[20]. From among the malignant tumor cases treated at our department during the 18-year period from 1966 to 1983, those which could be histopathologically diagnosed and were clinically oviously malignant were selected. However, multiple myeloma, malignant lymphoma and the like were each regarded as a single tumor according to the criteria of Akazaki et al.[1], and the multiple tumors occurring in the same organ such as the gastrointestinal tract, bladder, ureter, breast, etc. were excluded from the standpoint of their being inherently multicentric types of cancer. Included were some cases of multiple primary malignant neoplasm, the diagnosis of which could be established by autopsy. As regards the onset interval of multiple cancer,

*) 西亀正之, 片岡 健, 奥道恒夫, 山根 基, 中塚博文, 江崎治夫：肺と他臓器との重複癌症例の検討

the cases in which a secondary cancer developed within a year from the formation of the primary cancer were classified into the synchronous cancer group and those in which the interval was more than a year were classified into the metachronous cancer group.

## RESULTS

1) *MPMN cases in our department*

The total number of malignant tumor cases treated at our department during the period from 1966 to 1983 was 2,544 cases. Of this total, MPMN cases numbered 63 accounting for 2.5%, as shown in Table 1. The organs involved were colon-rectum in 24 cases, stomach (23), thyroid (16), and so on. The frequency was highest in colon-rectum (7.9%), followed by lung, thyroid, esophagus, ets. Except one case of triple cancer, all the other cases (62) were double cancer. Of the total cases (63),

**Table 1.** Incidence of Multiple Primary Malignant Neoplasms in various sites

| Site | No. Total malignancy | No. MPMN** | Incidence (%) |
|---|---|---|---|
| stomach | 832 | 23 | 2.8 |
| thyroid | 406 | 16 | 3.9 |
| colon | 304 | 24 | 7.9 |
| breast | 272 | 9 | 3.3 |
| lung | 260 | 11 | 4.2 |
| pancreas | 119 | 1 | 0.9 |
| biliary tract | 87 | 1 | 1.1 |
| esophagus | 82 | 3 | 3.7 |
| liver | 42 | 1 | 2.4 |
| others | 140 | 39 | — |
| Total | 2,544 | 127* | 2.5 |

* Double cancer 62 cases
Tripple cancer 1 case
** MPMN; multiple primary malignant neoplasms.

**Table 2-A.** Multiple Primary Malignant Neoplasms associated with Lung Cancer (synchronous)

| case | age | sex | first cancer | | | second cancer | | | interval (months) | prognosis (months) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | site | histology | therapy | site | histology | therapy | | |
| 1 | 57 | M | Lung | sq. c. c. | surg. chem. | Thyroid | foll. a. c. | surg. | 2 | 11 died |
| 2 | 69 | M | Lung | sm. c. c. | rad. | Appendix | pa. tu. a. c. | surg. | 1 | 2 died |
| 3 | 76 | M | Stomach | ad. c. | surg. | Lung | sq. c. c. | — | 2 | 0 died |
| 4 | 73 | M | Lung | sq. c. c. | rad. | Stomach | ad. c. | OK-432 injection | 1 | 6 died |

surg.: surgery chem.: chemotherapy rad.: radiation therapy ad. c.: adenocarcinoma foll. a. c.: follicular adenocarcinoma pa. tu. a c.: papillo-tubular adenocarcinoma sq. c. c.: squamous cell carcinoma sm. c. c.: small cell carcinoma

**Table 2-B.** Multiple Primary Malignant Neoplasms associated with Lung Cancer (metachronous)

| case | age | sex | first cancer | | | second cacer | | | interval (years. months) | prognosis (years. months) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | site | histology | therapy | site | histology | therapy | | |
| 5 | 66 | F | Uterus | sq. c. c. | rad. | Lung | sm. c. c. | chem. | 3. 11 | 3 died |
| 6 | 73 | M | Thyroid | plasma-cytoma | surg. rad. chem. | Lung | sq. c. c. | rad. | 1. 4 | 2 died |
| 7 | 64 | F | Breast | tubular ca. | surg. | Lung | sq. c. c. | surg. chem. | 4. 5 | 4 died |
| 8 | 66 | M | Bladder | tramsitional cell ca. | surg. rad. | Lung | ad. c. | surg. chem. | 5. 0 | 3 died |
| 9 | 74 | M | Sigmoid colon | ad. c. | surg. | Lung | ad. c. | surg. chem. | 7. 8 | 5 died |
| 10 | 67 | M | Stomach | ad. c. | surg. | Lung | ad. c. | surg. | 5. 0 | 1. 7 died |
| 11 | 56 | M | Larynx | sq. c. c. | surg. | Lung | sq. c. c. | surg. | 2. 5 | 1 alive |

24 were of synchronous type, and the sex ratio was nearly even at 31 males versus 32 females.

2) *MPMN cases involving the lung and some other organ*

There were 11 cases of MPMN involving the lung, and their frequency was 4.2% based on 260 cases of lung cancer (Table 2-A, 2-B). Of these 11 cases, 4 were synchronous and 7 metachronous. The mean onset interval between the first and second cancers was 2 years and 9 months. The counterpart organs involved were stomach in 3 cases, colon-rectum and thyroid in 2 cases each, and breast, uterus, bladder and larynx in 1 case each. Among synchronous cases, stomach was involved in 2 cases and colon-rectum and thyroid in 1 case each. There was no metachronous case in which lung cancer was the first cancer. By sex, male patients were predominant, 9 males against 2 females. However, the frequency of onset by sex in a total population of 260 cases of lung cancer (192 male and 68 female cases) was 4.7% for males and 2.9% for females, the former figure being about 1.6 times greater but the difference being not statistically significant. The ages of onset of MPMN are shown in Table 3. MPMN was frequently seen in patients over 50 years of age and there was none among patients up to 49 years (mean age 67.4**±6.6 years). In contrast, the mean age of all lung cancer cases was 59.8**±9.0 years. Thus, there was a tendency that MPMN involving the lung occurs among elderly patients (**$p<0.01$).

According to histological typing, squamous cell carcinoma was most frequent among MPMN cases, followed by adenocarcinoma and small cell carcinoma in that order. In the total population of lung cancer patients, adenocarcinoma and squamous cell carcinoma were predominant and nearly equal in incidence, accounting together for about 87% of the total. In the frequency of MPMN among all lung cancer cases, small cell carcinoma was the most frequent, although no statistical significance was found (Table 4). Fig. 1 shows the prognosis in terms of 5-year survival rate. Except one patient who is still living for about 1 year (Table 2-B, No. 11), the survival rate of MPMN cases was as low as about 50% of that of all lung cancer cases and a large majority of MPMN patients died early (mean survival: ca.

**Table 3.** Age Distribution of Multiple Primary Malignant Neoplasms in Lung Cancer Cases

| Age distribution | No. of total Lung cancer cases | No. of MPMN* cases | Incidence of MPMN (%) |
|---|---|---|---|
| below 39 | 5 | 0 | 0 |
| 40 - 49 | 32 | 0 | 0 |
| 50 - 59 | 83 | 2 | 2.4 |
| 60 - 69 | 103 | 5 | 4.9 |
| over 70 | 37 | 4 | 10.8 |
| total | 260 | 11 | 4.2 |

* MPMN : multiple primary malignant neoplasms

**Table 4.** Incidence of Multiple Primary Malignant Neoplasms; According to Histological Type

| Histological type | No. of Total lung ca. cases | No. of MPMN* cases | Incidence of MPMN (%) |
|---|---|---|---|
| Adeno ca. | 114 | 3 | 2.63[a] |
| Squamous cell ca. | 112 | 6 | 5.36[b] |
| Small cell ca. | 13 | 2 | 15.4 [c] |
| Large cell ca. | 10 | 0 | 0 |
| others | 11 | 0 | 0 |
| total | 260 | 11 | 4.2 |

Not significant difference among a, b & c

*MPMN: multiple primary malignant neoplasms

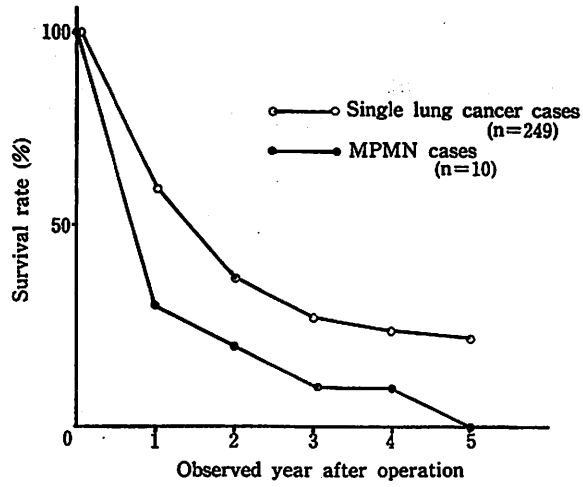


**Fig. 1.** Five years survival rate between single lung cancer cases and MPMN cases

1 year).

As shown in Table 5, a hereditary history of cancer within the third degree of consanguinity was found in 3 of 11 cases or 27.3%. A history of exposure to radioactive substances was observed in 2 cases (18.2%). By blood group (ABO system), all the 4 synchronous cases were of group B and 7 metachronous cases were of group A or O. Three of 7 metachronous MPMN cases had undergone radiaotherapy and/or chemotherapy after onset of the first cancer. As regards the smoking history, all but No. 4 and No. 5 belonged to the high risk group according to Brinkman Index. Of 2 cases of positive tuberculin reaction, No. 7 survived for about 4 year after discovered diagnosis of the second cancer while No. 11 is still showing a favorable clinical course even after 1 year. Four cases in which the absolute number and ratio of lymphocyte decreased were poor in prognosis, too, and all but No. 6 died within 3 months.

## DISCUSSION

1) *The definition and frequency of multiple primary malignant neoplasm*

In regard to the definition of MPMN, there have been many reports[1,2,12,20] since the first proposal of Billroth in 1889[3], but the criteria used most prevalently today are those proposed by Warren, S. and Gates, C. in 1932. Their criteria are as follows.

a) Each of the tumors must present a definite picture of malignancy.

b) Each must be distinct.

c) Probability of one being a metastasis of the other must be excluded.

However, these criteria are not altogether satisfactory. For example, multicentric cancer,

**Table. 5** Immunoepidemiologic study of Multiple Primary Malignant Neoplasms in the Lung

| case | F.H. | atomic bomb exposure | Brinkman index | blood type | therapy for 1st cancer | PPD skin test | Lymphocyte ratio (%) | Lymphocyte number (/mm³) |
|---|---|---|---|---|---|---|---|---|
| 1 | − | (−) | 510 | B | synchronous | (−) | 25 | 3,600 |
| 2 | + | (−) | 500 | B | synchronous | $\frac{0}{12\times13}$ | 21 | 1,490 |
| 3 | + | (−) | 1,000 | B | synchronous | (−) | 9 | 770 |
| 4 | + | (+) | — | B | synchronous | $\frac{0}{0\times0}$ | 23 | 1,800 |
| 5 | − | (−) | — | O | rad. | $\frac{0}{14\times19}$ | 7 | 660 |
| 6 | − | (−) | 500 | A | rad. chem. | $\frac{5\times5}{14\times14}$ | 9 | 410 |
| 7 | − | (−) | 400 | O | (−) | $\frac{12\times10}{46\times27}$ | 35 | 2,660 |
| 8 | − | (−) | 600 | A | rad. | $\frac{0}{13\times15}$ | 5 | 1,660 |
| 9 | − | (+) | 520 | A | (−) | (−) | 41 | 2,380 |
| 10 | − | (−) | 2,000 | O | (−) | $\frac{0}{12\times14}$ | 39 | 2,180 |
| 11 | − | (−) | 720 | A | (−) | $\frac{20\times30}{50\times60}$ | 43 | 2,000 |

F.H.: Family history of cancer

bilateral cancer, occult cancer and latent cancer of thyroid or prostate, carcinoma in situ of cervix of uterus, etc. cannot be classified offhandedly as multiple cancers against these criteria and particularly in regard to c) above, it is quite difficult to show a clear evidence. Among our cases, there was a case of lung cancer, No. 11 in Table 3, which developed 2 years and 5 months after operation for laryngeal cancer and was initially suspected to be a case of metastasis because histologically the two cancers were squamous cell carcinomas. However, in view of the fact that the first cancer was treated by curative operation and the second cancer developed toward the lumen of proximal bronchus in polypoid growth, the case was diagnosed as multiple primary cancer. Thus, all that can be done at the present is to make judgments by reference to clinical auxiliary factors such as the site, histological type and stage of cancer, radical curability of primary cancer, contents of therapy, etc.

The frequency of MPMN varies much from one reporter to another[1,10,17,19-21]. This variation seems to have arisen from the different definitions used, whether the cases were autopsy cases or clinical cases, the particularity of malignant tumors treated by each institution, and different statistical procedures employed. Generally speaking, the frequencies reported in western countries are higher than those reported in Japan but the average frequency of MPMN appears to be about 2 to 3%. The frequency of 2.5% in our department shows within the above range.

Broken down by organ, multiple primary malignant neoplasm in Japan predominantly involves the stomach and intestines[1,18], whereas the skin, hematopoietic system, etc. are often involved in Europe and America[15,21].

2) *Multiple primary malignant neoplasms involving lung cancer*

As shown in Table 6, the frequency of MPMN involving the lung and other organ (or organs) is estimated to be about 3 to 5%[4,11,13,14], which is not so different from the frequency of other MPMN. Our frequency is 4.2%. By sex, the frequency is 4.7% in males and 2.9% in females, being about 1.6 times greater for males. Many reports, however, mention nearly the same frequency for males and females[14,17].

As for the age of onset, many reporters including Baba et al.[2] and Morita[14] point out that the mean age of patients with multiple cancer involving the lung is higher than that of patients with lung cancer alone. Our data are consistent with their findings. This may be partly because lung cancer is generally so malignant that the first cancer of metachronous MPMN is less likely to be one involving the lung[4] and partly because the chemotherapy and radiotherapy for the first cancer tend to prevent or delay the onset of the lung cancer as a second cancer.

In terms of histological typing of multiple cancer, squamous cell carcinoma accounts for a large proportion of lung cancer cases[9,17], and such cases are generally characterized by long clinical courses. Therefore, it is possible that squamous cell carcinoma will continue to appear with a high frequency among MPMN cases involving the lung.

3) *Mechanism of onset of MPMN*

The mechanism of onset of MPMN is as unclear as that of simple cancer. Let us, therefore, ponder about some etiologic factors, mainly of multiple cancer involving the lung.

First, there are reports endorsing the time-honored suspicion that a history of smoking is correlated with the onset of MPMN, especially lung cancer, cancer of urinary bladder, stomach cancer and esophageal cancer[8,22]. In fact, 9 out of our 11 cases belonged to the high risk group. Smoking may be an important factor

**Table 6.** Multiple Primary Malignant Neoplasms in the Lung

| Reporter | year | No. of total lung cancer | No. of MPMN | Incidence (%) |
|---|---|---|---|---|
| Cahan et al.[4] | 1950 | 2,502 | 81 | 3.2 |
| Lee et al.[11] | 1982 | 5,178 | 261 | 5.0 |
| Moertel et al.[13] | 1959 | 1,588 | 95 | 4.1 |
| Morita et al.[14] | 1977 | 409 | 15 | 3.7 |
| Authors | 1984 | 260 | 11 | 4.2 |

for the development of MPMN. Regarding the presence or absence of family history of cancer, Mulvihill et al.[16] suggested that hereditary was involved in the onset of tumors including benign tumors. In this conception, a study from HLA typing has been reported[5]. However, concerning our cases, 3 (27.3%) of 11 patients had a family history of cancer and there was no so difference as compared with the percentage (about 28%) of the general population of malignant tumors. In view of lung cancer, interview of the past history and occupational history is important.

In the present study, 2 of 11 patients had a history of exposure to radioactive substances, suggesting the relation between cancer and radioactivity[18]. Concerning blood group, Fadhli et al.[6] stated that multiple primary cancers frequently occurred in patients with blood group A and less frequently in those with blood group O. However, such a tendency was not found in our cases of MPMN involving the lung. Was it a mere coincidence that 11 the 4 synchronous cases were of blood group B and 7 metachronous cases were of group A or O? There has been no report on this line of research and the above findings are of some interest. In regard to the combination of MPMN, geographic and racial characteristics cannot be neglected since multiple cancer involving the gastrointestinal system is predominant[1,10,14,17].

Moertal et al.[15] pointed out that chemotherapy, radiotherapy and/or surgical therapy might induce the onset of a second cancer. In our cases, 6 of 7 metachronous cases underwent surgery and 3 received radiotherapy and/or chemotherapy after surgery for the first cancer. In the treatment of malignant tumors, each case should be closely followed up with the possible development of a second cancer in mind instead of being obsessed with the risk of relapse, and there may be cases in which through examinations are in order. In the follow-up and prognosis of malignant tumors inclusive of multiple primary cancer, it is also important to take the immunomechanism into consideration[5,7]. While only tuberculin reactions and lymphocyte counts were reported in our study, it appears that even this much of data are correlated with prognosis to some extent.

The central object of elucidating the mechanism of onset of MPMN is to prevent occurence of second and third cancers, and studies involving detailed factor analyses from various aspects of medical science are awaited.

## REFERENCES


1. **Akazaki, K., Wakasa, H. et al.** 1961. Multiple primary malignant neoplasms. (author's transl.) Jap. J. Clinical Med. 19 : 1543-1551. (in Japanese)
2. **Baba, K., Shimosato, Y., Watanabe, S. and Tajima, T.** 1971. Statistics of multiple primary malignant neoplasms and related problems. Jap J. Cancer Clin. 17 : 424-436. (in Japanese)
3. **Billroth, T.** 1879. Cited by Warren, S. and Gates, O. 1932. Multiple primary malignant malignant tumors; A survey of the literature and statistical study. Am J. Cancer 16 : 1358-1414.
4. **Cahan, W. G., Butler, F. S., Watson, W. L. and Pool, J. L.** 1950. Multiple cancers, Primary in the lung and other sites. J. Thoracic Surg. 20 : 335-348.
5. **Dellen, A. L., Chretien, P. B., Potvin, C. and Rogentine, G. N.** 1975. Multiple primary malignant neoplasms; A search for an immunogenetic basis. Arch. Surg 110 : 156-160.
6. **Fadhli, H. A. and Dominguez, R.** 1963. ABO blood groups and multiple cancers. JAMA. 185 : 121-123.
7. **Fujii, T., Nishiki, M., Okumichi, T., Nakatsuka, H., Kurata, H., Ezaki, H. and Nakagawa, K.** 1980. A study on double cancer in the lung and other organs. Jap. J. Chest Diseases 40 : 744-749. (in Japanese)
8. **Fukui, I., Yokokawa, M., Ohwada, F. et al.** 1983 Primary multiple malignant tumors associated with bladder cancer. Jap. J. Cancer Clin 29 : 823-831. (in Japanese)
9. **Hashimoto, T., Kobayashi, T., Furuse, K. et al.** 1976. Multiple primary lung cancers. Jap. J. Cancer Clin. 22 : 1370-1375. (in Japanese)
10. **Kitaba ake, T., Kaneko, M., Kido, C., Chihara, T. and Ushizima, H.** 1960 Investigation on double cancer with case reports and statistic consideration. Jap. J. Cancer Clin. 6 : 337-345. (in Japanese)
11. **Lee, T. K., Myers, R. T., Schary, M. J. and Marshall, R. B.** 1982. Multiple primary malignant tumors (MPMT); Study of 68 autopsy cases (1963-1980). J. Am. Geriatr. Soc. 30 : 744-753.
12. **Moertel, C. G.** 1977 Multiple primary malignant neoplasms; Historical perspectives. Cancer 40 (Suppl.) : 1786-1792.
13. **Moertel, C. G., Andersen, H. A. and Baggenstoss, A. H.** 1959. The coexistence of primary lung cancer and other primary malignant neoplasms. Dis. Chest 35 : 343-347.
14. **Morita, T.** 1977. A clinicopathological study of

multiple malignant tumors with special reference to lung cancer. Jap. J. Cancer Clin. 23 : 1033-1042. (in Japanese)

15. **Moertel, C. G., Dockerty, M. B. and Baggenstoss, A. H.** 1961. Multiple primary malignant neoplasms; I Introduction and presentation of data. Cancer 14 : 221-230.
16. **Mulvihill, J. J. and Mckeen, E. A.** 1977. Discussion; Genetics of multiple primary tumors. Cancer 40 : 1867-1871.
17. **Nakamura, K. and Aizawa, M.** 1972. Investigation on double cancer with special reference to the combination. Jap. J. Cancer Clin. 18 : 662-666. (in Japanese)
18. **Nakatsuka, H., Kuroda, Y., Okumichi, T., Nishiki, M. and Ezaki, H.** 1982. A study on 36 patients with multiple primary malignant neoplasms. Jap. J Clinical Med. 43 : 576-583 (in Japanese)
19. **Tatsumura, T., Shegawa, Y., Nakagawa, M. et al.** 1979. Multiple primary malignant neoplasms. Jap. J. Cancer Clin. 25 : 1126-1130. (in Japanese)
20. **Warren, S. and Gates, O.** 1932. Multiple primary malignant tumors. A survey of the literature and a statistical study. Am. J. Cancer 16 : 1358-1414.
21. **Watson. T. A.** 1953. Incidence of multiple cancer. Cancer 6 : 365-371.
22. **Wynder, E. L., Mushinski, M. H. and Spivak, J. C.** 1977. Tobacco and alcohol consumption in relation of the development of multiple primary cancers. Cancer 40 : 1872-1878.