DOUBLE PRIMARY MALIGNANT NEOPLASMS

By B. C. Tan

SYNOPSIS

A review of reports on multiple primary malignant tumours shows that their incidence varied from 0·5% to 11·7% of all malignancies. One of the factors determining the apparent incidence is the criteria for diagnosis of this condition. 21 cases of double primary malignant tumours which satisfied specified criteria are described. They are grouped into 3 categories:

1. those that involved different tissues and organs;

2. those that affected common tissues shared by different organs; and

3. those that arose as a result of treatment.

The cases are mostly relatively young people, the majority of whom survived more than 5 years after the first treatment. It is expected that multiple primary malignancies will increase in incidence with improvement in treatment results. On the whole, the results of treatment of the second primary were satisfactory and a case is made for greater awareness and radical management of these cases.

INTRODUCTION

The occurrence of two or more primary malignant tumours in a patient was regarded at one time as an uncommon event. Bilroth in 1889 documented several such cases and these were then considered clinical rarities.

However, in recent years multiple primary malignancies have been reported with increasing frequency. Moertel in his study of 37,580 cases of malignant disease from the Mayo Clinic reported multiple primary malignant tumours in 10·6% of autopsy cases and 4·6% of surgical cases (Moertel, 1966). More recently, Berge and his colleagues found 572 cases of multiple primary malignancies out of an autopsy study of 4,895 cases of malignant disease—an incidence of 11·7% (Berge, Cederqvist and Schonebeck, 1969). Berge furthermore commented that the figure in the various studies varied from 0·5% to 11·7%. The incidence depends on:—

(i) whether it is based on clinical or autopsy material;

(ii) whether such lesions as basal celled carcinoma and latent microscopic prostatic carcinoma are included and

(iii) the criteria used to confirm the diagnosis of multiple primary malignancies.

Radiotherapy Department, Outram Road General Hospital, Singapore.

B. C. TAN, M.B., B.S., D.M.R.T., A.M. Senior Radiologist (Therapy).

Criteria for diagnosis of multiple primary malignancies

Warren and Gates proposed the following criteria:—

(i) Each tumour must give a definite picture of malignancy;

(ii) Each must be distinct;

(iii) The probability that one was a metastatic lesion from the other must be excluded (Warren and Gates 1932).

More recently, Werthamer and colleagues in describing a case of quadruple primary malignancy put forward more detailed criteria. He suggested that:—

(i) There must be histological evidence of the primary tumours;

(ii) Paired organ malignancies whether synchronous or metachronous must be considered as one tumour;

(iii) Multiple tumours in the same organ must be considered as a single primary tumour;

(iv) Lower intestinal tract as well as uterus are considered as single organs;

(v) A careful histological attempt to exclude metastases must be made (Werthamer, Jabush and Schulman 1961).

It must be pointed out that Moertel's figures included paired organ malignancies, multiple tumours in the same organ, as well as lesions in the uterus and lower intestinal tract. In the author's experience, however, cases like bilateral carcinomas of the breast are fairly common occurrences and therefore do not warrant inclusion

into such studies. For the same reason, multicentric tumours in a single organ as in the tongue, palate or cheek, found not infrequently in betelnut chewers, need not be included. Accordingly, in the following case reports the criteria of Werthamer has been closely adhered to.

CLINICAL MATERIAL

The 21 cases documented here represent patients who have been personally examined in routine follow-up at the Radiotherapy Department. No statistics of incidence, however, can be given in view of the incomplete follow up of patients. For purposes of discussion, the cases can be divided into 3 main categories:—

(i) Double primaries of different tissues or organs;
(ii) Double primaries of contiguous tissues shared by different organs; and
(iii) Double primaries arising as a result of treatment.

These cases are shown in Tables I, II and III.

COMMENTS

(i) Double primaries of different tissues or organs

There were 14 of these cases, most of whom were successfully treated and remained alive at the time of writing. It is interesting to note that the majority of the first primary growths in these cases were tumours which occurred most commonly and which generally responded well to radiotherapy. Thus, there were 5 cases of carcinoma of the cervix, 4 cases of carcinoma of the nasopharynx and 4 cases of carcinoma of the breast. These types of growth were the commonest tumours treated at the Radiotherapy Department, as can be shown in the following table.

It is worthy of note that there was not a single case of carcinoma of the bronchus occurring as a first primary, although this tumour was seen almost as frequently as carcinoma of the cervix. This is a reflection of the generally poor cure rates obtained with bronchogenic carcinoma, the patient seldom surviving long enough to develop a second primary.

It has been pointed out that malignant disease with a high cure rate and occurring early in life offered the highest possibility of development of a second primary (Clemmesen 1965). The average age of the patients at the time of the first primary in our study is 46·3, the youngest being 34 and the oldest 58. This is similar to the findings of Caselnova who found the average age to be in the 5th decade (Caselnova, McGowan, Kane and McCarron, 1968).

The time interval between the diagnosis of the first primary and the development of the second primary in the present study varied from 15 months to over 14 years and averaged 5·5 years. Moertel gives an average interval of 6·9 years with a range of 6 months to 36 years (Moertel 1966).

It is difficult to speculate as to what are the factors leading to multiple primary cancers of different organs. Moertel after much discussion concludes simply that an individual who has developed 2 or more cancers of different tissues of origin has probably developed a predisposition to malignant disease (Moertel 1966).

Peller's view that a tumour once developed could prevent immunologically the development of further tumours cannot be supported in view of the frequency of multiple primaries seen in the various series (Peller 1941).

(ii) Double primaries of common tissues shared by different organs

All the 5 cases in this group started as tumours around the oral cavity and developed second primaries lower down in the oesophagus. In contrast with the preceding group where the patients were all Chinese, there were 2 Indians in this group. This is not unexpected in view of the prevalence of oral cancers in this race. The average age in this category is 56·2 and the time interval between the first and second primary is 5·1 years.

Multicentric carcinomas developing in the contiguous mucosa of the alimentary tract in association with oral cancers is quite well documented (Videbaek 1944). This can probably be attributed to exposure to a common carcinogen.

(iii) Double primaries arising as a result of treatment

2 cases are shown in this group. One is a case of osteosarcoma of the mandible which developed 8 years after successful radiation therapy of a carcinoma of the nasopharynx. The mandible which was included in the radiation field received about 4,000 rads from deep X-ray therapy and the development of osteosarcoma after a period of 8 years is most probably radiation induced. The patient succumbed to the osteosarcoma with no evidence of recurrence of the first primary.

The other case is a carcinoma of the breast with lymphoedema of the right arm arising as a result of radical mastectomy followed by post operative radiation. A skin nodule 1·5 cm. in diameter, which proved on biopsy to be an angiosarcoma, developed in the right upper arm 7

TABLE I

DOUBLE PRIMARIES OF DIFFERENT TISSUES OR ORGANS

Case	Sex/ Age	Race	First Primary and Histology	Date Diagnosed	Treatment	Second Primary and Histology	Date Diagnosed	Treatment	Result	Last Follow-up
1. T. G. K.	F/34	Chinese	Nasopharyngeal Carcinoma "Lymphoepithelioma"	5.10.*54*	Deep X-ray Therapy	Carcinoma right breast "Carcinoma"	12.12.*68*	Simple Mastectomy + Deep X-ray Therapy	Alive & Well	26.6.73
2. T. F. M.	F/46	Chinese	Carcinoma left breast "Carcinoma"	17.6.*53*	Left Radical Mastectomy + Deep X-ray Therapy	Carcinoma Ovary	5.9.*63*	Total Hysterectomy Bilateral Salpingo-Oophorectomy + Deep X-ray Therapy	Alive & Well	30.6.73
3. T. S. S.	F/41	Chinese	Carcinoma left breast "Carcinoma"	30.7.*53*	Left Radical Mastectomy + Deep X-ray Therapy	1. Carcinoma right breast 2. Carcinoma Thyroid "Papillary Carcinoma"	26.7.*63*	1. Right Simple Mastectomy + Deep X-ray Therapy 2. Hemithyroidectomy + Thyroxine	Alive & Well	6.6.73
4. S. H. T.	M/45	Chinese	Nasopharyngeal Carcinoma "Anaplastic Carcinoma"	28.2.*61*	Deep X-ray Therapy	Carcinoma Colon "Well differentiated adenocarcinoma"	3.6.*70*	Right Hemicolectomy	Hepatic metastases	21.12.72
5. L. O. C.	F/40	Chinese	Carcinoma Cervix (Stage I) "Moderately to poorly differentiated squamous celled carcinoma"	26.4.*63*	Radium Insertion	Carcinoma left breast "Adenocarcinoma"	29.4.*70*	Radical Mastectomy + Cobalt Irradiation	Alive & Well	3.1.73
6. Y. Y. K.	F/56	Chinese	Carcinoma of Cervix "Poorly differentiated squamous celled carcinoma"	27.12.*63*	Radium Insertion + Deep X-ray Therapy	Carcinoma left breast "Scirrhous Carcinoma"	18.10.*67*	Left Radical Mastectomy + Deep X-ray Therapy	Alive & Well	26.6.73
7. Y. A. C.	F/43	Chinese	Carcinoma of Cervix "Well differentiated adenocarcinoma"	26.1.*66*	Radium Insertion + Deep X-ray Therapy	Nasopharyngeal Carcinoma "Anaplastic Carcinoma"	19.9.*67*	Deep X-ray Therapy	Alive & Well	18.7.73
8. L. S. L.	F/40	Chinese	Nasopharyngeal Carcinoma "Undifferentiated Carcinoma"	23.8.*66*	Deep X-ray Therapy	Carcinoma Cervix (Stage II) Moderately differentiated squamous celled carcinoma"	19.3.*69*	Radium Insertion + Cobalt Irradiation	Alive & Well	17.7.73
9. C. M. T.	F/41	Chinese	Carcinoma of Thyroid "Papillary Carcinoma"	23.9.*66*	Total Thyroidectomy + Thyroxine	Nasopharyngeal Carcinoma "Poorly differentiated carcinoma"	4.8.*71*	Cobalt Irradiation	Alive & Well	20.6.73

10. C. N. Y.	F/49	Chinese	Carcinoma of Cervix "Poorly differentiated adenocarcinoma"	27.7.*68*	Radium Insertion + Wertheim's Hysterectomy	Carcinoma of Bronchus "Primary carcinoma of bronchus"	27.11.*69*	Right lower lobectomy	Lost to follow-up	9.12.69
11. N. M.	F/52	Chinese	Carcinoma of right breast "Carcinoma"	15.1.*69*	Simple Mastectomy + Deep X-ray Therapy	Carcinoma of nasal septum "Squamous celled carcinoma"	8.4.*71*	Surgery + Cs^{137} Irradiation	Alive with tumour	28.7.73
12. K. N. Y.	F/58	Chinese	Carcinoma of right breast "Intraduct carcinoma"	19.8.*70*	Simple Mastectomy + Cobalt irradiation	Carcinoma of Cervix "Squamous celled carcinoma"	9.12.*72*	Patient absconded from treatment	Alive with tumour	6.1.73
13. K. S. C.	F/55	Chinese	Carcinoma of Cervix "Poorly differentiated squamous celled carcinoma"	20.12.*71*	Radium Insertion + Cobalt Therapy	Carcinoma of breast "Carcinoma Simplex"	13.3.*73*	Cobalt Irradiation	Alive & Well	13.6.73
14. Y. S. Y.	F/38	Chinese	Nasopharyngeal Carcinoma "Undifferentiated Carcinoma"	11.3.*70*	Cobalt Therapy	Carcinoma of Ovary "Mucinous cystadeno carcinoma"	27.4.*73*	Total Hysterectomy + Bilateral Salpingo-Oophorectomy + Cobalt Therapy	Alive & Well	20.9.73

TABLE II

DOUBLE PRIMARIES OF CONTIGUOUS TISSUES SHARED BY DIFFERENT ORGANS

Case	Sex/ Age	Race	First Primary and Histology	Date Diag-nosed	Treatment	Second Primary and Histology	Date Diag-nosed	Treatment	Result	Last Follow-up
1. S.I.	M/62	Indian	Carcinoma posterior 1/3 of Tongue "Poorly differentiated squamous celled carcinoma"	28.4.*59*	Deep X-ray Therapy	Post Cricoid Carcinoma "Well differentiated squamous celled carcinoma"	2.8.*72*	Cobalt Therapy	Alive & Well	17.7.73
2. S.M.	M/53	Indian	Carcinoma left Tonsil "Moderately differentiated squamous celled carcinoma"	10.10.*63*	Deep X-ray Therapy	Carcinoma mid-oesophagus "Moderately differentiated squamous celled carcinoma"	26.5.*66*	Deep X-ray Therapy	Lost to follow-up	1.12.66
3. S.C.B.	M/52	Chinese	Carcinoma of Tongue "Moderately differentiated squamous celled carcinoma"	1.12.*66*	Radium Implant	Carcinoma cervical oesophagus	16.11.*70*	Cobalt Irradiation	Lost to follow-up	4.1.71
4. O.A.B.	M/65	Chinese	Carcinoma of alveolus "Well differentiated squamous celled carcinoma"	10.1.*67*	Deep X-ray Therapy	Carcinoma lower oesophagus "Poorly differentiated squamous celled carcinoma"	2.6.*73*	Cobalt Irradiation	Died	5.7.73
5. C.H.K.	M/52	Chinese	Carcinoma of Tongue "Squamous celled carcinoma"	April *72*	Deep X-ray Therapy + Bleomycin	Carcinoma mid-oesophagus	18.9.*72*	Cobalt Irradiation	Alive with tumour	10.7.73

TABLE III

DOUBLE PRIMARIES ARISING AFTER TREATMENT OF FIRST PRIMARY

Case	Sex/ Age	Race	First Primary and Histology	Date Diag-nosed	Treatment	Second Primary and Histology	Date Diag-nosed	Treatment	Result	Last Follow-up
1. T.M.H.	M/49	Chinese	Carcinoma of Nasopharynx "Undifferentiated carcinoma"	13.6.*63*	Deep X-ray Therapy	Osteogenic Sarcoma of left mandible	10.6.*71*	Cobalt Irradiation + Cyclophosphamide	Died	20.7.72
2. H.P.L.	F/59	Chinese	Carcinoma of right breast "Lobular carcinoma of breast"	12.1.*66*	Radical Mastectomy + Deep X-ray Therapy	Angiosarcoma of right arm	22.2.*72*	Cs. 137 Irradiation Cyclophosphamide	Alive & Well	3.5.73

TABLE IV

Commonest Malignant Tumours treated at the Radiotherapy Department in the year 1972

1. Nasopharyngeal carcinoma	195 cases
2. Carcinoma of the Breast	160 cases
3. Carcinoma of the Cervix Uteri	154 cases
4. Carcinoma of the Bronchus	152 cases

years after treatment. The association of this type of tumour with chronic lymphatic obstruction described as the Stewart-Treves syndrome has been reported not infrequently in the literature (Chu and Treves 1963). The patient described above was treated with further irradiation and cyclophosphamide therapy, and remained well with no evidence of recurrence.

CONCLUSION

From the above study it would appear that the occurrence of double or multiple primary malignancies of different organs is largely a matter of coincidence, involving mainly the most commonly encountered tumours. Its frequency is dependent on the age at first diagnosis and the length of survival after the treatment of the original tumour. Most of the cases in this series occurred in relatively young patients who have survived well over 5 years after the first treatment. For this reason, as our treatment results improve, we could expect an increasing incidence of multiple primary malignancies.

The apparent incidence would also be expected to increase as we develop a greater awareness of this condition leading to better diagnosis. There is no reliable clinical means of distinguishing a second primary from a metastasis and diagnosis must be made by exploration and biopsy. It is important, therefore, when dealing with a relatively healthy patient who develops a second tumour after treatment of the first, not to assume that the latter is a metastasis, but rather to explore the possibility of this being a second, potentially curable, primary. It has been shown that in 70% of clinically evident multiple primary malignancies, the second tumour was the cause of death and in 71%, no evidence of the first primary was found at autopsy (Thoma 1964). Accordingly, emphasis must be placed on early diagnosis and radical management of the second primary.

With regard to tumours around the oral cavity, a search for further primary growths lower down the alimentary tract may prove of value; and there may be a place here for periodic radiological and endoscopic examinations.

Finally, it is worthy of note that therapeutic procedures in the management of the first primary lesion may themselves exert a carcinogenic influence. It is imperative, therefore that the cancer patient should be under continuous surveillance to the end of his life even if he is apparently "cured".

ACKNOWLEDGEMENT

I wish to thank Dr. K. B. Chia, Head, Radiotherapy Department for his encouragement and permission to publish this paper.

REFERENCES

1. Berge, T., Cederqvist, L. and Schonebeck, J.: "Multiple primary malignant tumours, an autopsy study of a circumscribed population". Acta path. microbiol. Scand., 76, 171—183, 1969.
2. Caselnova, D. A., McGowan, L., Kane, W. M. and McCarron, D. J.: "Multiple Primary Cancer—Report of a patient with four primary malignant neoplasms." Obs. and Gyn., 32, 826—833, 1968.
3. Chu, F. C. H. and Treves, N.: "Value of radiation therapy in post-mastectomy lymphangiosarcoma." Am. J. Roentgen, 89, 64—70, 1963.
4. Clemmesen, J.: "Statistical studies in the aetiology of malignant neoplasms." Acta path. microbiol. Scand., suppl., 174, 1965.
5. Moertel, C. G.: "Multiple Primary Malignant Neoplasms—their incidence and significance—Recent Results in Cancer Research, Springer—Verlag, Berlin, Heidelberg, New York, 1966.
6. Peller, S.: "Metachronous multiple malignancy in 5,876 patients." Am. J. of Hyg., 34, 1—11,1941.
7. Thoma, G. W.: "The incidence and significance of multiple primary malignant tumours, a study of 2,346 necropsies from a cancer research hospital." Am. J. Med. Sci., 247, 427—430, 1964.
8. Videbaek, A.: "Solitary and multiple carcinomas of upper alimentary tract, their location, age and sex incidence and correlation with Plummer—Vinson Syndrome." Acta Radiol. (Stockh.), 25, 339—350, 1944.
9. Warren, S. and Gates, O.: "Multiple primary malignant tumours: a survey of the literature and a statistical study." Am. J. Cancer, 16, 1358—1414, 1932.
10. Werthamer, S., Jabush, M. and Schulman, J.: "Multiple primary malignancies". J.A.M.A., 175, 558—562, 1961.