Metastatic Carcinomas from Occult Primary Tumors

A Study of 254 Patients

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From 1950 to 1973, 254 patients with metastatic cancers from occult primary tumors, comprising 0.5% of all the referred cancer patients were seen. The average age was 59 years. Clinical presentation was commonly in the form of metastatic lesions in lung, cervical lymph node, bone or liver. Radiological and radioisotopic investigations proved helpful in determining the extent of disease rather than the origin of primary tumor. Adenocarcinoma was the commonest type, followed by undifferentiated and squamous cell carcinomas. The origin of the primary tumor was established in 77 (30%) patients, mostly at autopsy. It was in the lung in 40% of the cases, followed by stomach, pancreas, kidney, ovary and colon. Some correlation was found between clinical presentation and the origin of the primary tumor. Histologically different second cancers were detected in 28 (11%) patients. Overall median and five-year survival rates were nine months and nine per cent respectively. Longer survival was seen in patients with squamous cell carcinoma metastases, middle and upper neck lymph node lesions, and those who had "curative" surgery. In localized metastatic lesions, surgical extirpation should be done. Depending on the histological type of the metastatic lesions, chemotherapy and/or radiation therapy have definite roles in the management of these patients. Periodic follow-up examinations also prove valuable.

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IN SURGICAL PRACTICE, patients with a metastatic cancer in the lymph node, peritoneum, liver, lung or bone from an occult primary lesion, are more common than expected. Specifically, three to four per cent of all cancers present with a metastatic lesion from an occult primary tumor.[3,6,11] The surgeon has not only to make a meticulous search for elusive primary tumors, but is also faced with the management of the overt lesion.

Very few studies have been reported in surgical literature on this problem, and most deal with lymph node metastases in the neck.[1,4,7,10] The purpose of this paper is to report on clinicopathologic findings, management, and survival of 254 patients with metastatic cancers from occult primary tumors seen at Roswell Park Memorial Institute in the last 24 years.

Materials and Methods

Between 1950 and 1973, a total of 54,502 new patients with different malignant neoplasms were referred to Roswell Park Memorial Institute. Of these, 404 patients had metastatic cancer from an occult primary tumor, in 150 cases the primary tumor was located during the diagnostic examinations at first admission. The remaining 254 patients, the subjects of this study, were treated for histologically proven metastatic cancer from an unknown primary site.

In the study group, there were 136 males (53.5%) and 118 females (46.5%); 245 Caucasians (96.5%) and nine Negroes (3.5%). The last ratio reflects on patient population at the Institute rather than the incidence in the two races. The age ranged from five to 85 years with a mean age of 57.7 years; but it should be noted that only 7.5% of these patients were below 40 and 3.9% were above 80 years of age (Fig. 1).

Over one-third of the patients were initially admitted to a general surgical service and nearly one-fourth to head and neck service. The distribution of the patients according to the service, at the time of admission, is seen in Figure 2. Only 13% of the patients were admitted to a medical service.

It was interesting to note that the hospital stay of the patients ranged from one to 300 days with a median value of 25 days. In contrast, it was 15 days for the patients with known primary tumors.

The median time interval from the onset of the symp-

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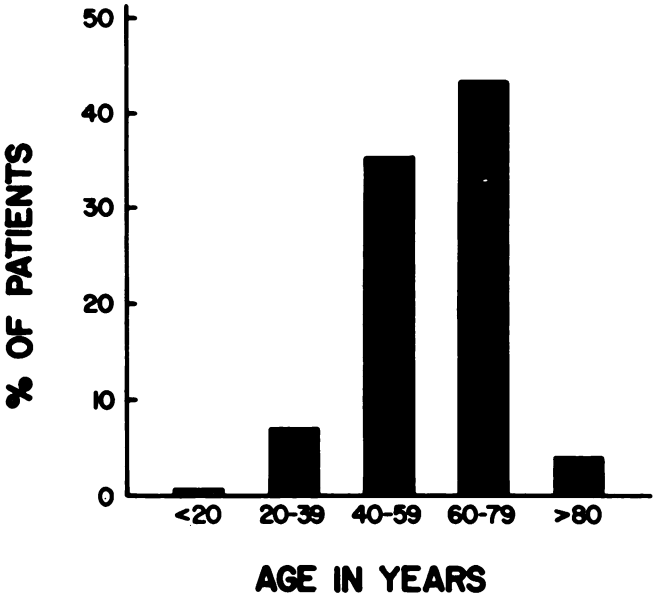

FIG. 1. Age distribution of 254 patients with metastatic cancers from an occult primary tumor.

toms to the histological diagnosis was four and one-half months. Frequently, the patients had multiple presenting symptoms and signs. The most common clinical presentations were in the form of pulmonary or pleural metastases, enlarged cervical lymph nodes, and weight loss, as it could be seen in Table 1.

To detect the site of the primary tumor, multiple radiological and radioisotopic studies were performed. However, these studies proved helpful for determining the extent of the disease, rather than the site of primary tumor. Table 2 shows the results of these studies. It is interesting to note that chest and skeletal roentgenologic examination showed lesions in 43% of the cases. Liver, bone, and brain scans showed lesions in 40% of the cases. In contrast, the thyroid scan whenever done, did not show any lesions.

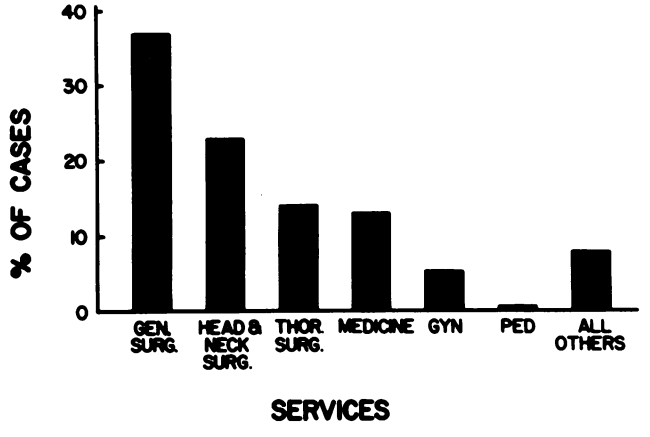

FIG. 2. Distribution of 254 cases according to the service, of initial admission.

TABLE 1. *Clinical Presentation*

Presenting Signs and Symptoms*	No. of Patients	Per cent
Pulmonary of Pleural Metastasis	99	39.0
Cervical Lymph Node Enlargement	92	36.2
Weight Loss	89	35.0
Osseous Metastases	53	20.9
Axillary/Groin Lymph Node Enlargement	33	13.0
Hepatic Metastases	31	12.2
Abdominal Mass/Ascites	29	11.4
Subcutaneous and Soft Tissue Metastases	29	11.4
Anemia	10	3.9
Jaundice	9	3.5
Pyrexia	3	1.2
Others	58	22.8

* Frequently multiple signs and symptoms were present.

Specimens for cytological examination from different sites were obtained. Malignant cells were identified in 105 (41.3%) cases and were suspected in 15 (3.7%). The cytological examination of pleural effusion and ascites, showed malignant cells in four out of five occasions and sputum in one out of three occasions (Table 2). The cytological examination identified adenocarcinoma in 50 instances, squamous cell carcinoma in seven, undifferentiated carcinoma in eight and in 19 instances, it was impossible to specify the cell type.

The histological diagnosis was made by biopsy materials in the majority of patients, frequently multiple biopsies were necessary to establish the diagnosis. The frequency distribution of the histological type of cancer is given in Table 3. Again, adenocarcinoma and undifferentiated carcinomas were the most commonly encountered.

Results

The diagnosis of the primary tumor, could be established in only 77 patients (30.3%), most often at autopsy. Autopsies were performed on 97 patients, and the primary tumor could be identified in 71 or 73%. Six primary tumors were diagnosed by laparotomy, repeated endoscopy, and biopsy of oropharynx and urinary bladder.

The distribution of the sites of the primary tumors is given in Table 4. The most common origin of the primary tumor was in lung in 40% of the patients, followed by pancreas, stomach, kidney, colon, ovary, or other organs; and lymphoma in three. Although no definite correlation was found between initial clinical presentation and the origin of the tumor, some trends emerged. Metastases in the lower cervical lymph nodes were commonly from cancer of the lung (10/31), stomach (3/5), pancreas (2/5), kidney (3/4) and

TABLE 2. *Methods of Investigation*

Type of Exam	No. Tested	No. Positive for Malignant Lesions	Suspicious
Radiological			
Chest	253	108 (42.7%)	
Skeletal	143	61 (42.6%)	
I.V.P.	173	15 (8.7%)	
Barium Enema	179	11 (6.1%)	
Upper G.I.	204	20 (9.8%)	
Mammogram	45	6 (13.3%)	
Plain Film, Sinuses	53	3 (5.6%)	
Cholangiogram	45	2 (4.4%)	
Angiogram	32	10 (31.2%)	
Radioisotopic Scans			
Liver	100	35 (35.0%)	
Pancreas	47	10 (21.3%)	
Thyroid	51	0 (0%)	
Renal	20	4 (20.0%)	
Bone	9	7 (77.8%)	
Brain	17	8 (47.0%)	
Lung	14	5 (35.7%)	
Cytological			
Sputum/Bronchial	164	55 (35.5%)	12
Ascites	18	13 (72.0%)	—
Pleural Effusion	23	21 (91.3%)	—
Gastric Wash	17	1 (5.8%)	1
Vaginal	83	12 (14.5%)	1
Urine	40	3 (7.5%)	1

lymphoma (2/3). Similarly, osseous metastases were common from cancer of the lung (12/31), stomach (2/5), kidney (1/4), lymphoma (1/3) and adrenal (1/3).

Intra-abdominal mass was an uncommon presentation in this group of patients. Only five out of 77 patients with a known malignancy, presented with abdominal mass; the primary tumor was in the colon in two and the others occurred in the lung, pancreas and the remaining patient had lymphoma.

Pyrexia was noted in lymphoma patients. Weight loss did not indicate the origin of the tumor. Metastatic lung lesions were commonly from ipsilateral or contralateral lung and stomach cancers. Similarly, pleural effusion was from primary tumors in lung, stomach, and ovary.

Treatment

Fifty (20%) patients had surgery with the intent of palliation or "cure." Radiation therapy was given to 84 (33.6%) patients, while chemotherapy was administered to 130 (52%) patients.

Although multi-modality therapy was used in many patients, for three groups the main treatment was extirpative surgery, radiation therapy, or chemotherapy. The survival of these patients according to the treatment, is given in Figure 3.

The extirpative surgery was commonly a radical neck or axillary dissection, and in some patients a wide excision of the soft tissue metastasis. Radiation therapy was used primarily for bone metastases, ascites or to the neck and nasopharynx.

Common chemotherapy drugs used singly or in combination were: 5-Flurouracil, Cytoxan, Vincristine, Methotrexate, and Nitrogen Mustard.

TABLE 3. *Histological Types of the Metastatic Cancers from Occult Primary Tumors*

Histological Type	Number	Per cent
Squamous Cell Carcinoma	37	14.5
Adenocarcinoma (including 12 mucin-producing and 7 papillary carcinomas)	103	40.5
Undifferentiated Carcinoma	85	33.5
Sarcoma	1	0.4
Undetermined and other types	28	11.1
TOTAL	254	100.0

Survival

The overall survival period ranged from one month to 215 months, with a median value of nine months. The five-year survival rate was nine per cent, while the three-year and two-year survival rates were 11% and 15% respectively. Eighteen patients were alive (7%). Of the patients who died, 93% died from the tumor, while seven per cent died from other causes. Interestingly, half the patients (nine) in the latter group did not have any disease present at the time of death.

Three factors played a major role in the significantly longer survival; these included initial clinical presentation, the histological type of cancer, and the type of therapy (Tables 5 and 6).

According to the clinical presentation, patients with high and mid cervical lymph node metastases had the

TABLE 4. *Origin of the Primary Tumor*

Organ	No. of Patients	Per cent
Lung	31	40.3
Pancreas	5	6.5
Stomach	5	6.5
Kidney	4	5.2
Colon	3	3.9
Ovary	3	3.9
Lymphoma	3	3.9
Liver	2	2.6
Uterus	2	2.6
Appendix	2	2.6
Adrenal	2	2.6
Oropharynx	1	1.3
Urinary Bladder	1	1.3
Others	13	16.8
TOTAL	77	100.0

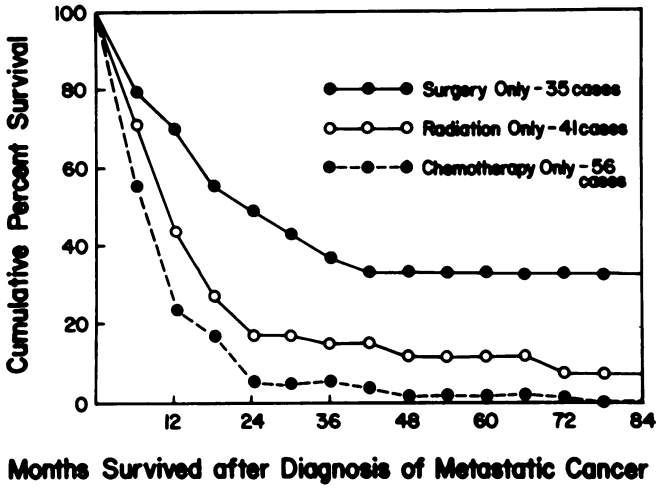

FIG. 3. Survival according to the type of treatment. Note the disease was localized in surgery group while disseminated in chemotherapy group.

highest median survival when compared to those with other presentations or those with supraclavicular lymph node metastases. No statistically significant difference in survival, was found among patients with other clinical presentations.

Median survival of patients with squamous cell carcinoma was longer (13.5 months) as compared to those with adenocarcinoma (six months) or undifferentiated (7.7 months) carcinoma (Table 4).

Patients who had "curative" or palliative surgery had the longest survival time, followed by those who received radiation therapy, and chemotherapy respectively (Fig. 3).

A variety of synchronous or metachronous second primary malignant tumors, histologically different from the first metastatic tumor (with an occult primary), were encountered in 28 instances (11%). These were squamous cell carcinoma of the head and neck seen in eight instances, basal cell carcinoma in six, breast carcinoma in three and lymphoma in two. The

TABLE 5. *Survival Data (by Life Table Analysis) According to the Site and Histological Type of Metastases*

Site of Metastases	No. of Patients	Median (mo)	5 Yr. Per cent
High & Mid-Neck Lymph Nodes	39	21	28 ($p < 0.001$)
Low Neck ± High or Mid-Neck Lymph Nodes	53	7	8.3
All Others	166	5–7	8
Histological Type			
Squamous	37	13.7	13.5 ($p < 0.001$)
Adenocarcinoma	103	6	5
Undifferentiated	85	7.7	9.4
Undetermined and Others	29	7	—

TABLE 6. *Survival Data (by Life Table Analysis) According to the Type of Therapy*

	No. of Patients	Median (mo)	5 Yr. Per cent
Surgery			
"Curative"/ Extirpative	35 (13.7%)	23	33.5 ($p < 0.001$)
Palliative	15 (6%)	7	0
Diagnostic Biopsies	204 (80.3%)	7	12.5
Radiation Therapy			
Complete Response	13 (15.5%)	24	20.8 ($p < 0.001$)
Partial Response	11 (13%)		
Static Disease	7 (8.4%)		
Progression of Disease	45 (53.6%)	8	6.5
Unknown	8 (9.5%)		
Chemotherapy			
Complete Response	4 (3.1%)	24	12.5
Partial Response	4 (3.1%)		
Static Disease	13 (10%)		
Progression	99 (76.2%)	6	0
Unknown	10 (7.7%)		

remaining cases were cancers of the ovary, kidney, stomach, pancreas, colon, rectum, urinary bladder, malignant melanoma, and multiple myeloma.

Discussion

Metastatic cancer from an occult primary tumor is of interest to surgeons, because the majority of the patients (60%) with this problem, were admitted to either general or head and neck surgical service; while only about 15% were admitted to medicine and pediatric services.

Metastatic cancer from an occult primary tumor, is not an uncommon problem. It has been reported that three to four per cent of all the cancer patients present with this problem.[3,6]

The incidence at our Institute is comparatively very low (0.5%) because the majority of patients are referred for a known cancer, many of which are advanced; in fact, at a stage when some occult primary tumors become overt. In addition, in one-third of the patients that are referred for an occult primary tumor, the diagnosis, was established at admission.

In this series of 254 patients, a slight male predominance was seen and the average age of the patient was 57 years. The majority of the patients were from 40 to 70 years of age. This corresponds to the series reported by Moertel and colleagues.[8]

The ratio of 9.6 to 0.4, white to black patients, refers to the ratio of the patients in our Institute patient population and does not indicate the actual incidence in two races.

The average hospital stay (25 days) of these patients was much longer than those with a known primary

tumor (15 days). This factor is significant with increasing cost of hospitalization. Roughly half the hospital stay was utilized for detecting the elusive primary tumor.

The patients had multiple presenting symptoms, but commonly, the clinical presentation was in the form of an enlargement of cervical, axillary or groin lymph nodes, pulmonary or pleural metastases, osseous and hepatic metastases. It was of interest to note pyrexa as a presenting symptom in three patients. It should be emphasized that painless soft tissue mass, jaundice, or anemia should be viewed with suspicion and warrents complete investigations to rule out an occult malignancy.

The symptoms from metastatic lesions were present for four to five months prior to the diagnosis of a metastatic cancer. The occult primary tumor did not cause any symptoms. This fact is well-known in cancers of the lung, kidney, pancreas, stomach, colon, and prostate.

An extensive radiological and radioisotopic work-up is necessary for detecting the primary tumor. It also determines the extent of the disease, because more than half the patients had multiple organ involvement. This is well illustrated in this series; half the patients had lesions in lung and other organs. Skeletal survey and liver scan whenever done, revealed metastatic lesions in 42 and 35% of the cases respectively.

It should be emphasized that cytologic examination of samples from sputum, pleural effusion, and ascitic fluid is extremely valuable to determine the cell type; this gives an additional lead for detecting the occult primary. In a few cases, this may be the only sample to identify the malignancy.

There was no case of primary tumor in the breast. Probably the availability of mammograms and easy accessibility to clinician exam decreases the chance of a primary tumor in the breast being missed.

Histologically, adenocarcinoma was the most common type, followed by undifferentiated carcinoma, and squamous cell carcinoma. This ratio corresponds to the series reported by Johnson, Holmes and their colleagues.

The diagnosis of the primary tumor was established in 77 patients (30%), mostly at autopsy. No definite correlation was found between the clinical presentation and the site of the primary tumor, but some trends were observed. Often, patients with lung carcinoma had multiple lung lesions, metastases in lower cervical lymph nodes, and bone. Some patients had axillary lymph node and soft tissue metastases. Patients with gastric and pancreatic carcinoma had weight loss, supraclavicular lymph node enlargement, and lung or liver metastases. Similarly, weight loss, ascites, and pleural effusion was the clinical presentation of patients with ovarian carcinoma. Patients with renal cell carcinoma had metastases in bone and cervical lymph nodes.

Final diagnosis of an occult tumor could not be established in 70% of the patients. Similar figures had been reported by Moertel in his series of 132 patients with adenocarcinoma.[8] Even at autopsy, the primary tumor was not found in 27% of the cases. It appears that the primary is presumably too small to be detected by our present means of clinical investigations or autopsy. The spontaneous regression of cancer could explain another possibility. As suggested by Everson and Cole,[2] the host immunologic defense mechanism might destroy a small primary tumor, but fail to destroy an established secondary tumor deposit.

It is a common observation that if the tumor is small in size, *i.e.*, T_0 or T_1, it has the least chance of regional or distant metastatic spread. However, from our observations on this group with the primary tumor too small to detect, widespread metastases were apparent. Thus, it appears that metastatic potential of the cancer does not depend on the size of the primary tumor, and the early metastatic lesions could further metastasize to other organs. Roth and his colleagues[9] have indicated that the metastatic potential of the cell from metastasis, does not differ from the cells of the primary tumor. This could explain the widespread metastases even if the primary tumor had definitely disappeared.

Twenty-eight patients (11%) had histologically different, second malignant tumor. Hence, these patients need periodic check-ups so that at least the second cancer would be detected, before it has metastasized.

The overall median and five-year survival rates were nine months and nine per cent respectively. When survival was correlated to the different variables, three statistically significant factors were found to prolong the survival. 1) The patients with squamous cell carcinoma had higher median survival, 14 months, than those with undifferentiated carcinoma, seven months, or adenocarcinoma, six months. 2) Patients with upper and middle neck lymph node metastases had higher median survival, 21 months, as compared to those with lower or supraclavicular lymph node metastases, seven months, or those with other types of metastases, five to seven months. 3) Patients who had "curative" surgery, *i.e.*, extirpation of all the overt cancer, had higher median survival than those who did not have extirpative surgery.

These factors could be explained on the basis that the upper and middle neck lymph node enlargement were mostly from squamous cell carcinoma and the occult primary could be in the nasopharynx, larynx,

or hypopharynx; these patients had radical neck dissections and in some radiation therapy to these fields was also given. Hence, all the overt disease was removed by the surgery and the possible occult disease was treated by radiation therapy.

Radiation therapy has a definite role in management of these patients. Those with osseous metastases from an occult primary get not only a symptomatic relief, but the bone lesions are also controlled. Patients with metastasis in lymph nodes from anaplastic carcinoma, respond well to the radiation therapy; combination chemotherapy should also be added to their treatment. The median duration of the response to radiation therapy in our series was ten months and it appears that this therapy prolongs the survival in responders. Another role of radiation therapy is in conjunction with surgery when the large metastatic lesions were excised incompletely, especially in those with anaplastic or squamous cell carcinoma metastases.

In general, response to chemotherapy was poor. Only six per cent of the patients had regression of the tumor. This is comparable to the response rate reported by Johnson and his colleagues.[5] The duration of the response was eight months in these patients. Because most of the patients who received chemotherapy had an advanced, widespread metastatic cancer, median survival was only five months.

Finally, when faced with a metastatic cancer with an occult primary, we would recommend a thorough search not only to detect the primary tumor, but also to know the extent of the disease. If the primary tumor is still occult and the metastatic disease is localized to one region only, a surgical excision if feasible, should be done. Either radiation therapy or chemotherapy could be administered for residual tumor depending on its histological type. Periodic follow-up is mandatory to detect the recurrence of the tumor, the occult primary becoming overt, or a second histologically different primary tumor.

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