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Treatment of Malignant Pheochromocytoma

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Pheochromocytoma is a tumor derived from chromaffin tissue, which secretes catecholamines. Today, about 90 percent of patients with this tumor are cured by surgical procedures. In 8 to 15 percent of patients with this tumor there is unresectable, recurrent or metastatic disease, which causes significant morbidity and mortality. The natural history of metastatic disease includes long-term survivors; many, however, die early of disseminated disease. The most common site of metastatic lesions is the skeleton. Palliation for these lesions can often be achieved with the use of radiation therapy. Other sites are, in general, less responsive to radiation therapy. Chemotherapy has been used in combination with radiation therapy, but the results generally have been disappointing. Chemotherapy with doxorubicin hydrochloride and cyclophosphamide in combination with radiation therapy has provided good palliation for skeletal disease for about five months, when disease progression was again noted. Further information is needed concerning the optimal chemotherapeutic treatment of this unusual tumor.

PHEOCHROMOCYTOMA is a tumor derived from cells in adrenal medullary or paraganglion tissue, and is characterized most often by the secretion of catecholamines. An uncommon tumor, it is recognized by the associated hypertension. Metastatic disease is defined by the presence of chromaffin tissue in areas where none is usually found, such as liver, lymph nodes, bone marrow, lungs or bone. Metastasis is present in 8 percent to 15 percent of all patients with pheochromocytoma.[1-4]

Today, the primary lesion is curable in 90 percent of patients by surgical operation alone. In the 1940's and 1950's, morbidity and mortality were invariably caused by cardiovascular complications, not by aggressive tumor, because patients often did not survive long enough for clinically significant problems from metastatic disease to be manifested. Today, effective antiadrenergic agents have significantly improved the quantity and quality of life for patients with nonresectable

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TABLE 1.—*Distribution of Metastatic Lesions in 41 Cases of Malignant Pheochromocytoma**

Location	26 autopsy cases	15 nonautopsy cases	Percent
Skeleton	12	6	44
Liver	12	3	37
Lymph node	11	4	37
Lungs	9	2	27
Central nervous system	4	0	10
Pleurae	4	0	10
Kidneys	2	0	5
Pancreas	1	0	2
Omentum	1	0	2

*From Schönebeck J: Malignant pheochromocytoma. Scand J Urol Nephrol 3:64-68, 1969. Reproduced with permission of the author and publisher.

tumors. The effect of these agents on the growth of the tumor or on its ability to metastasize, has not been defined. The natural history, even of metastatic disease, may be quite prolonged, and stable disease may persist for many years.[5]

Schönebeck reported the distribution of metastatic lesions in 41 patients[6] (Table 1). The skeleton, involved in 44 percent of patients, was the most common site. The liver and lymph nodes followed, with 37 percent each; lungs were affected in 27 percent; central nervous system, 10 percent; pleura, 10 percent; kidney, 5 percent; pancreas, 2 percent, and omentum, 2 percent.

This review summarizes reports of the use of radiotherapy and chemotherapy in the treatment of this most unusual disease.

Radiation Therapy in Metastatic Pheochromocytoma

The use of radiation in the treatment of malignant pheochromocytoma dates back to 1929.[2] Radiation therapy was applied to the primary lesion (before good surgical and anesthetic techniques had been developed), as adjunctive treatment after surgical procedures, in the treatment of local recurrence and in the treatment of metastatic disease. Overall, the tumor is considered to be relatively radioresistant. The physiological basis for this is thought to be the fact that catecholamines tend to lower tissue oxygen tension, thereby protecting these cells from radiation-induced damage.[3,7] It is well known that hypoxic cells are much less susceptible than normal or hyperoxic cells to radiation-induced injury. Results of radiation therapy are shown in Table 2.

Inconclusive Results

Numerous studies have documented the absolute resistance, or only partial response, of the pheochromocytoma to therapy. Graham summarized the data to 1949 on the use of radiation to treat the primary tumor. Operative mortality at that time was 26 percent. He concluded that radiation was ineffective treatment for the primary tumor.[2]

Engelman reported that a 12-year-old girl who received postoperative radiation therapy after incomplete surgical removal of a pheochromocy-

TABLE 2.—*Results of Radiation Therapy in the Treatment of Metastatic Malignant Pheochromocytoma*

Reference		Patients	Result	Comment
Boreus[9]	1968	1	Ineffective	Blood pressure remained elevated
Chong[5]	1974	1	Effective	11-year survival noted
Cryer[12]	1976	1	Ineffective	Died of progressive disease
Engelman[8]	1964	4	Ineffective	Recurrence in previously irradiated field
Gifford[1]	1964	11	Effective	Only two patients received radiation therapy; 1 alive 12 years after bone metastases; the other alive after two years
Graham[2]	1951	..	Ineffective	Literature review up to 1949
Higgins[21]	1966	1	Effective	No evidence of disease at nine months
Holsti[3]	1964	1	Ineffective	Recurrent lung metastasis
		2	Effective	Moderate to good palliation
James[7]	1972	9	Effective	3,500-4,000 rads may be of definite value
Joseph[20]	1967	1	Effective	Pronounced symptomatic relief
Kvale[19]	1957	..	Effective	May prolong life after recurrence
Moloney[18]	1966	1	Effective	Contributed to one 15-year survival
Philipps[14]	1976	1	Not stated	Upper femora treated prophylactically
Robinson[10]	1964	1	Ineffective	
Scharf[11]	1973	1	Ineffective	
Scharf[17]	1970	1	Partly effective	Decrease in exophthalmos with orbital involvement
Schönebeck[6]	1969	1	Partly effective	Some pain relief; patient died with diffuse disease
Scott[4]	1976	4	Ineffective	
Soffer[13]	1961	..	Ineffective	Some symptom control possible

toma did well for two years.[8] He then noted metastatic liver disease, as well as tumor, in the previously irradiated field. He too concluded that radiation is not effective therapy for this neoplasm.

Boreus reported that in a patient given radiotherapy postoperatively there was no lowering of blood pressure following this treatment.[9] Holsti reported treatment of several patients, one of whom had recurrent lung metastatic lesions after treatment with 4,900 rads.[3] A second patient received postoperative radiation of 5,800 rads. Seven months later metastasis to the liver occurred and more radiation was delivered. Following that, the patient remained asymptomatic for three years. In a third patient the tumor was attached to the periaortic sympathetic plexus and it infiltrated both the aorta and the inferior vena cava. Because of its inoperability, the tumor was exposed to 5,000 rads. This resulted in decreased catecholamine secretion and a decrease in the size of the tumor, as shown by angiography. The patient was also free from the abdominal pain, nausea, vomiting, sweating and syncope that had previously been present.

Robinson treated a patient with metastatic pheochromocytoma involving the lower scapula and right clavicle, who suffered progressive deterioration despite radiation therapy to the bones.[10] In this patient metastasis to the liver subsequently developed. Scharf treated a patient in whom there was metastatic abdominal lymph node involvement.[11] After treatment with radiation therapy and chemotherapy (drug not specified), the patient died of progressive metastatic disease with widespread lesions.

Schönebeck treated a patient in whom there was metastasis to bone, lymph nodes, liver and lung, and recorded that radiation therapy was partially successful in relieving pain.[6] Scott described four patients managed with radiation therapy and chemotherapy (drug not specified), all of whom died with disseminated disease, one at nine months, another at 2 years, the third at 3 years and the fourth at 11 years, after diagnosis.[4]

A 57-year-old man with malignant metastatic paraganglioma involving the lymph nodes and skeleton received 2,000 rads to involved iliac bones, along with antiadrenergic agents, but did poorly, and died about four months later.[12] Soffer stated that radiotherapy is ineffective in the treatment of pheochromocytoma, although he noted partial control of symptoms in some cases.[13] Philipps treated a 10-year-old girl with bone metastasis to the upper femora with 4,000 rads in an attempt to prevent pathologic fractures. The overall treatment of this patient appeared ineffective, according to Philipps, and he supplied no further specific information concerning the irradiated bone.[14] Other authors, without mentioning specific clinical research, stated that irradiation is ineffective in the treatment of this tumor.[15,16]

Beneficial Results

Not all reports present such a bleak picture, however. James, reporting on the x-ray therapy aspects of pheochromocytomas, mentioned nine patients who were treated with radiation therapy.[7] Two in this group received radiation to primary unresectable lesions. In one there was no effect from the therapy, but the other was alive and well ten years later. Five of six patients who received less than 2,500 rads had no apparent response, and all died within seven months. One patient with metastasis to bone received 4,800 rads and survived 12 years. James concluded that intensive radiation therapy to a dose of 3,500 to 4,000 rads may be of definite value.

Scharf, in discussing a case of orbital metastasis, noted a decrease in disease-associated exophthalmos after radiation therapy and chemotherapy.[17] Diffuse metastatic disease appeared, however, and the patient died six months later. Moloney reported success in treating his patients in whom there was metastasis to bone with radiation therapy.[18] He stated that high dose radiation therapy definitely contributed to a 15-year survival in one patient. Kvale felt that radiation therapy may prolong the life of a patient after recurrence.[19] Several of his patients, however, did have progressive disease despite radiation therapy. Joseph reported a patient's dramatic relief of symptoms, including pronounced lowering of blood pressure, after treatment of clavicular metastasis with radiotherapy.[20] The disease recurred, and further symptomatic benefit resulted from additional radiation therapy and chemotherapy.

Higgins treated, with up to 4,000 rads, a patient with pheochromocytoma of the urinary bladder which involved periaortic and internal iliac nodes; there was no evidence of disease at nine months.[21] Gifford noted that one patient was alive 12 years after treatment for metastatic bone disease, and another was alive 2 years after radiation therapy.[1] He concluded that radiation therapy was effective in these patients.

Chong reported postoperative radiation therapy to a patient in whom nonresectable lesions were found at surgical operation.[5] Metastasis to bone developed four years later and remained stable for seven years.

At Mount Zion Hospital and Medical Center, we treated a 70-year-old man who had been admitted in May 1975 for evaluation of low back pain thought to be caused by degenerative disc disease. In the hospital, palpitations, sweating, dyspnea and transient blood pressure elevations up to 300/190 mm of mercury occurred. At surgical operation, a large left adrenal tumor was found. There was no gross evidence of dissemination at operation, but on pathologic examination evidence of local invasion was found.

In January 1976 severe back pain and vertebral collapse occurred, and the patient was treated with a T-6 to L-3 field, 3,700-rad total dose in 22 fractions over 37 days, with good local pain relief. In the following months, however, progressive back pain and metastasis to the lower dorsal vertebrae were discovered. During this admission, lower lumbar and sacral fields received 3,600 rads in 18 fractions over 25 days. Because of extensive progressive disease and a bone scan showing multiple diffuse sites of involvement, the patient was placed on systemic chemotherapy using cyclophosphamide and doxorubicin hydrochloride in combination with radiation therapy. Now, eight months following his last admission, he remains relatively free of pain and is ambulatory. The disease has progressed slowly, involving new areas of the skeleton, and the patient is receiving local radiation therapy for these metastatic lesions. He is still receiving chemotherapy and tolerating it well. It appears that this combined modality treatment may have slowed the progression of disease, but did not prevent it.

Discussion

There is no overall consensus on the value of radiation therapy in this disease. Often, careful follow-up and details of the original and subsequent treatment programs are not provided. It does appear that the use of radiation therapy to treat primary lesions is not indicated. Its use postoperatively as adjuvant therapy has not been helpful in preventing local recurrence or dissemination and it has, therefore, not been of proven value.

The treatment of bone and, perhaps, lymph node metastatic lesions, does appear to provide symptomatic relief, and radiation therapy should be used when needed for palliation. There are no data pertaining to treatment for liver or bone marrow involvement. Doses of approximately 4,000 rads seem to provide the best responses. In summary, radiation therapy may be of definite value in treating bone and lymph node disease, and is capable of providing excellent, often long-term, pain relief. Since metastatic lesions have been shown to secrete catecholamines[22] this therapy may delay adverse cardiovascular effects of these compounds as well.

Chemotherapy

The literature contains few reports of the use of chemotherapy in treating pheochromocytoma, (see Table 3). Moreover, chemotherapy has al-

TABLE 3.—*Results of Chemotherapy in the Treatment of Metastatic Pheochromocytoma*

Reference	*Drugs*	*Radiation Therapy Also*	*Effect*	*Comment*
Joseph[20] 1967	Cyclophosphamide	+	Effective	Pronounced symptomatic relief
Moloney[18] 1966	Cyclophosphamide	−	Ineffective	Patient died of progressive disease
	Nitrogen mustard	+	Ineffective	
	Thiotepa	+	Ineffective	
Philipps[14] 1976	Vincristine and cyclophosphamide	+	Ineffective	Patient died of pseudomonas infection
	Doxorubicin hydrochloride	−	Ineffective	
Rosenbaum* .. 1976	Doxorubicin hydrochloride and cyclophosphamide	+	Effective	Symptomatic relief
Scharf[11] 1973	Cyclophosphamide, methotrexate	+	Ineffective	.....
Scott[4] 1976	Unspecified	?	Possibly effective	9-month, 2-, 3-, and 11-year survival

*Mount Zion Hospital and Medical Center, San Francisco.

ways been used in combination with radiation therapy, making it difficult to evaluate specific drug effects. Scharf used methotrexate and cyclophosphamide in combination with radiation therapy to treat a patient with abdominal nodal disease, without apparent benefit; the patient died of disseminated metastatic disease.[11] Another patient was noted to have decreased exophthalmos after treatment for orbital metastasis with chemotherapy and radiation therapy.[17]

Joseph used radiations to treat a patient with a recurrent pheochromocytoma, with resultant pronounced symptomatic relief and a decrease in blood pressure.[20] He gave cyclophosphamide, 2,600 mg over 14 days, following it with a maintenance dose of 150 mg daily by mouth. Scott reports the treatment of four patients with metastatic pheochromocytoma, using chemotherapy and radiation therapy, and mentions survivals of nine months and 2, 3 and 11 years after diagnosis.[4] Moloney treated a patient with metastasis to bone with thiotepa, 210 mg given intramuscularly in seven weekly doses of 30 mg, and noted a result of decreased cervical pain.[18] Arm pain progressed, however, and the bone was irradiated with 2,000 rads, producing good relief. Metastasis to the lungs then developed, and 30 mg of nitrogen mustard was given intravenously without response. Cyclophosphamide was then tried, and decreased levels of urine catecholamines resulted, but the patient died four months later of progressive disease.

Phillips used vincristine, 1.5 mg per sq meter of body surface, and cyclophosphamide, 300 mg per sq meter, intravenously weekly for six weeks, then every other week for 24 weeks, and noted slow deterioration of the patient's condition. The patient then received two courses of doxorubicin hydrochloride, but died subsequently of Pseudomonas pneumonia and sepsis.[14]

At Mount Zion Hospital and Medical Center, we treated a patient (a case also discussed in the section on beneficial radiotherapy effects) who had progressive metastatic bone disease, with radiation therapy and doxorubicin hydrochloride and cyclophosphamide—doxorubicin hydrocholoride, 40 mg per sq meter of body surface on day 1, and cyclophosphamide, 200 mg per sq meter by mouth on days 4 to 6, the cycle being repeated every three to four weeks. This combination, in conjunction with radiation therapy, was effective in relieving significant back pain, and decreased the patient's narcotic requirements, for a period of five months. Despite this treatment, however, skeletal disease continued to progress, at a slower rate than before the treatment.

Discussion

No controlled study exists in the English language literature to guide therapy for this disease. Some of the best responses have occurred with alkylating agents used singly, and perhaps even more benefit resulted from using a combination of alkylating agent and doxorubicin hydrochloride. Definite suggestions for drug use await further data.

Conclusions

While patients with pheochromocytoma can usually be cured with surgical procedures, patients with metastatic disease present a difficult problem. Life can be prolonged by the use of antiadrenergic agents which counteract the cardiovascular effects of the tumor. Perhaps, as more patients are treated with these agents and their lives thereby prolonged, we will see more metastatic disease. Metastasis to liver, lung or bone does cause morbidity and mortality in itself.

These metastatic lesions are relatively radioresistant, but significant palliation of metastasis to bone is possible with radiation therapy. Chemotherapy has almost always been used with radiation therapy, and therefore its effects are difficult to define. The control of disseminated metastatic disease has not been accomplished by using radiation therapy or chemotherapy alone or in combination. Further studies are awaited to better define the use of new methods of radiotherapy and new drug combinations in the treatment of this unusual disease.

Addendum

Hamilton[23] recently has reported the failure of streptozocin to affect either the catecholamine excretion or the tumor growth in two patients.

Our patient died in August 1977. This was 27 months after diagnosis, and 19 months after symptomatic metastatic disease was noted.

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Complications of Diuretics

RECENTLY THERE have been several reports of an intriguing syndrome of interstitial nephritis, especially after the use of furosemide. . . . For some reason this has been reported primarily in patients who have some form of preexisting renal disease and usually membranous glomerulonephritis. The syndrome is fairly clear-cut in that the patients have a peripheral eosinophilia, pronounced oliguria and the other manifestations of some sort of an allergic disorder. Stopping the administration of diuretics has completely brought renal function back to what it was at the time the agents were first utilized. . . . We have seen a number of patients with membranous glomerulonephritis who are receiving furosemide, but we have not clearly witnessed this syndrome ourselves.

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