Courses of Malignant Pheochromocytoma

Implications for Therapy

JAMES C. SISSON,[a] BARRY L. SHULKIN,[b] AND NAZANENE H. ESFANDIARI[c]

[a]*Division of Nuclear Medicine, Department of Radiology, University of Michigan Health System, Ann Arbor, Michigan 48109, USA*

[b]*Division of Nuclear Medicine, Department of Radiological Sciences, St. Jude Children's Research Hospital, Memphis, Tennessee 38105, USA*

[c]*Division of Endocrinology and Metabolism, Department of Internal Medicine, University of Michigan Health System, Ann Arbor, Michigan 48109, USA*

ABSTRACT: Survival of patients with metastatic pheochromocytoma that have exceeded 30 years without therapy to reduce tumors have been reported. We reviewed the records of 38 patients with malignant pheochromocytoma who had received ^{131}I-metaiodiobenzylguanidine (^{131}I-MIBG) treatments between 1981 and 1996 to evaluate longevity. Survival from diagnosis to last follow-up exceeded 5 years in 21 of 38 (55%) and $\geq$10 years in 50%. In 17 of 21, the interval from diagnosis to ^{131}I-MIBG therapy was greater than 5 years. Survival following ^{131}I-MIBG was $\geq$5 years in 12 of 17 and $\geq$10 years in 7 of 17 patients despite continued evidence of excessive circulating catecholamines. Objective responses to ^{131}I-MIBG therapy were seen in about 30% and were usually of a few years, duration, but one individual exhibited marked reductions in volume and function of tumors that have persisted for 21 years. No feature, including a remission of $>$5 years following surgical excision, was found to predict prolonged survival. In summary, many patients with malignant pheochromocytoma will follow a course extending over many years. The role of ^{131}I-MIBG therapy in longevity is uncertain, but this radiopharmaceutical reduces evidence of tumors in some patients. Criteria for selecting patients who will benefit from treatment remain to be determined.

KEYWORDS: malignant pheochromocytoma; metaiodobenzylguanidine; patient longevity; long-term survival

Address for correspondence: James C. Sisson, M.D., Division of Nuclear Medicine, UH B1 G505D, University of Michigan Health System, Ann Arbor, MI 48109-0028. Voice: 734-936-5387; fax: 734-936-8182.
e-mail: jsisson@umich.edu

Ann. N.Y. Acad. Sci. 1073: 505–511 (2006).
doi: 10.1196/annals.1353.053

INTRODUCTION

In the strategy of therapy for potentially lethal diseases, prolongation of life is paramount. To appreciate beneficial effects, the probable courses of the disorder without treatment must be taken into account. Survival of patients with malignant pheochromocytoma, even those with distant metastases, has exceeded 10 years.[1–10] Tumor doubling time is then likely to be more than 2 years. These patterns prompted the review of patients with malignant pheochromocytoma initially seen at the University Michigan from 1981 to 1995 for treatments with ^{131}I-metaiodobenzylguanidine (MIBG). The periods of time before and after the therapies were given special attention.

A number of patients who eventually developed malignant pheochromocytoma appeared to have a benign, completely resected, tumor at the outset; more than 5 years between diagnosis and recurrence has not been rare.[5,6,11–13] These observations have led some to recommend that all patients treated for pheochromocytoma should have reevaluations for extended periods of time with the expectation of eventually uncovering malignancy.[11–13] How this manifestation affects survival has not been closely examined. Nine of our patients treated with ^{131}I-MIBG exhibited this phenomenon. For these individuals, the intervals between initial operation and recrudescence are recorded, and these periods are related to their subsequent survival.

MATERIALS AND METHODS

Thirty-eight patients were treated with one to six intravenous infusions of ^{131}I-MIBG for malignant pheochromocytoma between 1981 and 1995 (treatments completed in 1996). Nearly all received multiple infusions, often at intervals of 3 to 4 months but some were extended through a period of 3 years, and one patient received four courses of therapy over 4.5 years. Results have been published for 28 patients treated with ^{131}I-MIBG alone[14] and 6 who received the radiopharmaceutical followed by chemotherapy.[15] Four additional patients were given ^{131}I-MIBG between those two studies. The available records were reviewed, but for three patients too little information was available to assess the intervals in question.

RESULTS

Of the 38 patients, 21 (55%) were known to have survived for >5 years (7–45 years of age), and 50% were alive for ≥ 10 years following the diagnosis of pheochromocytoma (TABLE 1). Of these 21 patients, the age at diagnosis ranged from 10 to 69 years; only 3 of these patients were females. Information on the remaining 17 patients was sparse: the age at diagnosis ranged from 14 to 66 years; seven were females; and at least three died within 5 years of diagnosis.

Manifestations of excessive catecholamines, symptoms, and hypertension were present in each of the 21 subjects listed in TABLE 1. The pheochromocytoma in patient 11 arose as a component of MEN 2 A. Associated disorders of polycythemia in patients 8 and 18 and a familial hypercoagulation state in patient 12 suggested the possibilities of syndromes, but no genetic tests for germline mutations that result in pheochromocytomas were done. In only patient 11, who manifested MEN 2 A, was there a family history of pheochromocytoma.

The time from diagnosis of pheochromocytoma to treatment with ^{131}I-MIBG ranged from 0.1 years to 20 years (TABLE 1). This interval exceeded 5 years in all but 4 patients, and in 13 it was $\geq$10 years. None of the patients attained a complete remission following treatments (as noted previously).[14,15] In our prior evaluations, about 30% of those treated with ^{131}I-MIBG were shown to have objective decreases in tumor volume and/or hormone metabolite secretions from the tumors. Recent information recorded that patient 1 exhibited a marked reduction in tumor volume and function that has persisted for 21 years after radiopharmaceutical therapy.

From the longevity data available on 17 patients, the interval after ^{131}I-MIBG treatments was at least 5 years for 12 patients, $>$10 years for 7, and $>$20 years for 3 (TABLE 1), each with evidence of persisting tumors. However, in the 12 patients surviving for at least 5 years, a relationship was not apparent between the interval spanning diagnosis to ^{131}I-MIBG therapy, ranging from 0.1 years to 20 years, and the subsequent survival of 5–21 years. Nor was the occurrence of partial remissions, seen in patients 1, 2, 4, 9, and 12, associated with a distinct pattern of post-therapy survival, 4–21 years (TABLE 1). Moreover, patients 6, 8, 16, 18, and 21 manifested no objective responses to treatment, but their survivals were among the longest.

Ten patients manifested recurrences more than 5 years after the initial resection of a pheochromocytoma that was thought to be curative (TABLE 1, footnote[a]). These individuals had been cared for by a variety of physicians in multiple institutions, and it is unknown how frequently, and with what laboratory tests, evaluations were carried out in the interlude. These individuals appeared to live longer after initial diagnosis, but, from the incomplete follow-up data, there was no real difference in survival subsequent to ^{131}I-MIBG treatments.

DISCUSSION

Ascertainment bias will afflict studies of any rare tumor. Some malignant pheochromocytomas may cause inanition and death within a few months of diagnosis, and patients with such tumors would have been excluded from our study. Nevertheless, it appears that, in a number of individuals, malignant pheochromocytoma may progress very slowly, even over decades. This concept is supported in 11 reports of $\geq$10-year survival in the presence of metastatic

TABLE 1. Patients with malignant pheochromocytoma: known survival > 5 years

Patient	Age at initial diagnosis (year)	Gender (m/f)	Primary tumor site	Metastasis major site	Initial diagnosis to recurrence[a] (year)	Initial diagnosis to MIBG Rx (year)	MIBG Rx to follow-up (year)	Total survival (year)	Status at follow-up	MIBG treatments	
										No.	total (mCi/GBq)
1	18	f	extra adr	bone		0.1	21	21	alive[b]	2	400/14.8
2	13	f	extra adr	bone		2	12	14	alive	3	767/28.4
3	40	m	extra adr	bone		2	8	10	alive	3	385/14.2
4	63	m	l adrenal	bone		3	4	7	dead	3	608/22.5
5	39	m	r adrenal	mediastinum		6	5	11	alive	2	507/18.8
6	30	m	l adrenal	lung		7	27	34	alive	2	430/15.9
7	48	m	l adrenal	bone, liver		8		8	unknown[c]	2	312/11.5
8[d]	17	m	extra adr	regional		8	17	25	dead	2	246/ 9.1
9	51	m	l adrenal	regional		10	3	13	dead	6	825/30.5
10	11	m	thorax	bone		11		11	unknown[c]	4	916/33.9
11[e]	25	m	r adrenal	liver	12	12	5	17	alive	2	360/13.3
12[f]	39	f	r adrenal	liver	10	12	5	17	dead	3	854/31.6
13	48	m	r adrenal	bone	12	13		13	unknown[c]	1	325/12.0
14	42	m	r adrenal	regional	12	14	4	18	alive	1	200/ 7.4
15	56	m	r adrenal	bone	11	14	1	15	dead	2	429/15.9
16	23	m	r adrenal	liver	6	14	22	36	alive	3	587/21.7
17	33	m	r adrenal	mediastinum	8	15		15	unknown[c]	1	240/ 8.9
18[d]	10	m	extra adr	bone		16	16	32	dead	4	605/22.4
19	36	m	l adrenal	lung	8	16	1	17	alive	2	544/20.1
20	69	m	extra adr	liver	10	19	6	16	alive	2	419/15.5
21	15	m	r adrenal	bone	15	20	25	45	alive	3	480/17.7

[a]Patients whose recurrence was more than 5 years after diagnosis. In others, there was persistence or early recurrence.
[b]Persisting marked reduction in tumor.
[c]No information after last treatment with ^{131}I-MIBG.
[d]Polycythemia.
[e]MEN2A.
[f]Familial hypercoaguability.

disease: one patient dying at 20 years[1]; three reaching ≥20 years[2]; one living for 25 years[3]; one alive at 21 years[4]; two living longer than 20 years[5]; two of 14 patients, longest 22 years[6]; one surviving 26 years[7]; one alive for more than 30 years[8]; one alive at 16 years;[9] one dead after 11 years.[10]

In our 38 patients, survivals from time of diagnosis were greater than 5 years in at least 55% and greater than 10 years in 50%. The role of ^{131}I-MIBG treatment in longevity remains uncertain. An interval of ≥10 years from diagnosis to treatment was present in 13 patients and already gave evidence of slow progression of disease. Some patients had objective improvements following ^{131}I-MIBG treatments, but the benefits were incomplete, and, except in two patients, sustained for only a few years. A pattern of infrequent, partial, and temporary responses to ^{131}I-MIBG is similar to that reported by others, as noted in reviews of the literature.[16,17] In recent reports, rates of objective improvements have been similar in six[10] and 33 patients.[18] However, 3 of 12 individuals treated with high-dose ^{131}I-MIBG exhibited complete remissions; 2 of the remitted pheochromocytomas were nonsecretory, but the disappearance of scintigraphic and CT evidence of disease has endured for 8.5 years in one.[19] In addition, two patients had marked partial responses to multiple ^{131}I-MIBG therapies, and, in one, diminutions of tumor have persisted for 16 years.[10] And one of our patients enjoyed substantial reductions in tumor volume and hormonal markers that have been sustained for 21 years. These latest observations give hope of long-term effects from ^{131}I-MIBG therapy, but enhanced survival will require study of numerous patients over decades.

When considering therapy for a patient with malignant pheochromocytoma, is there any way to predict the course of disease? Observations for a period of many months may be insufficient to predict accurately the long-term course a patient will take; for example, two of our patients (patients 18 and 21) appeared to have developed extensive metastases during the few years following diagnosis and then manifested stable patterns of disease for a prolonged period before ^{131}I-MIBG treatment. It is possible that growth-inhibiting substances, released by paracrine or autocrine mechanisms from the tumors, and/or activation of autoimmune forces brought about this pattern of malignant growth. Identification of such inhibiting factors could not only predict the course of disease but also lay a basis for new therapeutics.

Research into tumor-suppressor genes,[20] angiogenetic forces,[21] and proteomics[22] may lead to accurate predictions of which tumors will progress rapidly. Other types of analyses have shown that plasma methoxytyramine and dopamine levels have been associated with multiple deposits of tumor;[23] these, and possibly other, catecholamine-related products may be portents of aggressive malignancy.

Without predictors of the course of malignant pheochromocytoma, it will be difficult to withhold treatment in a symptomatic patient while awaiting a pattern of progression to appear. Objective responses observed in indices of tumor function and volume over a year or two following treatments may be the best guides of success.

Why some malignant pheochromocytomas recur years after apparently complete resection is unknown. The reappearance of tumor more than 5 years after surgical excision was seen in 10 of our patients. This early delay in tumor progression was not associated with a greater overall longevity than that seen in the patients whose residual malignancy was observed sooner. In the literature, 3–8% of patients who were originally thought to harbor benign disease have developed recurrences after 5 years: one patient (cohort not described)[5]; two of 14 patients[6]; three of 98[11]; 14 of 176[12]; and five of 121.[13] In at least one series, urinary catecholamines and metabolites were found to be normal after the operation.[11] For patients with apparently benign pheochromocytoma, prediction of events will be difficult, but proteomics offers some hope,[22] and, if measured at regular intervals, the plasma-free metanephrines, which offer high sensitivities,[24,25] may provide an early clue.

In summary, patients with malignant pheochromocytoma may exhibit a slow progression of disease extending over decades. Years of observation are necessary to project the ultimate course. However, without early prognosticators, therapy that is found to help at least some patients cannot be withheld. Still, success must include accurate measurements of survival. For the few patients who will have delayed recurrence after initial excision, methods must be devised to detect these resurgent tumors at the earliest time to give the best opportunity for cure through reoperation.

ACKNOWLEDGMENTS

Evaluations and treatments of patients were supported by the General Clinical Research Center at the University of Michigan, Grant No. M01-RR00042. Carol Kruise was especially helpful in preparing this manuscript. This research was approved by the IRB for Medicine at the University of Michigan Health System.

REFERENCES

1. Traub, Y.M. & J.B. Rosenfeld. 1970. Malignant pheochromocytoma with pleural metastasis of unusually long duration. Chest **58:** 546–550.
2. Remine, R.H. *et al*. 1974. Current management of pheochromocytoma. Ann. Surg. **179:** 740–747.
3. Van den Broek, P.J. & J. De Graeff. 1978. Prolonged survival in a patient with pulmonary metastases of malignant pheochromocytoma. Neth. J. Med. **21:** 245–247.
4. Abemayor, E. *et al*. 1980. Multiple sequential pulmonary resections for metastatic pheochromocytoma with long-term survival. Am. J. Surg. **140:** 696–697.
5. Brennan, M.F. & H.R. Keiser. 1982. Persistent and recurrent pheochromocytoma: the role of surgery. World J. Surg. **6:** 397–402.
6. Mornex, R *et al*. 1992. Malignant pheochromocytoma: a series of 14 cases observed between 1966 and 1990. J. Endocrinol. Invest. **15:** 643–649.

7. YOSHIDA, S.M. *et al*. 2001. Twenty-six-years' survival with multiple bone metastasis of malignant pheochromocytoma. Arch. Orthop. Trauma. Surg. **121:** 598–600.
8. YOUNG, A.L. *et al*. 2002. Familial malignant catecholamine-secreting paraganglioma with prolonged survival associated with mutation in the succinate dehydrogenase B gene. J. Clin. Endocrinol. Metab. **87:** 4101–4105.
9. MARNIX, G.E.H. *et al*. 2005. Repeated [^{131}I]metaiodobenzylguanidine therapy in two patients with malignant pheochromocytoma. J. Clin. Endocrinol. Metab. **90:** 5888–5895.
10. BOMANJI, J.B. *et al*. 2003. Treatment of neuroendocrine tumours in adults with ^{131}I-MIBG therapy. Clin. Oncol. **15:** 193–198.
11. VAN HEERDEN, J.A. *et al*. 1990. Long-term evaluation following resection of apparently benign pheochromocytoma(s)/paraganglioma(s). World J. Surg. **14:** 325–329.
12. AMAR, L. *et al*. 2005. Year of diagnosis, features at presentation, and risk of recurrence in patients with pheochromocytoma or secreting paraganglioma. J. Clin. Endocrinol. Metab. **90:** 2110–2116.
13. KHORAM-MANESH, A. *et al*. 2005. Long-term outcome of a large series of patients surgically treated for pheochromocytoma. J. Intern. Med. **258:** 55–66.
14. SHAPIRO, B. *et al*. 1991. Radiopharmaceutical therapy of malignant pheochromocytoma with [^{131}I]metaiodobenzylguanidine: results from ten years of experience. J. Nucl. Med. Biol. Med. **35:** 269–276.
15. SISSON, J.C. *et al*. 1999. Treatment of malignant pheochromocytomas with 131-I metaiodiobenzylguanidine and chemotherapy. Am. J. Clin. Oncol. **22:** 364–370.
16. KOH, K-C. *et al*. 1997. The treatment of malignant pheochromocytoma with iodine-131 metaiodobenzylguanidine (^{131}I-MIBG): a comprehensive review of 116 reported patients. J. Endocrinol. Invest. **20:** 648–658.
17. SISSON, J.C. 2002. Radiopharmaceutical treatment of pheochromocytoma. Ann. N.Y. Acad. Sci. **970:** 54–60.
18. SAFFORD, S.D. *et al*. 2003. Iodine-131 metaiodobenzylguanidine is an effective treatment for malignant pheochromocytoma and paraganglioma. Surgery **134:** 956–963.
19. ROSE, B. *et al*. 2003. High-dose ^{131}I-metaiodobenzylguanidine therapy for 12 patients with malignant pheochomocytoma. Cancer **98:** 239–248.
20. OHTA, S. *et al*. 2005. Downregulation of metastasis suppressor genes in malignant pheochromocytoma. Int. J. Cancer **114:** 139–143.
21. ROOIJENS, P.P. *et al*. 2004. The significance of angiogenesis in malignant pheochromocytoma. Endocr. Path. **15:** 39–45.
22. BROUWERS, F.M. *et al*. 2005. Low molecular weight proteomic information distinguishes metastatic from benign pheochromocytoma. Endocr. Relat. Cancer **12:** 263–272.
23. EISENHOFER, G. *et al*. 2005. Biochemical and clinical manifestations of dopamine-producing paragangliomas: utility of plasma methoxytyramine. J. Clin. Endocrinol. Metab. **90:** 2068–2075.
24. SAWKA, A.M. *et al*. 2003. A comparison of biochemical tests for pheochromocytoma: measurement of fractionated plasma metanephrines compared with the combination of 24-hour urinary metanephrines and catecholamines. J. Clin. Endocrinol. Metab. **88:** 553–558.
25. EISENHOFER, G. *et al*. 2003. Biochemical diagnosis of pheochromocytoma: how to distinguish true- from false-positive test results. J. Clin. Endocrinol. Metab. **88:** 2656–2666.