World J. Surg. 14, 325–329, 1990

World Journal of Surgery

Long-Term Evaluation following Resection of Apparently Benign Pheochromocytoma(s)/Paraganglioma(s)

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In the absence of distant disease, the pathologic diagnosis of malignancy in pheochromocytoma or paraganglioma is impossible. In an effort to establish the true incidence of recurrence in this disease, we have analyzed long-term follow-up (average, 15.8 years) of 98 patients who underwent complete resection of localized, noninvasive, histologically-benign pheochromocytomas and paragangliomas at our institution between 1960 and 1976.

Eighty-eight patients had nonfamilial, sporadic pheochromoctyoma/paraganglioma. Nine had multiple endocrine neoplasia (MEN) type 2 (2A: 7, 2B: 2), and 1 had familial pheochromocytoma. Seventy-nine patients had single pheochromocytomas; 10 had single extraadrenal tumors (paragangliomas); and 9 had multicentric or bilateral adrenal tumors.

Six patients (6.5%) developed recurrent pheochromocytoma after documentation of normal postoperative urinary catecholamine levels. One of these patients had MEN 2A. The recurrences developed at intervals from 5 to 13 years following initial resection. These were distant in 3 patients, local in 2, and both local and distant in a single patient. None of the recurrences occurred in the 13 patients who, on pathologic rereview, had either local or vascular invasion. No paraganglioma recurred.

Life-long follow-up of all patients who have had pheochromocytomas or paragangliomas resected is mandatory.

Although the histological diagnosis of a pheochromocytoma and extraadrenal paraganglioma is relatively easy, determination of the benignancy or malignancy of such tumors on microscopic grounds is not. Cellular pleomorphism and atypia are not reliable indicators of malignancy as in most other organs, and, in the absence of regional nodal or distant spread of either pheochromocytomas or paragangliomas, the pathologist is often unable to label these tumors as malignant [1]. In light of this ambiguity, it is not surprising to note reports of recurrence following complete resection of apparently histologically benign tumors. Scott and Halter [2] reported 5 such patients in 1984. Long-term surveillance following resection of "benign" catecholamine-secreting tumors is, therefore, imperative.

In an effort to establish the true incidence of recurrence after resection of localized, noninvasive, histologically-benign pheochromocytomas or extraadrenal paragangliomas resected at our institution, we undertook this study of 98 patients, concentrating on long-term follow-up.

Presented at the International Association of Endocrine Surgeons in Toronto, Ontario, Canada, September, 1989

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Methods

Between 1960 and 1976, a total of 98 patients underwent complete resection of localized pheochromocytomas and paragangliomas at our institution. The medical records of these patients were reviewed, and additional follow-up obtained by personal interview or correspondence with the patients and/or their physicians. Two patients (2%) died in the perioperative period. The 96 surviving patients were followed for a minimum of 5 years, with a mean follow-up of 15.8 years (range, 5–27). All pathologic specimens were reviewed by a single pathologist (J.A.C.). DNA analysis by flow cytometry was performed on patients with recurrent tumors.

Results

Patient Characteristics

Of the 98 patients undergoing resection, the great majority (88) had nonfamilial, sporadic tumors; 7 had multiple endocrine neoplasia type 2A (MEN 2A); 2 had MEN 2B; and 1 patient had familial pheochromocytoma. The mean age of the patients at the time of diagnosis was 46.2 years (range, 3–78). Sex distribution was equal (49:49).

Pathologic Findings

Gross. Seventy-nine patients had single pheochromocytomas (45 right-sided, 34 left-sided); 10 patients had single extraadrenal tumors (paragangliomas); and 9 had multicentric or bilateral adrenal tumors.

The weight of the resected tumors (84 cases) ranged from 4.8 g (partial adrenalectomy) to 480 g. Of the 96 adrenal tumors resected, 69 were removed by total adrenalectomy and 27 by subtotal resection of the affected gland. The tumor was rup-

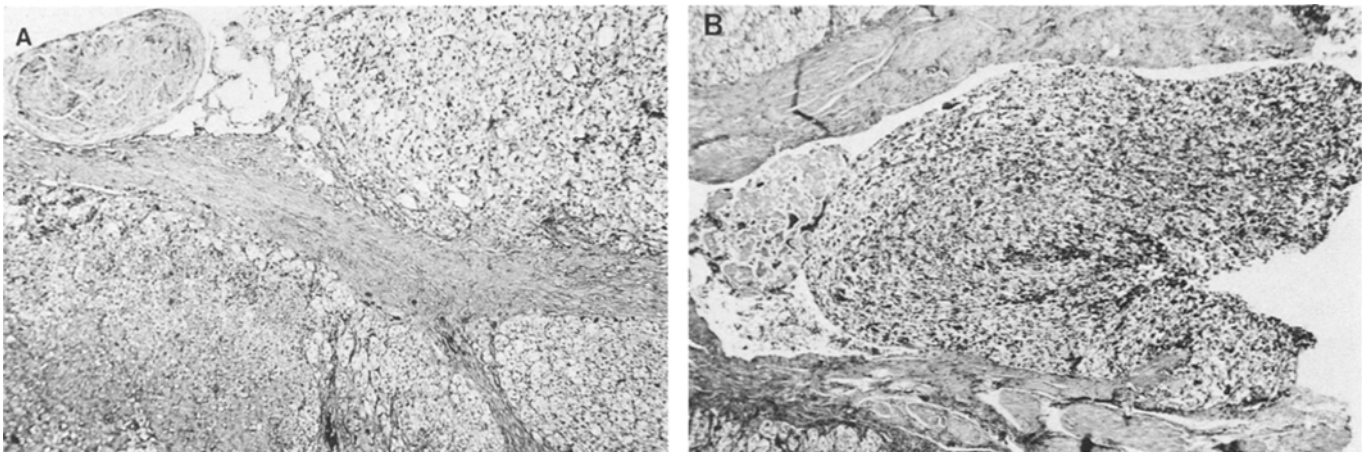

Fig. 1A. Pheochromocytoma (lower left) has penetrated fibrous capsule (band sloping from left to right) and invaded periadrenal fat (upper right). Hematoxylin and eosin ×40. **B.** Large tumor thrombus of pheochromocytoma in the adrenal vein. Hematoxylin and eosin ×40.

tured during removal in 2 patients, and 1 tumor was needle biopsied intraoperatively. All other tumors were removed without tumor violation.

At the time of resection of pheochromocytoma, a total of 34 additional procedures, most commonly splenectomy, were carried out in these patients.

Microscopic. All histology was rereviewed and the original diagnosis of pheochromocytoma/paraganglioma confirmed. At the time of this rereview, additional sections from blocks of the stored tumors were examined. Microscopic evidence of minimal local tumor invasion (penetration of the tumor capsule and involvement of periadrenal fat) was found in 9 (9.2%) patients (Fig. 1A). Vascular invasion (involvement of adrenal vein) was demonstrated in another 4 (4.1%) patients (Fig. 1B). These findings were not noted at the time of the initial pathologic examination.

Recurrence

Nine patients developed recurrent pheochromocytoma. In 3 of these patients, however, neither urinary catecholamines or catecholamine metabolites returned to normal following initial resection and these patients must be considered to have persistent rather then recurrent disease. Of the 93 remaining patients that had complete resection of their tumors and were available for follow-up, 6 (6.5%) developed a recurrence after a period during which normal catecholamine levels were documented. By Kaplan-Meier calculation, the cumulative probability of recurrence of pheochromocytoma was zero at 5 years after initial resection, 0.02 at 10 years, 0.07 at 15 years, and 0.09 from 20 to 30 years after the initial procedure (Fig. 2). The recurrences developed at intervals from 5 to 13 years following initial resection, and were local in 2 patients, distant (spinal cord × 2 and bone) in 3, and both local and distant (lung) in a single patient (Table 1).

Four patients with recurrence had undergone resection of unicentric, nonfamilial, sporadic pheochromocytomas. No patient with a paraganglioma developed recurrence after documentation of normal postoperative catecholamine levels.

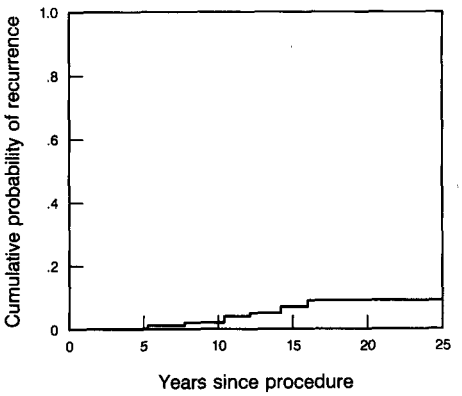

Fig. 2. Cumulative probability of recurrence (Kaplan-Meier).

One patient developing recurrent pheochromocytoma had MEN 2A. He developed a metachronous lesion in residual adrenal tissue 13.6 years after bilateral subtotal adrenalectomy for bilateral, multicentric pheochromocytomas. Another patient (whose son developed a neuroblastoma, but who otherwise had a negative family history) developed recurrent pheochromocytoma in residual left adrenal tissue 9 years after undergoing right total and left subtotal adrenalectomy for bilateral pheochromocytomas.

The 2 patients whose tumors were ruptured intraoperatively did not develop recurrent disease (follow-up of 5 and 23 years, respectively). The patient who underwent intraoperative needle biopsy of her adrenal tumor subsequently developed a metastatic lesion of the femur. Postoperative catecholamine levels, however, did not return to normal after the initial resection.

None of the recurrences occurred in the 13 patients who, on pathologic rereview, had either local or vascular invasion. The long-term follow-up of these 13 patients is summarized in Table 2.

Ploidy Data

We were able to obtain nuclear deoxyribonucleic acid ploidy data by flow cytometry for 5 of the 6 patients who developed

Table 1. Recurrent pheochromocytomas (6.5%).

Age/sex	Site of primary lesion(s)	Operation	Size (g)	Time to recurrence (mo)	Site	Outcome	Remarks
42/M	Right and left adrenal	Right total, left subtotal	Right 11 Left 4	107	Left adrenal remnant	Unknown	Son with neuroblastoma
54/F	Left adrenal	Left partial	117	59	Spinal cord	Died—stroke (64 mo)	–
49/F	Left adrenal	Left total	186	90	Bone, lung, pleura	Died—metastatic pheochromocytoma (94 mo)	–
62/F	Right adrenal	Right total	9 × 9 × 6.5 cm[a]	1) 105	1) Right adrenal bed	Died—metastatic pheochromocytomas (147 mo)	–
				2) 128	2) Lung and bone		
49/M	Left adrenal	Left total	165	125	Spinal cord	Died—metastatic pheochromocytoma (127 mo)	–
27/M	Right and left adrenal	Bilateral subtotal	Right 29 Left 60	164	Right adrenal remnant	Alive—without disease	MEN IIa

[a]Weight not recorded

Table 2. Long-term follow-up of patients with histological features suggesting malignancy.

	Survival (mo)
Vascular invasion (4)	70, 146, 224, 301
Local minimal invasion (9)	95, 167, 171, 207, 222, 138, 226, 265, 280

recurrent disease. None of these patients demonstrated a normal (euploid) histogram. One patient had a tetraploid (increase in 4c) pattern, and 4 had an aneuploid pattern.

Discussion

This study has shown that the overall rate of disease recurrence, either local or distant, after complete resection of localized pheochromocytoma is 6.5%, a rate similar to that reported by others. The previously cited work of Scott and Halter [2] noted recurrence of pheochromocytoma in 5 of 54 patients initially thought to have benign tumors. One of these patients, however, initially had a tumor that grossly infiltrated the vena cava and left renal vein. If this patient is excluded, the recurrence rate in their series is 7.5%. The sites of recurrence were not documented in this series. None of the 4 patients with MEN II had recurrent disease. In 1974, Harrison and associates [3] reported 7 patients with recurrent pheochromocytoma. Three of these patients had distant metastasis, 2 had local lymph node recurrences, and 1 had a local, nonlymph node recurrence. One patient had a biochemical recurrence with no defined site of disease. It is unknown if any of these patients had MEN II. Five of these 7 patients had initial operations at other institutions. Of 23 patients first treated by Harrison and associates, 2 (8.7%) developed recurrence.

Measurement of normal catecholamine levels after initial resection is necessary to identify those patients with unrecognized metastatic or multicentric disease. In this way, 3 patients in the current report were found to have persistent rather than recurrent disease. With such patients excluded, recurrence of pheochromocytoma may result from: (a) The development of a metachronous primary tumor in retained adrenal or extraadrenal paraganglionic tissue, (b) Intraoperative disruption of the original tumor with secondary implantation, (c) The development of metastatic disease [4].

Two patients in our series developed metachronous pheochromocytoma in retained adrenal tissue; the tumors may be considered evolving rather than truly recurrent. Both patients presented with bilateral pheochromocytoma. One had MEN 2A, and the other, although multiple endocrine neoplasia could not be demonstrated, had a son who developed a neuroblastoma. The occurrence of contralateral pheochromocytoma after successful removal of a benign pheochromocytoma was initially reported by Sander and colleagues [5] in 1971, and subsequently by Vary and coworkers [6]. The potential for development of pheochromocytomas in the adrenal medullary tissue of patients with multiple endocrine neoplasia was described by Carney and associates [7] in 1975. In an effort to decrease the number of MEN 2 patients developing recurrent pheochromocytoma, van Heerden and colleagues [8] have recommended bilateral total adrenalectomy for those patients with MEN 2 and elevated catecholamines levels. In that report, 3 (17.6%) of 17 patients developed recurrent pheochromocytoma, 2 after subtotal adrenalectomy.

Bloom and Fonkalsrud [9] reported their experience with 7 pediatric patients with pheochromocytoma. Four of these patients developed "recurrent disease," all in the contralateral gland. Two patients developed a second recurrence after subtotal adrenalectomy. One of these patients had MEN 2A and 2 had familial pheochromocytomas. The Mayo Clinic experience with pheochromocytoma in the pediatric age group demonstrated recurrence in only 1 (7.1%) of 14 patients available for follow-up [10]. This patient was 1 of 3 with MEN 2. Two additional patients had familial pheochromocytomas.

Local recurrence did not develop in the 2 patients whose pheochromocytomas were ruptured intraoperatively. This mechanism of recurrence, however, has been well-documented both experimentally [11] and clinically [12–14] and could ex-

plain the development of locally-recurrent pheochromocytoma in 1 patient from the current report who developed recurrent local disease plus lung and bone metastases. Pathologic examination of tissue from her second operation does not suggest locally metastatic, i.e., nodal disease. To minimize this mechanism of recurrence, intraoperative needle biopsy of these tumors should be avoided.

Four of our patients developed distant metastatic disease from 5 to 10.5 years following complete excision of sporadic, solitary pheochromocytomas. These metastases proved fatal in every instance, with survival ranging from 1 to 19 months after the diagnosis of recurrence (mean, 7.3). This poor outlook is similar to the prognosis found for patients with initially malignant tumors by Remine and coworkers [15] in 1974.

This study, once again, emphasizes the lack of histological markers for malignancy. In the absence of distant disease, the surgical pathologist is often thwarted in his/her ability to separate benign tumors from those which are malignant. Of our patients with definite vascular invasion or local infiltration, no patient developed recurrent disease after a mean follow-up of 15.8 years. The phenomenon of gross vascular invasion, evidenced by a tumor thrombus in the adrenal vein, and absence of distant metastasis is surprising, but perhaps has an explanation. The musculature of the central adrenal vein is unique, having 2–6 longitudinally running muscle bundles of varying sizes, often eccentrically situated. The distribution of the muscle bundles results in muscle being frequently absent from significant portions of the wall of the vein, pheochromocytes being separated from the lumen of the vein by endothelium and a minimal amount of subendothelial connective tissue. Under normal circumstances, it is not uncommon to see an endothelial-covered protrusion of pheochromocytes into the lumen of the vessel. Therefore, it is not at all surprising that with formation of tumor in the adrenal medulla, protrusion of the tumor cells, ultimately a tumor plug, into the central adrenal vein occurs. This mechanism may explain why the gross tumor thrombi in the adrenal vein associated with pheochromocytoma do not have the same significance in terms of metastasis as the renal vein tumor thrombi of renal cell carcinoma, for example.

Seeking other prognostic markers of malignancy, we [16] evaluated nuclear deoxyribonucleic acid patterns in patients with pheochromocytomas. In this study, we found that all patients with a normal histogram followed a benign course while 31% of those patients with a tetraploid/polypoid pattern and 39% of those classified as aneuploid had evidence of malignant tumors. In the current report, ploidy data was obtained on 5 of the 6 patients with recurrent disease. One patient had a tetraploid pattern with 4 demonstrating an aneuploid histogram. DNA ploidy may be of value in this difficult differentiation although the large overlap in the behavior of euploid versus aneuploid tumors is frustrating.

Management of patients with apparently localized pheochromocytoma must be directed toward minimizing the risk of recurrence. Aggressive resection of all adrenal medullary tissue in patients with pheochromocytoma and MEN 2, and in those with familial pheochromocytoma is recommended. Careful exposure and meticulous dissection of these tumors should be undertaken to prevent rupture of the tumor. Needle biopsy pre- and intraoperatively should be avoided. Finally, the lack of histologic markers of malignancy and the 6.5% incidence of recurrence mandate lifelong follow-up (annual fractionated urinary catecholamines or urinary metanephrines) of patients who have undergone resection of either pheochromocytoma or paraganglioma.

Résumé

En l'absence de lésions pathologiques à distance, le diagnostic de malignité en matière de phéochromocytome ou de paraganglion est impossible. Pour déterminer la fréquence vraie de récidive nous avons analysé le suivi à long terme (moyenne, 15.8 ans) de 98 patients ayant eu une résection complète de phéochromocytome et de paraganglions bénins localisés et non invasifs opérés à la Clinique Mayo entre 1960 et 1976.

Quatre-vingt-huit patients avaient un phéochromocytome ou paraganglion sporadique, non familial. Neuf patients avaient une MEN de type 2 (2A: 7, 2B: 2), et un patient avait un phéochromocytome familial. Soixante-neuf patients avaient un phéochromocytome simple; 10 avaient une tumeur extrasurrénalienne simple (paraganglion); et 9 avaient des tumeurs surrénales bilatérales ou multicentriques.

Six patients (6.5%) ont eu une récidive de leur phéochromocytome après normalisation des catécholamines urinaires en postopératoire. Un de ces patients avait une MEN 2A. La récidive s'est manifestée entre 5 et 13 ans après la résection. Elle était à distance chez 3 patients, locale chez 2 patients, et à la fois locale et à distance chez un. Il n'y avait aucune récidive chez les 13 patients qui avaient soit une invasion locale ou vasculaire lorsque les coupes histologiques ont été revues. Il n'y avait aucune récidive de paraganglion.

La surveillance permanente de tout patient ayant un phéochromocytome ou un paraganglion semble s'imposer.

Resumen

En ausencia de metástasis distantes, el diagnóstico histopatológico de malignidad en un feocromocitoma o en un paraganglioma es imposible. Con el objeto de establecer la verdadera incidencia de recurrencia de esta enfermedad, hemos analizado el seguimiento a largo plazo (promedio, 15.8 años) de 98 pacientes sometidos a resección completa de feocromocitomas y paragangliomas localizados, no invasivos e histológicamente benignos en nuestra institución entre los años 1960 y 1976.

Ochenta y ocho pacientes tenían feocromocitoma/paraganglioma no familiar, de tipo esporádico. Nueve tenían el síndrome de neoplasia endocrina múltiple (NEM) tipo 2 (2A: 7, 2B: 2) y uno feocromocitoma familiar. Setenta y nueve pacientes tenían feocromocitoma único; 10 tenían tumores extra adrenales (paragangliomas) y 9 tumores adrenales multicéntricos o bilaterales.

Seis pacientes (6.5%) desarrollaron feocromocitoma recurrente después de haberse documentado niveles postoperatorios normales de catecolaminas; uno de ellos tenía el síndrome NEM 2A. Las recurrencias se desarrollaron a intervalos de 5 a 13 años después de la resección inicial, distantes en 3 pacientes, locales en 2, y locales y distantes en sólo un paciente. Ninguna de las recurrencias ocurrió en los 13 pacientes que en la revisión histopatológica presentaban invasión local o vascular. Ningún paraganglioma exhibió recurrencia.

El seguimiento de por vida en pacientes que hayan tenido feocromocitomas o paragangliomas es mandatorio.

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Invited Commentary

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Twenty-three years after "benign" pheochromocytoma excision and 3 months after fruitless retroperitoneal exploration for recurrent pheochromocytoma, a 54-year-old man dies: Postmortem—Diffuse pulmonary pheochromocytoma nodules are found (below the resolution of a normal admission chest x-ray).

Six months after "heroic" resection of a malignant right adrenal pheochromocytoma, with cell saver, 8 blood transfusions, and cardiopulmonary bypass standby, a 73-year-old woman dies: Postmortem—Massive tumor recurrence obliterates the right flank and the right upper abdomen. Tumor norepinephrine concentration is strikingly lower than is found in benign pheochromocytoma.

The cell biology of these 2 tumors differs vastly. In one, rapid tumor recurrence and uninhibited growth made our original surgery futile. In the other patient, "benign" cells implanted and grew indolently for many years. We call both "malignant" pheochromocytoma. Any attempt to further understand the unregulated growth of recurrent and particularly malignant pheochromocytoma is welcome in an era when our current therapy is so inadequate.

Flow cytometry with DNA analysis is the most up-to-date tool we have. Dr. van Heerden and his colleagues tell us there is no difference in the variety of tumors they studied. This should not keep them from looking further. It seems appropriate that the center in which the first successful pheochromocytoma surgery in this country was done has since persistently contributed so richly to our unfolding understanding of the disease and remains at the edge of progress today.

The clinical lessons are obvious: (a) Avoid hazardous surgery for rapidly recurrent disease. (b) Now that MIBG scanning is available, localize accurately all recurrent disease. Not all recurrences will image. (c) Judiciously remove isolated recurrences. The benefit may be long term.

We now follow, 8 and 10 years after their primary operations, 2 patients with huge recurrent retroperitoneal masses of malignant pheochromocytoma. Their response to spermidine synthesis inhibition was transient in one and absent in the other. Both responded more convincingly to the NIH combined chemotherapy protocol. Who can predict their future? We can look for further insight, if not by surgeons, themselves, by those inspired by the concerns of surgeons such as those of the Mayo Clinic.