Changing trends in the surgical management of phaeochromocytoma

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Limited Role for Meta-Iodo-Benzyl-Guanidine Scintigraphy in Imaging Phaeochromocytoma in MEN type 2 patients
Abstract

Objective: To compare diagnostic applicability of computed tomography (CT) and magnetic resonance imaging (MRI) combined with meta-iodo-benzyl-guanidine scintigraphy (MIBG scintigraphy) in the pre-operative localization of MEN type 2-related phaeochromocytoma.

Design: Retrospective.

Setting: University Hospital.

Materials: 17 MEN type 2 patients (33 adrenal glands) who underwent surgery for phaeochromocytoma. MIBG scintigraphy, CT and MRI were used to localize phaeochromocytoma. On histopathology, an adrenomedullary lesion > 1 cm was classified as phaeochromocytoma.

Main outcome measures: Sensitivity, specificity and diagnostic accuracy of CT and MRI combined and MIBG scintigraphy compared to histopathological findings.

Results: Sensitivity of CT and MRI combined (27 adrenal glands) was 87%, with a specificity of 100% and a diagnostic accuracy of 89%. MIBG scintigraphy (31 adrenal glands) had a sensitivity of 92%, a specificity of only 17% and a diagnostic accuracy of 77%.

Conclusion: If the surgical policy is followed that unilateral adrenalectomy is performed when only one adrenal gland contains phaeochromocytoma, MRI should be the method of choice. Scintigraphy can then be restricted to those cases with negative MR.

Submitted for publication
INTRODUCTION

Phaeochromocytoma will develop in 30% to 50% of patients with Multiple Endocrine Neoplasia type 2 (MEN 2)\(^1,2\) At present, there is no consensus regarding the optimal preoperative localization strategy for these catecholamine secreting tumours in this patient category. Modern techniques for localization of phaeochromocytoma are Computed Tomography (CT), Magnetic Resonance Imaging (MRI) and Meta-Iodo-Benzyl-Guanidine (MIBG) scintigraphy. All these modalities yield an accuracy of over 80% in detecting phaeochromocytoma, each with its own advantages and limitations\(^3-11\).

Thus far, it has been our surgical policy to perform total bilateral adrenalectomy in MEN 2 carriers in whom phaeochromocytoma is diagnosed. While this procedure has the advantage that development of phaeochromocytoma in an initially uninvolved adrenal gland is prevented, life long dependence on gluco-and mineralocorticosteroids replacement therapy may be associated with a considerable risk of Addisonian crisis\(^12-14\). To avoid these risks, an alternative policy of performing only unilateral adrenalectomy in cases of unilateral phaeochromocytoma has been advocated\(^13\). If this strategy is followed, it is of major clinical interest to compare preoperative localization techniques of MEN 2 related phaeochromocytomas to avoid unnecessary adrenalectomies. In this study, we have compared diagnostic accuracy of MIBG scintigraphy with CT and MRI combined in all MEN patients who underwent bilateral adrenalectomy between 1983 and 1996 at our institution.

PATIENTS AND METHODS

From 1983-1996 16 MEN type 2A patients and 1 MEN type 2B patient (mean age 38 years, range 19-61) underwent surgery for phaeochromocytoma after localization with MIBG-scintigraphy combined with CT or MR Imaging. These cases belonged to MEN 2 families and in all families a clinical diagnosis of MEN syndrome was confirmed by the presence of a RET mutation when this genetic marker became available. Bilateral adrenalectomy had been performed in all but one patient. This patient underwent unilateral adrenalectomy following contralateral adrenalectomy for phaeochromocytoma ten years earlier. In all patients, phaeochromocytoma was pre-operatively diagnosed by elevated levels of urinary catecholamine metabolites and/or plasma catecholamine levels. In 10 patients, no clinical symptoms related to phaeochromocytoma were present. In these patients phaeochromocytoma was diagnosed biochemically as part of their clinical follow-up. The sequence of localization examinations was the same as used in non-familial sporadic phaeochromocytoma in our institution. MIBG scintigraphy was the initial examination followed by CT (before 1987, 4 patients) or MR Imaging (1987-1996).
Chapter 4

in 9 patients) directed by the scintigraphic results. In one pregnant patient only MR Imaging was performed preoperatively. Three patients underwent only MIBG scintigraphy preoperatively.

CT studies were performed with a Philips scanner (Tomoscan 350) with the use of continuous 5-10 mm sections through the adrenal region in the axial plane. MR Images were obtained with a 1.5 Tesla superconducting magnet (Philips Gyroscan) with a spin-echo pulse sequence (TR 650-865 msec; TE 20-40 msec and TR 1885-2400 msec; TE 80-110 msec) in order to achieve T1 and T2 weighted images, respectively. The images were formatted in axial and coronal planes with a 5 mm slice thickness.

MIBG was labelled with $^{123}$I. To perform MIBG scintigraphy thyroidal iodine uptake was blocked by administration of potassium iodide-solution, followed by whole body scintigraphy 6 and 24 hours after intravenous injection of 150 MBq of the radiopharmacon. Planar images were obtained by a gamma camera (Siemens LFOV and Siemens DIACAM)). All CT and MRI images were re-evaluated by one expert radiologist, whereas MIBG studies were separately evaluated by an expert nuclear medicine specialist without prior knowledge of the histopathological diagnosis. The radiologist and nuclear medicine specialist described their findings independently. CT and MRI images were described as positive or negative. MIBG scintigrams were categorized as normal, slightly increased uptake or definitely increased uptake. A slightly increased uptake was categorized as “positive”. These results were compared with the histopathological findings after surgery. The histopathological classification was as follows: nodules measuring more than 1 cm in diameter were designated phaeochromocytoma, nodules measuring less than 1 cm were designated nodular medullary hyperplasia and the term “diffuse medullary hyperplasia” was applied to those cases in which diffuse enlargement of the medulla without a nodule was present.

RESULTS

Thirty-three adrenal glands from 17 patients were available for histopathological examination. Twenty-seven specimens showed phaeochromocytoma. Mean tumour size was 3.1 cm (range 1-13 cm). In four adrenal glands (4 patients) diffuse medullary hyperplasia was seen, one adrenal gland was classified as nodular hyperplasia, and one adrenal gland was histopathologically normal. There was no evidence of extra-adrenal phaeochromocytoma or malignancy in any of these patients, both pre- and peroperatively as well as during follow-up (mean 8 years, range 1.5-14 years). Table 1 shows the results of pre-operative localization in these 17 patients with CT or MRI and MIBG scintigraphy. MIBG scintigraphy could not differentiate between medullary hyperplasia and phaeochromocytoma in 5 adrenal glands. Histopathologic
Table 1
Sensitivity, specificity and diagnostic accuracy of Magnetic Resonance Imaging/Computed Tomography and MIBG scintigraphy in pre-operative localization of histopathologically proven phaeochromocytoma in a total of 33 adrenal glands in 17 MEN type 2 patients

<table>
<thead>
<tr>
<th>Phaeochromocytoma</th>
<th>Pos</th>
<th>Neg</th>
<th>Pos</th>
<th>Neg</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI /CT (n=27)</td>
<td>Yes</td>
<td>20</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>87%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specificity</td>
<td>100%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accuracy</td>
<td>89%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MIBG (n=31)</td>
<td>Yes</td>
<td>23</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>92%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specificity</td>
<td>17%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accuracy</td>
<td>77%</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

examination showed hyperplasia in four out of these five adrenal glands. In one adrenal gland a small phaeochromocytoma was found.
All three false negative results of morphological imaging procedures (CT: 1/8 and MRI: 2/19) occurred in asymptomatic and small phaeochromocytomas. In these three cases, MIBG scintigraphy showed a slightly increased uptake. MRI was true negative in four adrenal glands. In three out of these four glands MIBG scintigraphy could not discriminate between hyperplasia and phaeochromocytoma. When intermediate MIBG results were classified as positive and hyperplasia was not classified as phaeochromocytoma, MIBG scintigraphy had a high sensitivity but a very low specificity (Table 1). CT and MRI combined had a similar sensitivity compared to MIBG scintigraphy but also a high specificity.

DISCUSSION

In implementing the surgical policy of performing preventive bilateral adrenalectomy in MEN type 2-related phaeochromocytoma, preoperative determination of uni- or bilateral involvement provides no relevant information and has no influence on the choice of surgical procedure. Moreover, the risk of extra-adrenal involvement and malignancy is very low in these familial phaeochromocytomas, in contrast to solitary phaeochromocytomas. Therefore, the need for preoperative localization of MEN 2-related phaeochromocytomas can be questioned when bilateral preventive adrenalectomy is the operation of choice.

If bilateral preventive adrenalectomy is not performed in MEN 2 patients with unilateral involvement, then determination of the presence of unilateral or bilateral phaeochromocytoma(s) becomes very important. MIBG scintigraphy is the most
sensitive functional imaging procedure for hyperfunctioning adrenal medulla and extra-adrenal phaeochromocytomas. Therefore, scintigraphy can be of great value for localizing sporadic phaeochromocytoma since these tumours are extra-adrenal in over 10% of patients. In contrast, the present study demonstrates that MIBG scintigraphy is of limited value in discriminating medullary hyperplasia from a small phaeochromocytoma as seen in MEN 2 patients. Medullary hyperplasia is regarded as a histopathological precursor of phaeochromocytoma but progression to phaeochromocytoma does not necessarily occur. Adrenalectomy in case of positive MIBG scintigraphy will lead to excision of not only phaeochromocytomas, but also hyperplastic adrenals as shown in our study. MRI and CT both have a high sensitivity in detecting adrenal phaeochromocytoma. The obvious advantage of these morphological imaging procedures over MIBG scintigraphy is the high specificity with respect to differentiating medullary hyperplasia from small phaeochromocytomas. A limitation of our retrospective study design is the comparison of CT techniques as...
used before 1987 with MR-Imaging, but recent literature has shown current CT and MRI techniques to be equivalent in locating adrenal tumours. Advantages of MRI over CT and MIBG are the avoidance of ionizing radiation and no need for intravenous iodinated contrast agents. Moreover, with this technique multiplanar images can be obtained. Due to these advantages MR Imaging can be regarded as the preferred imaging procedure in MEN 2 carriers with elevated catecholamine levels. If the approach of carrying out unilateral adrenalectomy in cases of unilateral phaeochromocytoma is followed, MIBG scintigraphy should be restricted to those MEN 2 patients with biochemically proven phaeochromocytoma in whom MRI fails to detect an adrenal mass. Figure 1 is an algorithm following these suggestions.

In conclusion, localization strategy for MEN 2-related phaeochromocytomas differs from localization of solitary phaeochromocytomas and is strongly related to surgical policy. When standard bilateral adrenalectomy is proposed, preoperative localization of phaeochromocytoma generally has no or very limited clinical implications and can be avoided. When only the involved gland is removed, MRI should be the primary choice for localizing phaeochromocytoma. MIBG remains useful in case of non-diagnostic MRI findings.
REFERENCES


diagnosis and surgical strategy for adrenal medullary disease in MEN II gene

13. Tibbin S, Symling JF, Ingermannsson S Telenius Berg M. Unilateral versus
bilateral adrenalectomy in multiple endocrine neoplasia IIA. World J Surg 1983;
7: 201-206.

14. Lee JE, Curley SA, Gagel RF, Evans DB, Hickey RC. Cortical sparing
adrenalectomy for patients with bilateral pheochromocytoma. Surgery 1996;
120: 1067-1071.

15. Carney JA, Sizemore GW, Sheps SG. Adrenal medullary disease in multiple

16. Cassanova S, Rosenberg-Bourgin M, Farkas DC, Calmettes C, Feingold N,
Heshmati M et al. Pheochromocytoma in multiple endocrine neoplasia type 2a;
survey of 100 cases. Clin Endocrinol (oxf) 1993; 38: 531-537.

17. Heerden JA van, Sizemore GW, Carney JA, Grant CSReMine WH, Sheps SG.
Surgical management of the adrenal glands in the multiple endocrine neoplasia

scintigraphy in preoperative and postoperative evaluation paragangliomas:

19. Modegiani E, Vasen HFA, Raue K et al. Pheochromocytoma in Multiple

metaiodobenzylguanidine for the locating of suspected pheochromocytoma: