Asymptomatic Adrenal Tumours: Criteria for Endoscopic Removal

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ABSTRACT

Objective: Assessment of criteria for videoscopic removal of adrenal lesions discovered incidentally.

Design: Open prospective study.

Subjects: 63 patients operated on for 65 adrenal tumours.

Outcome Measures: Relevance of proposed criteria: secreting adrenal lesion; diameter larger than 4 cm or increase in size at any re-evaluation; computed tomogram of intratumoral necrosis, haemorrhage, or irregular margins; high concentrations of dehydroepiandrosterone sulphate (DHEAS).

Results: Laparoscopic adrenalectomy was successful in 61 patients (97%). There were 4 minor complications. Criteria allowed us to identify correctly: phaeochromocytoma (n = 23), primary hyperaldosteronism (n = 18), Cushing’s adenoma or disease (n = 7), single metastasis (n = 4), adenoma with DHEAS or cortisol hypersecretion (n = 3). 8 non-secreting incidental tumours (13%) were operated on.

Conclusion: Simple criteria for videoendoscopic adrenalectomy for lesions discovered incidentally allowed us to reduce the number of doubtful indications (positive predictive value 87%).

Key words: laparoscopy, retroperitoneum, adrenalectomy, phaeochromocytoma, hyperaldosteronism.

INTRODUCTION

Asymptomatic and apparently “non-functioning” adrenal tumours may be discovered during the course of investigations for unrelated conditions. For instance, unsuspected adrenal masses are detected in 2% of abdominal computed tomograms (CT) (4). We still do not know whether such tumours are indeed silent or whether they produce inactive precursor hormones or active hormones in insufficient amounts to produce signs or symptoms, nor do we know their natural history or whether with time they will start to “function”. However, the quest for diagnostic certainty must be tempered by the need to avoid iatrogenic complications, so we may question the somewhat irrational management strategy that some surgeons elect for such tumours: to operate on all of them despite the fact that a policy of exploring all incidental adrenal lesions is not generally accepted.

Open adrenalectomy is not a common operation and the newly developed laparoscopic approach is even more rarely used by surgeons dealing with endocrine disorders. However, the advantages of the endoscopic approach has led some surgeons to widen their indications for adrenalectomy to a doubtful degree so as to increase their operative series unjustifiably. Despite our reported preliminary results about the feasibility and safety of endoscopic adrenalectomy (1), we refused to lower the threshold for removing incidentally-found adrenal tumours. The simple criteria adopted for open adrenal surgery (8) should also be followed for videoendoscopic surgery.

The current study aims to assess these criteria for videoendoscopic adrenalectomy for lesions discovered incidentally: secreting adrenal lesion; diameter larger than 4 cm or increase in size at any re-evaluation; CT of intratumoral necrosis, haemorrhage, or irregular margins; or high concentrations of dehydroepiandrosterone sulphate (DHEAS). We report our experience with such criteria in a prospective multicentre study, conducted by the Belgian Group for Endoscopic Surgery (BGES).

PATIENTS AND METHODS

Source of Data

A check list was sent to those members of the BGES who were already experienced in laparoscopic surgical techniques and open adrenalectomy for endocrine disorders, and who were planning to use the new endoscopic approach to collect data prospectively about videoendoscopic adrenalectomy. The report form (1) includes information about the patient’s age,
sex, clinical features (preoperative risk factors, American Society of Anesthesiology (ASA) clinical status classification, previous abdominal surgery, preoperative diagnosis of adrenal disease, blood pressure, preoperative imaging techniques, coexisting conditions, and preoperative pharmacological preparation). Data were also obtained about the proposed surgical technique (laparoscopic, retroperitoneoscopic, or both), duration of operation, transfusion requirement, morbidity, anaesthetic considerations, pathological results, hospital stay, and follow-up. It is important to mention that this study includes all adrenalectomies done in the parent institutions by four surgical teams once they started with this new surgical approach: the first endoscopic adrenalectomy was done in October 1993, another team started in 1994, and two in 1995. The two first cases done in 1993 and in early 1994 were not incidental adrenal tumours, but starting with the third case our protocol included proposed criteria for resection of such tumours (8).

Validation
Data were acquired from four university surgical teams. All cases were operated on between October 1993 and September 1997. The database was managed by project coordinators designated by the board of the BGES.

Statistical analysis
The sensitivity, specificity, and predictive values for adhering or not adhering to the proposed criteria were calculated by standard methods. For the purpose of computing these values, true positive, true negative, false positive and false negative results were calculated (patients whose tumours met at least one of the four criteria compared with those that met none of the four criteria). True positives are defined as those tumours that met one to four criteria and that were operated on for a definite indication (pheochromocytoma, Conn’s or Cushing’s syndromes, carcinoma, or metastasis). False positives are those tumours that met one of four criteria, but that after operation were found to be benign, non-secreting tumours. True negatives are those tumours that met none of the four criteria, that were not operated on, and follow-up of which showed that they had been correctly identified as incidental findings. Theoretically, false negatives are those tumours that met none of the criteria, but were shown after operation to have been secreting or cancerous lesions, or both, that had to be operated on. However, according to our protocol, patients whose tumours met none of the criteria were not operated on but carefully followed up. This means that there were no false negative tumours (n = 0), which introduces an investigation bias. In the current series, therefore, the only rate that can be pertinently proposed for the evaluation of criteria studied is the positive predictive value, which is not influenced by either the false negative or true negative rate.

RESULTS
Sixty three patients had a videoendoscopic adrenalectomy, 42 women and 21 men with a median age of 41 (range 12–74). Of the 65 adrenalectomies, 36 were on the left, 25 on the right, and two were bilateral (Table I). Thirty one patients (49%) had had a previous abdominal operation, and six patients with multiple endocrine neoplasia syndrome (five pheochromocytomas and one Cushing’s disease) had previously had the other adrenal operated on. Seventeen patients (27%) had a body mass index [weight (kg) ÷ height (m^2)] of over 30, which means that they were regarded as clinically obese (5). The 63 patients had a total of 102 coexisting clinical risk factors. Preoperative risk according to the ASA classification were grade I (n = 17), grade II (n = 35) and grade III (n = 11). All 63 patients had a preoperative CT scan. Patients suspect of having pheochromocytoma also had meta-iodobenzylguanidine (MIBG) scintigrams.

The initial endoscopic approach to the adrenal was transperitoneal in 60 patients (59 supracolic and one transmesocolic to gain access to the left adrenal), and retroperitoneal in three. Sixty patients were operated on in the lateral decubitus position and three in the semilateral position. The median diameter of the tumours was 4 cm (range 1.5–12). The median duration of the procedure was 120 minutes (range 60–360), and the median postoperative stay was 4 days (range 2–13).

Endoscopic adrenalectomy was successful in 61 patients (97%). The two unsuccessful procedures were bilateral, one for Cushing’s disease and one for ACTH-secreting metastases from a malignant thymoma. Conversion was justified by bleeding in the first case.
and difficult endoscopic dissection in the second case. Postoperative complications for the overall series were two pleural effusions and one basilar artery thrombosis two weeks postoperatively. One patient operated on for a left pheochromocytoma and a 12-cm diameter cyst of the upper pole of the left kidney had to be reoperated on 12 hours later for bleeding in the retroperitoneal space. Oozing was found and controlled laparoscopically. This patient was the only one who required a blood transfusion. The median duration of follow-up was 9 months (range 2–48). Only one patient (operated on for a unilateral pheochromocytoma) had an abnormal catecholamine concentration, which was caused by adrenal hyperplasia on the other side.

During the study period, 20 patients had had abdominal CT for unrelated clinical problems that showed unexpected adrenal tumours. Sixteen of those who fulfilled the criteria were operated on and are included in the series of 63 endoscopic adrenalectomies. There was no significant difference in age, sex, tumour size, or risk factors between the patients with non-incidentally and incidentally discovered adrenal tumours. Autonomous production of cortisol by these apparently non-functioning adrenal masses was sought by a 48-hour dexamethasone suppression test (2 mg), or recognised by lack of a normal circadian rhythm for cortisol and chronically suppressed ACTH (a high cortisol $\div$ ACTH ratio). Aldosterone, DHEAS, androgen, and oestrogen concentrations were also measured. To exclude autonomous adrenal medullary function, 24-hour urinary noradrenaline, adrenaline, vanillylmandelic acid (VMA), metanephrine, and normetanephrine concentrations were also measured. A clonidine suppression test was done for four patients, whose urinary catecholamine concentrations were raised, and was normal. After these investigations we were reasonably certain that eight of the tumours were secreting: three phaeochromocytomas, one cortisol hypersecretion (pre-Cushing’s syndrome), and four hyperaldosteronism.

Eight other patients with non-secreting incidental tumours were also operated on (false positives): one 31-year-old man for a raised DHEAS and seven patients because the diameter of the tumour was more than 4 cm or had increased in size on re-evaluation, and whose CT showed intratumoural necrosis, haemorrhage, or irregular margins). One, which measured 6 cm, was a schwannoma and the other seven were non-functional benign adenomas. These eight patients make up 13% of the total series of 63 who were operated on. In the meantime, four other tumours found incidentally met none of the criteria and were not operated on. They were free of symptoms and still not secreting respectively 42, 30, 24, and 18 months after diagnosis. They are followed up by serial CT at six-monthly intervals for the first year and then yearly thereafter; and by an annual 24-hour urine screen for VMA, metanephrine, catecholamine, 17-hydroxycorticosterone, and 17-ketosteroid concentrations. The serum potassium concentration is also measured each year. So far, none of these four patients (true negatives) have met the proposed criteria for operation and are, therefore, not included in the endoscopic adrenalectomy series.

If one considers the overall series of 63 who were operated on (true positives and false positives) and the four who were not operated on (true negatives), adherence to the criteria allowed us to estimate the positive predictive value of the criteria and correctly identify definite indications for adrenalectomy (positive predictive value 87%; 95%-confidence interval 77–94).

DISCUSSION

When a modern organ-imaging technique is used to follow-up patients with known malignant disease and shows a mass in the adrenals, one is not dealing with an incidental finding. This is also true when an adrenal mass is discovered by CT or ultrasound scan ordered because of the clinical suspicion of abnormal adrenal function. Management of the incidentally found tumour must be guided by the high incidence of benign and clinically unimportant adrenal adenomas compared with the rarity of occult non-functioning adrenocortical carcinoma or functioning adrenocortical carcinoma (4). The feasibility of laparoscopic adrenalectomy has led some investigators (2, 3) to suggest that this new approach should lower the threshold for removing adrenal tumours found incidentally. However, the value of removing such tumours, whether endoscopically or by the open technique, remains controversial (6, 7, 10, 11).

Despite our previously reported experience about the feasibility, the better postoperative comfort, and the safety of endoscopic adrenalectomy (1), we refused to lower the threshold for removing incidental tumours. Even if criteria for operative and non-operative treatment are still being debated, not all such tumours should be operated on. We therefore question the somewhat irrational management strategy that some minimally invasive surgeons adopt for such tumours: that is to operate on any incidentally discovered and non-functioning adrenal tumours that could just be left in place. A recently updated series (2) concerns 50 new cases in less than two years in Canada, the population of which is the same as that of the Benelux countries. This series of 50 new cases of videoscopic adrenalectomies can certainly be explained by the superb technique of the surgeons, but we also question their
14% incidence of debatable adrenal lesions vaguely classified as other or data not available, in addition to the 15% of adrenal lesions classified as non-functioning adrenal tumours found incidentally, which makes up 29% of their series.

This is the reason why we have adopted the four simple criteria recommended in a recent large study (8) for removal of these tumours, that seem to fit reasonably within the framework of current knowledge. As this policy was recommended for open adrenal surgery, we have followed it for video-surgical surgery. Adhering to these criteria allowed us to obtain a high incidence of clear-cut endocrine indications for surgical removal of tumours at high risk of endocrine disorders, or malignancy, or both (phaeochromocytoma, Conn’s and Cushing’s syndromes, metastatic, or other secreting lesions make up 87% of our series of endoscopic adrenalectomies). The remaining 13% that have debatable indications is low compared with those in other series (2, 3, 10). If surgeons are able to do a laparoscopic adrenalectomy safely, it may sometimes influence the therapeutic option in as much as the nature of the adrenal mass may be resolved less invasively and with less disability than by open surgery. Nevertheless, there is always a risk that a laparoscopic procedure will have to be converted to an open operation. Consequently, the availability of laparoscopic adrenalectomy should not change the indications for advising operation in a patient with an incidental adrenal mass (7).

For patients with hyper tension and an apparently non-functioning adrenal mass, phaeochromocytoma should always be excluded, as well as normokalaemic primary hyperaldosteronism, which is much more common than previously suspected. Low DHEAS concentrations have been suggested as a marker for an adrenal adenoma secreting cortisol at a rate not sufficient to cause overt Cushing’s syndrome (pre-Cushing’s syndrome). Several workers have found, however, that the sensitivity and specificity were only in the 50%–70% range. Part of this problem may relate to the normal fall in DHEAS secretion with age, so that its use as a screening test might be more accurate in younger patients. On the other hand, among clinically diagnosed primary adrenal cancers, excessive adrenal androgen secretion is the most common hormonal abnormality, suggesting that increased DHEAS secretion may be used as a screening test, particularly in young patients. However, there are few data on which to base this among patients with incidentally-found adrenal lesions.

Applying a screening test with less than 100% specificity for a rare disease to large relatively unselected populations produces many false positives, and results in further costly evaluation and the potential for unnecessary surgery. The potential major benefit of early removal of a rare adrenal carcinoma must be balanced against the morbidity and mortality of surgery for the far more common benign lesions. Similarly, the benefit of detection of malignancy by fine needle biopsy must be balanced against the small but real risk of procedural complications in those without the disease.

Observation alone also entails costs, both monetary and psychological, particularly for young patients. The specific willingness of the patient to have the tumour removed deserves consideration, even if it is not a rational criterion and was discarded in our protocol. How the costs and benefits of various strategies of hormonal screening, and radiological and invasive techniques for evaluation of incidental adrenal tumours compare with other diagnostic problems (such as treatment of hypertension or hypercholesterolaemia) await further study. The role of magnetic resonance imaging (MRI) is still under discussion (9). It has been used to distinguish between benign adenomas and malignant adrenal tumours by comparing the intensity of the lesion signal to the signal intensity of liver, striated muscle, or fat. Benign adenomas usually have a low intensity ratio, whereas malignant masses and phaeochromocytomas have a high signal intensity ratio (9). Contrast enhancement after injecting gadolinium diethylenetriaminepenta-acetic acid (Gd-DTPA) and comparing intensity ratios before and after contrast enhancement has further aided the differential diagnosis (6). The range of criteria vary, however, when using different MRI techniques and equipment, so if a strategy using MRI is promising it has still to be confirmed, and in the meantime we have to rely on more classic criteria.

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REFERENCES

5. Hodge AM, Zimmet PZ. The epidemiology of obesity.


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