

Adrenal incidentalomas in the laparoscopic era and the role of correct surgical indications: observations from 255 consecutive adrenalectomies in an Italian series

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Accepted for publication Feb. 9, 2009

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Background: The purpose of our study was to evaluate the impact of laparoscopic adrenalectomy on patients with incidentalomas. We analyzed the results of a multicentre trial that was performed to evaluate the effectiveness of imaging (computed tomography and magnetic resonance imaging) to obtain a correct preoperative diagnosis.

Methods: We obtained our data from the results of a questionnaire that was distributed by mail or email in May 2005 to several surgical units operating in the Campania Region, Italy. Lap Club, a collaborative laparoscopic surgery study group founded in Naples in 1995, distributed the questionnaire. Thirteen centres participated in the audit. In all, we analyzed 255 adrenalectomies performed on 250 patients. We performed statistical analysis using SPSS software.

Results: The distribution of pathologic findings demonstrates that the number of lesions caused by cancer discovered from a preoperative indication of incidentaloma has been even smaller (1/114, 0.8%) than the previous numbers reported in the literature. Moreover, whereas most patients with adrenal cancer had lesions larger than 6 cm (7/8, 87.5%), the majority of patients with adrenal metastases had lesions 6 cm or smaller (10/12, 83.3%). Different indications for adrenalectomy emerged on comparison of endocrine surgery units with general surgery units. This difference appears to be significant ($p < 0.001$), especially on evaluation of the number of nonfunctioning adenomas and the number of endocrine lesions that were observed and treated.

Conclusion: Laparoscopy remains the gold standard method for adrenalectomy, but its availability must not obligate physicians to treat with surgery when an incidentaloma is detected through imaging. Adrenal malignancies when metastatic are often 6 cm or smaller. If they are single and they originated from a non-small lung cancer, they must be removed. The endocrine surgery unit remains the best setting to evaluate and treat adrenal gland surgical pathology.

Contexte : Notre étude avait pour objectif d'évaluer l'impact de la surrénalectomie par laparoscopie sur les patients présentant un incidentalome. Nous avons analysé les résultats d'un essai multicentrique visant à évaluer l'efficacité de l'imagerie (tomographie par ordinateur et imagerie par résonance magnétique) pour obtenir un diagnostic préopératoire exact.

Méthodes : Nous avons tiré nos données des résultats d'un questionnaire distribué par la poste ou par courriel en mai 2005 à plusieurs unités de chirurgie électorale dans la région de Campanie, en Italie. Lap Club, groupe collaboratif d'étude de la chirurgie par laparoscopie fondé à Naples en 1995, a distribué le questionnaire. Treize centres ont participé à l'étude. Nous avons analysé au total 255 surrénalectomies pratiquées sur 250 patients. Nous avons procédé à l'analyse statistique au moyen du logiciel SPSS.

Résultats : La distribution des résultats pathologiques démontre que le nombre de lésions causées par le cancer découvertes à la suite d'une indication préopératoire d'incidentalome est encore plus faible (1/114, 0,8 %) que les totaux précédents signalés dans les publications. De plus, alors que la plupart des patients atteints d'un cancer des surrénales avaient une lésion de plus de 6 cm (7/8, 87,5 %), la majorité de ceux qui présentaient des métastases aux surrénales avaient des lésions de 6 cm ou moins (10/12, 83,3 %). La comparaison entre les unités de chirurgie endocrinienne et les unités de chirurgie générale a dégagé des indications différentes pour la surrénalectomie. Cette différence semble importante ($p < 0,001$), particulièrement pour ce qui

est de l'évaluation du nombre d'adénomes non fonctionnels et du nombre de lésions endocriniennes observées et traitées.

Conclusion : La laparoscopie demeure la méthode de choix pour la surrénalectomie, mais sa disponibilité ne doit pas obliger les médecins à procéder par chirurgie lorsque l'on détecte un incidentalome à l'imagerie. Par ailleurs, les métastases aux surrénales sont souvent de 6 cm ou moins. Si elles sont uniques et proviennent d'un cancer du poumon non à petites cellules, il faut les exciser. L'unité de chirurgie endocrinienne demeure le meilleur contexte pour évaluer et traiter la pathologie chirurgicale des surrénales.

Incidentally discovered adrenal masses, also known as "incidentalomas," are seen in 4%–10% of patients undergoing imaging modalities, mainly computed tomography (CT), for other clinical indications.^{1,2} Most of these lesions are found to be benign, nonfunctioning adenomas.³ These patients should undergo biochemical testing to rule out any subclinical adrenal secretion.^{3,4} About 5% of incidentalomas are adrenocortical carcinomas.⁴ Adrenocortical carcinomas represent 2% of all tumours 4 cm or less in diameter, 6% of tumours ranging from 4.1 to 6 cm, and 25% of tumours larger than 6 cm.³ Imaging modalities, especially CT and magnetic resonance imaging (MRI), are the main tools to diagnose and monitor these lesions.³⁻⁵ The role of fine-needle aspiration cytology in the diagnostic workup of these patients remains controversial. Most authors consider this approach only in cancer patients^{3,5} to rule out any metastases, whereas in other series,⁶ fine-needle aspiration cytology is considered the strategy of choice in all patients to distinguish between benign and malignant non-functioning adrenal masses. Since 1992,⁷ laparoscopic adrenalectomy has been the preferred modality in the treatment of benign adrenal lesions. Its superiority over conventional adrenalectomy in terms of postoperative recovery, hospital stay and overall cost is well documented,⁸ leading some authors to define this surgical approach as a new gold standard.⁹ Several experts have therefore tried to define guidelines to manage the treatment of incidentalomas. Although these reports conclude that regardless of the surgical approach (open or laparoscopic) the indications to surgery have not changed,^{1-5,10-12} some studies have demonstrated that the introduction of laparoscopy has caused an

increase in the number of adrenalectomies performed on patients with incidentalomas.^{13,14} We analyzed the results of a multicentre trial performed to evaluate the effectiveness of imaging (CT and MRI) to obtain a correct preoperative diagnosis. Following this design, we have compared the result of imaging with final diagnosis on histology, especially for those lesions ranging from 4 to 6 cm in diameter, for which surveillance is generally recommended.¹²

METHODS

We obtained our data from the results of a questionnaire that was distributed by mail or email in May 2005 to several surgical units operating in the Campania Region, Italy. Lap Club, a collaborative laparoscopic surgery study group founded in Naples in 1995, distributed the questionnaire. The study was completed in December 2007. The questionnaire requested the following: patients' initials, age and sex, comorbidities, preoperative diagnostic workup, preoperative diagnosis (if any), preoperative pharmacological treatment (if any), date of operation, operative time, type of laparoscopic surgical approach (supine or lateral transabdominal, retroperitoneal), number of trocars used, intra- or postoperative complications, specimen dimensions, final pathological findings and follow-up. We performed statistical analysis with SPSS version 11.5 and assigned significance at $p < 0.05$.

RESULTS

Thirteen surgeons working in 13 centres participated in the audit as reported: 5 university centres (3 from the

Table 1. Main clinical features of the series

| Feature | No.* |
|----------------------|--------------|
| Centres | 13 |
| Adrenalectomies | 255 |
| Patients | 250 |
| Female sex | 158 |
| Male sex | 92 |
| Ratio male:female | 1.0:1.7 |
| Mean age (range), yr | 46.4 (21–78) |
| Mortality | 0.0 |
| Morbidity, % | 1.6 |
| Conversion rate, % | 4.4 |

*Unless otherwise indicated.

Table 2. Indications for surgery for 255 laparoscopic adrenalectomies performed on 250 patients

| Indication | No. (%) of patients |
|--------------------------|---------------------|
| Nonfunctioning lesion | |
| ≤ 6 cm | 114 (45.6) |
| > 6 cm | 7 (2.8) |
| Adrenal Cushing syndrome | 33 (13.2) |
| Pheochromocytoma | 48 (19.2) |
| Conn syndrome | 14 (5.6) |
| Angiomyolipoma | 18 (7.2) |
| Ganglioneuroma | 2 (0.8) |

Table 3. Postoperative diagnoses for 250 patients who underwent laparoscopic adrenalectomy

| Diagnosis | No. (%) of patients |
|--------------------------|---------------------|
| Adrenocortical adenoma | 113 (45.2) |
| Adrenocortical cancer | 8 (3.2) |
| Cushing adenoma | 27 (10.8) |
| Cushing bilateral lesion | 5 (2.0) |
| Pheochromocytoma | 48 (19.2) |
| Conn adenoma | 14 (5.6) |
| Angiomyolipoma | 18 (7.2) |
| Ganglioneuroma | 2 (0.8) |
| Metastasis | 12 (4.8) |
| Cyst | 2 (0.8) |

Second University of Naples and 2 from the University of Naples "Federico II", 4 regional hospitals and 4 private hospitals. Advanced laparoscopic procedures were routinely performed in these units. There were only 2 endocrine surgery units among the 13 centres, one from the Second University of Naples and the other from the University of Naples "Federico II".

From January 1993 to November 2005, 255 laparoscopic adrenalectomies were performed on 250 patients. No partial adrenalectomies were performed. Table 1 summarizes the main clinical features of this series. The indications for surgery are reported in Table 2. All patients reported in this table had a preoperative diagnosis mainly reached by biochemical testing, ultrasonography, CT and, when requested in the case of functioning lesions, by nuclear scanning or nuclear MRI. The majority of patients (244/250, 97.6%) underwent surgery in the Gagner⁷ position. Six patients (2.4%) were in the supine transabdominal position. No patient was treated by a posterior retroperitoneal approach. Overall, 136 operations (53.8%) were performed using 4 trocars, and 100 were performed using 3 trocars. In 9 of 250 (3.6%) and 4 of 250 (1.6%) patients, respectively, 5 or 6 ports were used. The mean operative time was 149 (range 55–350) minutes. Intraoperative complications occurred in 11 patients (4.4%). Five patients had intraoperative bleeding, 3 patients suffered from a vena cava tear and 3 had a spleen injury. The conversion rate to open surgery was 4.4% (11/250). The decision was made to convert to open surgery for one patient owing to the vena cava lesion, for 5 patients owing to uncontrolled bleeding that worsened the laparoscopic vision, and for 5 patients owing to large masses that were difficult to manage using laparoscopy. Thirty-five patients (14.0%) suffered from an intraoperative hypertensive peak: the systolic range was 180–300 mm Hg whereas the diastolic range was 90–120 mm Hg. No deaths occurred during this audit.

The postoperative diagnosis was confirmed in most patients, as shown in Table 3. Adrenal metastases originated from diagnosed lung cancer in 11 of 12 patients and from gastric cancer in the remaining patient. Mean size of the lesions was 3.4 (range 1.5–14.0) cm in diameter. When considering all 8 instances of cancer at final diagnosis, it is interesting to observe how only 1 instance of cancer (1/114, 0.8%)

came from nonfunctioning lesions 6 cm or smaller, whereas 7/7 came from lesions larger than 6 cm. In this case (1/8 instances of adrenocortical cancer), the preoperative dimension was 2 cm. Table 4 summarizes the relation between specimen dimensions and final diagnoses on histology.

It must be remarked how adrenal metastases in our series are not related to larger dimensions. Of 12 adrenal metastases, 11 were solitary lesions coming from a non-small lung cancer, and 10 of 12 (83.3%) were 6 cm or smaller. The general morbidity was 1.6% (4/250), including 1 infection at the site of the trocar insertion, 2 cases of mild postoperative bleeding and 1 case of uncontrolled change in blood pressure. The mean hospital stay was 3.7 days. The rate of cure in cases of hormonally active adrenal lesions (94/250) was 100%. The overall survival of patients treated for metastatic non-small lung cancer is 9 of 12 (75.0%). The distribution of pathologic findings shown in Table 5 demonstrates the different indications for adrenalectomy in endocrine surgery units (group A) compared with general surgery units (group B). This appears to be significant ($\chi^2 = 18.83$, $p < 0.001$), especially when one evaluates the number of nonfunctioning adenomas and the number of endocrine lesions (Cushing adenoma, Cushing bilateral hyperplasia, Conn adenoma, pheochromocytoma) that were observed and treated in these units. On the other hand, in a comparison of patients in group A versus patients in group B, we observe no significant difference (χ^2 or Student t test if required) in preoperative (sex, mean age, mass dimension), intraoperative (conversion rate) or postoperative (morbidity, mean hospital stay) parameters ($p > 0.05$).

DISCUSSION

Incidentaloma is defined as a nonfunctioning, asymptomatic adrenal gland lesion discovered on abdominal imaging that was performed for other clinical indications.^{1–9} When the laparoscopic experience for adrenal glands started in the early 1990s, the main indications for adrenalectomy were for functioning lesions, mainly Conn and Cushing adenomas. Although the first report of a laparoscopic adrenalectomy described a pheochromocytoma,⁷ from then on some caution was recommended in dealing with these tumours. As surgeons gained skill with minimally invasive access, adrenal lesions that were once considered

Table 4. Specimen dimensions and final diagnoses on histology

| Diagnosis | Dimension; no. (%) of patients | | |
|----------------|--------------------------------|-----------|----------|
| | < 4 cm | 4–6 cm | > 6 cm |
| Cancer | 1 (12.5) | 0 | 7 (87.5) |
| Adenoma | 135 (64.9) | 68 (32.7) | 5 (2.4) |
| Angiomyolipoma | 6 (33.3) | 7 (38.9) | 5 (27.8) |
| Ganglioneuroma | 2 (100.0) | 0 | 0 |
| Metastasis | 3 (25.0) | 7 (58.3) | 2 (16.7) |
| Cyst | 0 | 1 (50.0) | 1 (50.0) |

Table 5. Pathologic findings in general and endocrine surgery units for 250 patients who underwent laparoscopic adrenalectomies

| Surgery unit | Finding; no. (%) of patients | | | |
|--------------|------------------------------|--------------------|-----------|-------|
| | Nonfunctioning adenomas | Secerning adenomas | Others | Total |
| Endocrine | 18 (29.0) | 41 (66.1) | 3 (4.8) | 62 |
| General | 95 (50.5) | 54 (28.7) | 39 (20.7) | 188 |
| Total | 113 (45.2) | 95 (38.0) | 42 (16.8) | 250 |

safe to be resected only by open surgery were operated on with laparoscopy. In this fashion, bilateral operation, pheochromocytoma, virilizing tumours and some small malignancies, primary or metastases, have been included among those with indications for a laparoscopic adrenalectomy.¹⁵⁻¹⁷ Laparoscopy has now become the treatment chosen or, in some cases, the gold surgical standard for adrenalectomy. This means that the use of this approach for these types of pathology has not changed the endocrinologist's indication for referring the patient to a surgeon. Currently, open surgery is recommended only for lesions larger than 10 cm or tumours showing clear malignant features at preoperative imaging.¹⁴⁻²⁰

However, although it has been clearly stated in several articles^{1-5,10-12} that laparoscopy has not changed the indications for adrenal surgery, some reports have shown an increased number of adrenalectomies performed since 1992.¹³⁻¹⁵ The answer to this controversial issue is somewhat offered in those articles themselves, and is probably represented by the huge number of small incidentalomas removed in the past few years. The authors of those articles have advocated that improved imaging techniques and the risk of incidentalomas hiding cancer, ranging from 5% up to 25%–98% for lesions larger than 6 cm in diameter,^{16-18,20-23} in addition to the reported underestimation of tumour size on CT,²⁴ are the main reasons for the increased number of adrenalectomies performed. Nevertheless, it must be considered that if imaging improvement has led to a better chance of detecting a lesion and thus obtaining a preoperative diagnosis, little has changed over the years in the indication to remove an incidentaloma.^{10,15} This indication is determined by the size of the lesion because, in any case, despite technical upgrading, no imaging tool can offer a certain preoperative diagnosis, especially in small nonfunctioning adrenal lesions. Throughout the years, indications for the removal of an incidentaloma have varied, according to the authors, from a 5–6 cm threshold to 2–3 cm.²¹⁻²³ The observation of the present series shows how the number of the lesions removed (45.2%) is higher than the normal percentage of incidentalomas resected in most series (18.2%).²⁰⁻²⁶

This leads to another aspect of our discussion. Before 1992, adrenal surgery was managed almost exclusively by endocrine surgeons, often working in an endocrine environment. The remarkable spread of laparoscopic techniques has in the past 10 years lead many endocrinologists to refer patients not to endocrine surgeons but to skilled laparoscopic surgeons who perform adrenalectomy as well as other laparoscopic operations. In this way, some common experience between endocrinologists and endocrine surgeons has probably been lost, which our study appears to emphasize. If we consider the adrenalectomies performed in this audit, we can note that the operations performed in the only 2 endocrine surgery units (Table 5) have in percentage the same indications described by the literature.^{15,25,26} On the other hand, in almost all the general surgery units in which

laparoscopic adrenalectomy has been performed, the main indication remains incidentalomas. A relevant part of the learning curve of laparoscopic adrenalectomy has probably been represented by incidentally discovered adrenal lesions, which would not have been indicated for surgery at all before 1992.

Nevertheless, one more feature of this debate must be considered. Although an indication for surgery has led to laparoscopic adrenalectomy for an incidentaloma in 45.6% (114/250) of patients scheduled to receive surgery, which generated a large series of incidentally discovered and treated adrenal masses, by considering lesions smaller than 6 cm,¹⁴ the number of lesions caused by cancer discovered would have been even smaller (1/114, 0.8%) than the percentage reported in most large series.^{14,22,26} This study confirms that there is no reason for surgical indications for resection of incidentalomas to change (although the debate remains open) and that although a large number of unnecessary surgical procedures have been performed, the incidence of adrenocortical instances of cancer presenting as incidentally discovered adrenal masses has not increased when compared with documented studies performed previously. Adrenal metastases can be removed by laparoscopy when their size is within the limits suggested by the literature.¹⁵⁻¹⁸ As reported,²⁷ solitary lesions coming from non-small lung cancer must be removed. Although preliminary, data in our series appear to confirm this indication.

Endocrine surgery units remain the best setting to evaluate and treat the adrenal gland surgical pathology. In our opinion this it is not related to a greater experience offered by endocrine surgeons compared with general surgeons, but to a referral bias. Endocrine surgery units in Italy work in direct contact with endocrinologists, thus receiving and treating patients presenting more appropriate indications to surgery. Laparoscopy remains a gold standard as stated, but its availability must not force or obligate physicians to treat with surgery, regardless of the surgical unit, endocrine or general, when an incidentaloma is detected through imaging.

Competing interests: None declared.

Contributors: Drs. Conzo and Musella designed the study. Drs. Conzo, Tricarico, Belli, Candela, Corcione, Marzano, Vincenti, Musella and De Martino acquired the data, which Drs. Conzo, Tricarico, Del Genio, Ferulano, Giardiello, Livrea, Marzano, Porcelli, Sperlongano, Musella and Palazzo analyzed. Dr. Musella wrote the article. All authors reviewed the article and approved its publication.

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