

Open versus endoscopic adrenalectomy in the treatment of localized (stage I/II) adrenocortical carcinoma: Results of a multiinstitutional Italian survey

Celestino Pio Lombardi, MD,^a Marco Raffaelli, MD,^a Carmela De Crea, MD,^a Marco Boniardi, MD,^b Giorgio De Toma, MD,^c Luigi Antonio Marzano, MD,^d Paolo Miccoli, MD,^e Francesco Minni, MD,^f Mario Morino, MD,^g Maria Rosa Pelizzo, MD,^h Andrea Pietrabissa, MD,ⁱ Andrea Renda, MD,^j Andrea Valeri, MD,^k and Rocco Bellantone, MD,^a Rome, Milan, Naples, Pisa, Bologna, Turin, Padova, Pavia, and Florence, Italy

Background. We compared the oncologic effectiveness of open adrenalectomy and endoscopic adrenalectomy in the treatment of patients with localized adrenocortical carcinoma.

Methods. One hundred fifty-six patients with localized adrenocortical carcinoma (stage I/II) who underwent R0 resection were included in an Italian multiinstitutional surgical survey. They were divided into 2 groups based on the operative approach (either conventional or endoscopic).

Results. One hundred twenty-six patients underwent open adrenalectomy and 30 patients underwent endoscopic adrenalectomy. The 2 groups were well matched for age, sex, lesion size, and stage (P = NS). The mean follow-up time was similar for the 2 groups (P = NS). The local recurrence rate was 19% for open adrenalectomy and 21% for endoscopic adrenalectomy, whereas distant metastases were recorded in 31% of patients in the conventional adrenalectomy group and 17% in the endoscopic adrenalectomy group (P = NS). The mean time to recurrence was 27 ± 27 months in the conventional open adrenalectomy group and 29 ± 33 months in the endoscopic adrenalectomy group (P = NS). No significant differences were found between the 2 groups in terms of 5-year disease-free survival (38.3% vs 58.2%) and 5-year overall survival rates (48% vs 67%; P = NS).

Conclusion. The operative approach does not affect the oncologic outcome of patients with localized adrenocortical carcinoma, if the principles of surgical oncology are respected. (Surgery 2012;152:1158-64.)

From the Division of Endocrine and Metabolic Surgery,^a Università Cattolica del Sacro Cuore, Rome; Department of General Surgery and Videolaparoscopy,^b Niguarda Ca' Grande Hospital, Milan; Division of General Surgery "P. Valdoni,"^c University "La Sapienza," Rome; Division of General and Endocrine Surgery,^d University "Federico II," Naples; Departments of Surgery,^e University of Pisa, Pisa; University "Alma Mater Studiorum,"^f "S. Orsola-Malpighi" Hospital, Bologna; Division of Digestive, Colorectal and Minimal Invasive Surgery,^g University of Turin, Turin; Department of Medical and Surgical Sciences,^h University of Padova, Padova; Fondazione IRCCS Policlinico S. Matteo,ⁱ University of Pavia, Pavia; Department of Surgery,^j University "Federico II," Naples; and the Division of General I, Emergency and Minimally-invasive Surgery,^k Azienda Ospedaliero-Universitaria Careggi SOD, Florence, Italy

AFTER THE INTRODUCTION OF ENDOSCOPIC ADRENALECTOMY (EA) into clinical practice, it emerged as

the treatment of choice for most adrenal surgical disorders.¹ Most experts agree that EA is the criterion standard treatment for small to medium sized (≤6 cm) benign adrenal tumors, both functioning and nonfunctioning.¹⁻³ The role of EA in patients with adrenal malignancies is still controversial.⁴ Open adrenalectomy (OA) is the procedure of choice for invasive adrenal cortical carcinoma (ACC), allowing for a large, complete, and oncologically consistent en bloc resection.⁵⁻⁷ The increasing experience with EA and the excellent

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Reprint requests: Marco Raffaelli, MD, Istituto di Semeiotica Chirurgica, U.O. Chirurgia Endocrina e Metabolica, Università Cattolica del Sacro Cuore, Policlinico A. Gemelli, L.go A. Gemelli 8, 00168, Rome, Italy. E-mail: marcoraffaelli@rm.unicatt.it. 0039-6060/\$ - see front matter

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results of this procedure have led some authors to also propose it for large and potentially malignant adrenal tumors.^{4, 8-10} Moreover, with the widespread diffusion of EA, the number of patients with adrenal incidentaloma referred to adrenalectomy has increased.¹¹ This finding could imply a risk of unexpected diagnosis of localized ACC at final histology.¹² Indeed, the diagnosis of ACC is frequently made in up to 10% of patients with adrenal incidentaloma.¹³

Operative resection is of the utmost importance in the treatment of localized ACC (stage I/II) because margin-free complete resection is the only means to achieve long-term cure.¹⁴ Some reports have shown an increased risk of positive margin or tumor spill,¹² peritoneal carcinomatosis,^{15,16} and earlier recurrence¹² in patients undergoing EA for localized ACC. Similar findings have led an international consensus conference to strongly discourage EA for the treatment of known or suspicious ACC.¹⁴ In contrast, recently published studies have suggested that EA could achieve similar results in terms of recurrence rate as OA in the case of localized ACC.^{8,17-19} While OA is mandatory in cases of local invasion, strong evidence to recommend or discourage the endoscopic approach in patients with localized ACC is lacking.⁸

The aim of this study was to compare the oncologic effectiveness of OA versus EA in the treatment of patients with localized ACC based on a database of an Italian multiinstitutional surgical survey.

METHODS

After the previous experience with an Italian Registry of ACC,^{7,20} a new Italian multiinstitutional surgical survey was started in December 2003 with the aim to evaluate the medical care of ACC patients and to better characterize the clinical course and the outcome of this disease in Italy.²¹

A specific call was sent to the heads of Italian Surgical Divisions. After acceptance to participate by the center, a structured patient form specifically developed for this study was sent to collect comprehensive information on the diagnostic procedures, treatment, and follow-up of patients operated on for ACC. The completed form was sent back to the coordinating center via e-mail. A specific e-mail address (surrene@rm.unicatt.it) was created with this purpose.

The patient form included detailed information about demographics, primary diagnosis (including functional status), imaging studies, operative and pathologic data, adjuvant treatment(s), and follow-up data. Participating centers were asked to complete the forms (1 per enrolled patient) after

reviewing the medical records of the recruited patients and to provide follow-up information at the time of any relevant change in the course of the disease at least every 6 months. The recruitment and the follow-up of the included patients for this study were closed in July, 2010. All of the collected data were entered into a specifically designed database (Excel; Microsoft, Redmond, WA) by trained medical personnel.

Study design. Among the patients included in the survey, those who underwent radical surgery (R0 resection) for a localized (stage I/II) ACC were included in the present study.

The assessment of the preoperative work-up was based on treatment guidelines of the National Institutes of Health (NIH) state-of-the-science statement on management of the clinically unapparent adrenal mass of 2002²² and the recommendations from the European Network for the Study of Adrenal Tumors (ENSAT) on the care of ACC patients.⁹

Computed tomographic (CT) scans or, alternatively, magnetic resonance imaging (MRI) scans of the abdomen and a CT scan of the thorax were recommended for a complete radiologic evaluation.^{9,22}

The postoperative stage was based on the criteria proposed by MacFarlane and revised by Sullivan et al.²³ Overall survival (OS) for the study population was calculated from the date of the diagnosis to the date of the death, or to the date of the last follow-up evaluation for the patients who were still alive. Disease-free survival (DFS) was calculated from the date of diagnosis to the date of diagnosis of tumor recurrence, or to the date of last follow-up evaluation for patients without recurrence. Disease recurrence was diagnosed on the basis of clinical, laboratory, and radiologic evidence; histologic confirmation of the recurrence was not required.

The included patients were divided in 2 groups based on the operative approach: the OA group (OA-G) and the EA group (EA-G). A comparative analysis between the 2 groups was performed and included the following parameters: patients demographics, preoperative diagnosis, functional status, tumor size, lymph node dissection if any, complications, hospital stay, postoperative tumor stage, adjuvant therapy, and follow-up results.

Statistical analysis. Statistical analysis was performed using SPSS software (version 10.0; SPSS Inc, Chicago, IL). Continuous variables were expressed in terms of mean or median (as appropriate) \pm the standard deviation (SD), followed by the range. The χ^2 test was used for categorical

variables, and analyses of variance (ANOVAs) were used for continuous variables. OS and DFS curves were calculated according to the Kaplan–Meier method and were compared by means of the log-rank test. Regardless of the test used, $P < .05$ was considered significant.

Study endpoints. The primary endpoint was to compare the oncologic effectiveness of the open and endoscopic approach as evaluated by the OS and DFS. Secondary outcome assessment included the comparison of the mean time to recurrence and the type of recurrence (ie, local and/or distant).

RESULTS

At the time that the database for this study was closed (July 2010), 278 patients were recruited. Among them, 156 had a R0 resection for a stage I or II ACC and were included in the present study. The characteristics of the study population are listed in the Table. One hundred twenty-six patients underwent OA (OA-G), and the remaining 30 patients underwent EA (EA-G; Table). EA was accomplished using the lateral transabdominal approach in 29 cases and by the posterior retroperitoneoscopic approach in the remaining case. No conversion to OA was necessary in patients who underwent EA. Among the 122 excluded patients with stage III and IV ACC, 1 male patient underwent laparoscopic exploration to evaluate the resectability of the lesion as the first step of the operative procedure. After conversion to an open procedure, adrenalectomy and nephrectomy and splenectomy and distal pancreatectomy were performed. He died of unrelated causes (hepatic failure caused by cirrhosis) 3 months after the procedures.

The 2 groups were well matched for age, sex distribution, lesion size, and stage ($P = \text{NS}$; Table). A significantly greater rate of patients in the EA-G had a preoperative diagnosis of adrenal incidentaloma (25/30 vs 59/126), whereas the rate of secreting tumor was significantly greater in the OA-G (58/126 vs 4/30; $P = .001$; Table).

No case of tumor fragmentation was recorded in either group. Some lymph node dissection was performed in 24 patients: 1 in the EA-G (3%) and 23 in the OA-G (18%; $P = .079$). The mean operative time was similar in the OA-G and the EA-G (129 ± 54 vs 135 ± 65 , respectively; $P = .598$; Table).

Postoperative complications were registered in 7 out of 126 patients in the OA-G and 1 out of 30 patients in the EA-G ($P = .97$). The mean hospital stay was significantly shorter in the EA-G than in the OA-G (5.3 ± 3.7 vs 9.3 ± 6.2 ; $P < .001$).

The follow-up evaluation was completed in 134 patients: 110 in the OA-G and 24 in the EA-G. The mean follow-up time was 42 ± 35 months (range, 1–192 months): 40 ± 34 months (range, 1–192) in the OA-G and 50 ± 37 (range, 2–120) in the EA-G ($P = .192$; Table).

The rate of patients who underwent adjuvant therapy was 37% (41/110) in the OA-G and 38% (9/24) in the EA-G ($P = .832$).

The rate of local recurrence was 19% (21/110) and 21% (5/24) in the OA-G and in the EA-G, respectively. The rate of distant metastasis was 31% (34/110) in the OA-G and 17% (4/24) in the EA-G ($P = .497$). A combined pattern of recurrent disease (local recurrence and distant metastasis) was observed in 6% (7/110) of OA patients and 4% (1/24) of EA patients. The mean time to recurrence was 27 ± 27 months in the OA-G and 29 ± 33 months in the EA-G ($P = .839$).

At the most recent follow-up, 34% (46/134) of the patients had died, including 41 of 110 (37%) OA patients and 5 of 24 (21%) EA patients ($P = .194$).

The median DFS was 48 months in the OA-G and 72 months in the EA-G ($P = .120$). The median OS was 60 and 108 months for OA and EA patients, respectively ($P = .200$; Table). Five-year DFS and 5-year OS are shown in Figs 1 and 2, respectively.

DISCUSSION

ACC is a rare malignant tumor with an incidence of 1 to 2 million patients per year.⁸ ACC has a poor prognosis, with an overall 5-year survival rate ranging from 15% to 60% that correlates with disease stage at diagnosis.^{6,7,9} In spite of recent advances in terms of adjuvant treatment, including mitotane and chemotherapy protocols,^{9,14} complete local excision has, until now, been the only curative treatment.^{5,14} Even in recurrent disease, repeat resection can positively influence patient outcome.²⁰

Thirty percent of ACCs are stage I or II at presentation.⁸ Tumors in these stages are confined to the adrenal capsule, without invasion of the surrounding tissue, adjacent organs, lymph node, or distant metastases. At least from a theoretic point of view, they are amenable to curative local surgical resection.⁸ For all of these reasons, a comprehensive operative procedure, respecting the oncologic principles of R0 en bloc resection and without tumor grasping or tumor capsule rupture, is crucial.⁸

For localized neoplasms, an appropriate surgical resection should include adrenal gland and perirenal fat. In spite of recent reports

Table. Characteristics of the study population and comparative analysis between the open adrenalectomy and endoscopic adrenalectomy groups

No. of patients	All patients	OA-G	EA-G	P value
	156	126	30	
Age (yrs), mean ± SD (range)	47.7 ± 15.6 (10–81)	46.6 ± 15.1 (10–74)	52.0 ± 17.0 (26–81)	.088
Sex (male/female)	56/100	45/81	11/19	.909
Laterality (right/left)	87/69	64/62	23/7	.018
Preoperative diagnosis, n				.001
Secreting tumor	62	58	4	
Nonsecreting tumor	10	9	1	
Incidentaloma	83	59	25	
Lymph node dissection	24	23	1	.079
Operation time (min), mean ± SD (range)	131 ± 57 (30–300)	129 ± 54 (50–250)	135 ± 65 (30–300)	.598
Tumor size (mm), mean ± SD (range)	83.8 ± 43.0 (30–210)	90.4 ± 46.3 (30–210)	77.3 ± 34.3 (30–150)	.147
Tumor stage				
I	34	24	10	.145
II	122	102	20	
Postoperative complications	8	7	1	.972
Hospital stay (d), mean ± SD (range)	8.1 ± 5.8 (4–42)	9.3 ± 6.2 (4–42)	5.3 ± 3.7 (2–20)	<.001
No. who completed follow-up	134	110	24	.885
Follow-up time (mos), mean ± SD (range)	42 ± 35 (1–192)	40 ± 34 (1–192)	50 ± 37 (2–120)	.192
Adjuvant therapy	50	41	9	.832
Mitotane	18	14	4	
Polychemotherapy	10	6	4	
Mitotane plus polychemotherapy	22	21	1	
Recurrence	56	48	8	
Local	18	14	4	.497
Distant	30	27	3	
Local and distant	8	7	1	
Time of recurrence (mos), mean ± SD (range)	27 ± 28 (1–115)	27 ± 27 (1–115)	29 ± 33 (9–87)	.839
5-yr disease-free survival	43.1%	38.3%	58.2%	.120
Median disease-free survival (mos)	60	48	72	
5-yr overall survival	51.5%	47.5%	66.5%	.200
Median overall survival (mos)	72	60	108	

EA-G, Endoscopic adrenalectomy group; OA-G, open adrenalectomy group; SD, standard deviation.

indicating that locoregional lymph node dissection may improve tumor staging and lead to a favorable oncologic outcome in patients with localized ACC,²⁴ there is no precise definition of locoregional lymph node dissection and no consensus about its role in the management of ACC patients.^{8,9}

In contrast, early after its introduction into clinical practice, EA emerged as the treatment of choice for most adrenal masses^{1,2}—including large and potentially malignant tumors^{4,10}—because of its unequivocal advantages over OA in terms of postoperative recovery. In addition, it has been shown that after the introduction of EA, a greater

percentage of patients with adrenal incidentaloma were selected for adrenalectomy.¹¹ Moreover, about 10% of the resected adrenal incidentaloma have a pathologic diagnosis of ACC,¹³ and on occasion ACCs have been unknowingly removed using a laparoscopic approach.¹² Indeed, in the absence of radiologic evidence of the invasion of surrounding tissues, lymph node involvement, intravenous thrombus, or distant metastases, may be difficult to predict malignancy in adrenal incidentaloma.^{13,22} As a consequence, the role of EA in the treatment of ACC has emerged as one of the most controversial and debated points in adrenal surgery. After early case reports describing

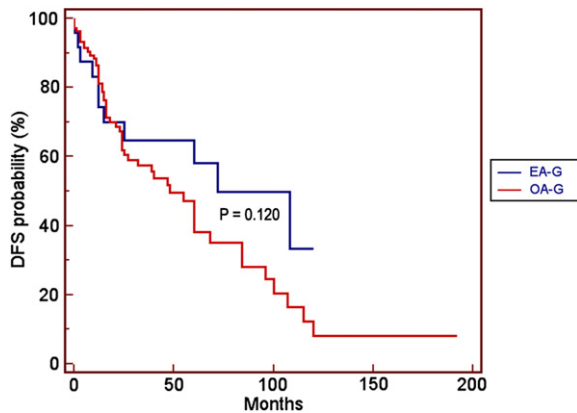


Fig 1. Five-year disease-free survival (DFS) in the open adrenalectomy (OA-G) and endoscopic adrenalectomy (EA-G) groups. (Color version of figure is available online.)

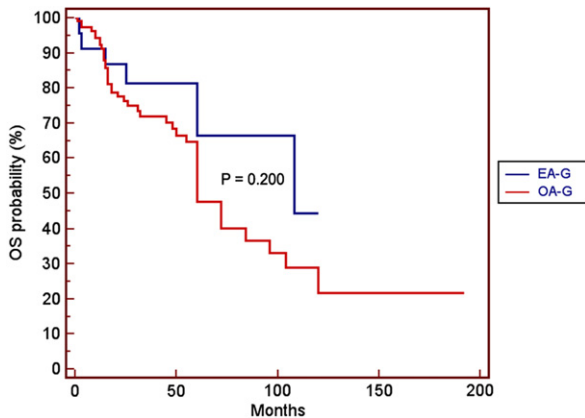


Fig 2. Five-year overall survival (OS) in the open adrenalectomy (OA-G) and endoscopic adrenalectomy (EA-G) groups. (Color version of figure is available online.)

tumor dissemination after EA,⁸ more recent reports based on single tertiary care referral center experiences determined important concerns about the endoscopic removal of adrenal tumors, revealing an increased risk of positive margin or tumor spill,^{12,15} peritoneal carcinomatosis,^{15,16} and earlier recurrence¹² for EA. On the basis of such results, Miller et al¹² concluded that “Although feasible in many cases and tempting, laparoscopic resection should not be attempted in patients with tumors suspicious for or known to be adrenocortical carcinoma.” However, similar findings should be considered in the context of selection bias, related to the referral of patients to a tertiary care referral center for treatment of recurrent disease, after initial laparoscopic surgery in other nonreferral centers.^{8,12,15,16} Recently published comparative studies based on single-center¹⁸

or multiinstitutional series¹⁹ found that the oncologic outcomes of localized ACC after EA could be similar to those seen after laparoscopic resection.

In a study by Porpiglia et al,¹⁸ 43 patients underwent operations for a stage I or II ACC at the author’s institution or were referred after resection for postoperative management and treatment; 18 underwent EA and 25 underwent OA. Only patients who underwent radical R0 surgery were included. The 3-year survival rate was 84% for patients who underwent OA and 100% for those who underwent EA. The recurrence rate was 64% in the open group compared to 66% in the laparoscopic group.¹⁸ Similarly, in a study by Brix et al¹⁹ based on data from a German ACC registry, 152 patients with ENSAT stage I–III ACC neoplasms measuring <10 cm were included; 35 underwent EA and 117 underwent OA. The recurrence rate was 77% for the EA-G and 69% for the OA-G.¹⁹ The authors did not find any significant difference in terms of DFS or OS.¹⁹

The results of the present study confirm such previous reports. No significant differences were found between the EA-G and OA-G in terms of 5-year OS and DFS rates (Table). Moreover, survival rates were similar to those reported in the literature for stage I and II neoplasms.^{6,7,25} Indeed, the 5-year survival rates for patients with localized ACC who underwent radical surgery have been reported to be 38% and 61%.^{6,7,25}

A previously published study suggested that EA is associated with a significantly lesser time to local recurrence and a significantly greater local recurrence rate.¹² Unfortunately, about 50% of the cases included in that paper had positive margins or intraoperative tumor rupture during EA compared to 18% of those who underwent OA.¹² Indeed, the manipulation of the adrenal neoplasms with endoscopic instruments implies the theoretic risk of inadvertent tumor capsule fracture and tumor cell seeding, with consequent local and port site recurrence and peritoneal carcinomatosis. This worry is particularly true for large adrenal neoplasms and in the case of difficult dissection because of tumor adhesion with adjacent structures.

However, surgical experience plays a crucial role in the oncologic results. Indeed, recent reports indicated that center volume and surgeon experience are of key importance for the oncologic outcome of patients with adrenal neoplasms.^{5,21,25}

Conversely, in the present series, all patients underwent R0 radical surgery and a minority of them also underwent some lymph node dissection, with no significant difference between the EA-G

and the OA-G (1/30 vs 23/126; $P = \text{NS}$). We found no significant difference in terms of mean time to recurrence and of type of recurrence (local versus distant) between the EA-G and the OA-G (Table). As we have reported recently,²¹ despite this study being multiinstitutional, most of the patients of the present series were treated at high-volume centers. This finding could at least in part explain the results obtained in terms of OS and DFS. In other words, it seems clear that the operative approach does not affect the prognosis of patients with stages I and II ACC if the principles of oncologic surgery are respected.

In contrast, the results of the present study confirm that EA is associated with a better postoperative outcome. Indeed, even if complication rates were not significantly different between the 2 groups, EA is associated with a significantly shorter hospital stay (Table).

Considering the well known advantages related to EA and the fact that there is no significant difference in terms of oncologic outcome, it is difficult to argue that large and/or potentially malignant adrenal masses should not undergo EA, in absence of the evidence of local invasion or distant metastases. Obviously, conversion to the open approach is recommended in cases where signs of local invasion are found or the dissection is difficult and implies the risk of tumor capsule rupture.^{8,10} Conversion should not be considered a defeat for the surgeon but rather a different way to safely accomplish the surgical procedure.

The present study is based on a multiinstitutional retrospective survey, and this is its main limitation. Moreover, the follow-up is relatively short and the sample size is relatively small; additional series would be of great value. Prospective randomized trials on this topic are not likely to be performed, because the disease is rare, and most of the diagnoses in localized neoplasms are pathologic. Another potential bias of the present retrospective study could be related to patient selection for the 2 approaches. Indeed, in clinical practice, smaller tumors are selected for EA while locally infiltrating and metastatic tumors (stage III/IV) are selected mandatorily for OA. However, we included only patients with pathologically proven localized (stage I/II) ACCs who underwent R0 resection. This allowed for minimization of this potential selection bias, as indicated by the fact that no significant difference concerning tumor size and stage was found between the 2 groups (Table).

In conclusion, our results suggest that in patients with stage I and II ACC, EA is not inferior

to OA in terms of oncologic outcome. As a consequence, EA performed by experienced surgeons respecting the principles of radical R0 resection—without tumor capsule rupture and removing the periaxonal fat—is justified for large and potentially malignant adrenal masses and for selected cases of stage I and II ACC. OA is mandatory in cases of pre- or intraoperative evidence of adjacent organ invasion and lymph node involvement or distant metastases (stage III/IV ACC).

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DISCUSSION

Dr Paul Gauger (Ann Arbor, MI): Can you explain a little further, your study group, as it relates to staging, and at what point you made that determination? To Dr Miller's point, you talked about including only stage I and stage II tumors. Was that the preoperative stage, and when the upstaging occurred with pathologic results? How did you

treat that statistically? Was that patient then excluded from the data we saw today?

Dr Carmela De Crea (Rome, Italy): This was a retrospective study. And we included just patients in stages I and II on the basis of pathology. We know that there is a potential patient selection bias, because, generally, in clinical practice, you include a smaller lesion for the laparoscopic approach and a larger lesion for the open approach. So we chose to include only stage I and II patients based on final histology reports.

Dr Jeffrey Lee (Houston, TX): I think the audience is left to square the results of your analysis with those that were just presented from the University of Michigan that mirror the results from M. D. Anderson pretty much exactly.

And I have 2 questions.

One is, were any patients who underwent laparoscopic adrenalectomy excluded from analysis because they had either tumor fracture or contamination or incomplete resection? In other words, did you limit the analysis to only patients who, in your judgment, had had complete resection of intact tumors?

And the second question: is there a possibility, a bias, because of the survey nature of the collection of the data, as opposed to a single individual or group of individuals reviewing all of the available clinical data? In other words, the complete lack of peritoneal carcinomatosis in any of the patients in your series suggests an unusual natural history that we just do not see here in the United States, certainly either at Michigan or at M. D. Anderson.

Dr Carmela De Crea (Rome, Italy): No case of tumor fragmentation was reported. Among the 122 patients that were excluded, we had 1 case of a conversion from laparoscopic to open technique.

With regard to your second question, bias is possible because it is a retrospective multiinstitutional survey. But I think, considering the rarity of this disease, that it is difficult to try to do a prospective randomized study.

Dr Marybeth Hughes (Bethesda, MD): Because you only had 30 patients in the laparoscopic group, and 24 came for follow-up, do you think that your *N* is insufficient to make your conclusions and rule out a type I error?

Dr Carmela De Crea (Rome, Italy): Again, this is a limitation related to the retrospective nature of the study. Actually, our conclusion underlined that in the case of invasive local carcinoma, an open approach is clearly indicated and mandatory. We also know that the surgeon's experience is crucial for the resection of this disease. Our data suggest that in experienced hands, laparoscopic adrenalectomy can be safely performed in patients with preoperatively unknown adrenocortical carcinoma, when the principles of surgical oncology are respected and any tumor fragmentation or capsule fracture are avoided.