Resection of adrenocortical carcinoma is less complete and local recurrence occurs sooner and more often after laparoscopic adrenalectomy than after open adrenalectomy

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Background. *Controversy surrounds the use of laparoscopy for resection of adrenocortical carcinoma. We evaluated the hypothesis that outcome is equivalent in patients undergoing laparoscopic adrenalectomy versus open adrenalectomy.*

Methods. *This is a retrospective review of 217 patients (156 patients with stage I–III cancer) with adrenocortical carcinoma referred to a single institution between 2005 and 2011. Outcome and operative data were assessed for the subset undergoing resection with curative intent. Student* t *and Fisher exact tests and the Kaplan–Meier method were used to compare data (*$P \leq .05$ *was considered statistically significant).*

Results. *One hundred fifty-six patients (64% female; median age, 47 years [range, 18–80]; median follow-up, 26.5 months [range, 1–188]) were identified. Forty-six patients underwent laparoscopic adrenalectomy, and 110 underwent open adrenalectomy. Twenty-seven percent of laparoscopic adrenalectomy patients had stage III cancer. After laparoscopic adrenalectomy, 30% had positive margins or intraoperative tumor spill compared to 16% of the open adrenalectomy patients (*$P = .04$*). Overall survival for patients with stage II cancer was longer in those undergoing open adrenalectomy (*$P = .002$*). Time to visible tumor bed recurrence or peritoneal recurrence in stage II patients was shorter in laparoscopic adrenalectomy patients (*$P = .002$*).*

Conclusion. *Open adrenalectomy is superior to laparoscopic adrenalectomy for adrenocortical carcinoma based on completeness of resection, site and timing of initial tumor recurrence, and survival in stage II patients. Intraoperative evaluation is insensitive for the detection of stage III tumors. (Surgery 2012;152:1150-7.)*

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Adrenocortical carcinoma (ACC) is a rare and lethal disease with an annual incidence of approximately 2 per 1,000,000 patients. Because historical data indicate that both local recurrence and distant metastases after initial resection is frequent, even in patients with stage I and stage II cancer, ensuring a complete, margin-negative tumor resection at the initial operation is crucial. While an open surgical approach has been the mainstay of treatment for decades, a few recent reports have challenged the need for open resection as a radical oncologic approach and instead advocate for laparoscopic adrenalectomy (LA)—the criterion standard for benign adrenal disease—as the treatment of choice in the initial surgical approach to ACC in select cases. Most accounts of laparoscopically resected ACC are included in papers discussing LA in general, comprised of only a few cases, and suffer from a lack of long-term oncologic follow-up. In the past few years, several European and American centers have reported results from larger cohorts of patients undergoing laparoscopy for ACC.[1-6]

Most clinicians who oppose the use of LA in this context dispute the ability to perform an

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oncologically equivalent resection compared to open adrenalectomy (OA). Commonly accepted oncologic principles are not widely reported for either LA or OA. However, based on the integration of laparoscopic resection for other types of cancer, the concern for adherence to these principles is likely to be higher for LA. Comparisons of LA to OA may show no difference if both types of operations are performed poorly, because the aggressive biologic behavior of ACC is different from other tumors and does not allow for intraoperative misadventures and poor technical skills.

Two central questions must be answered: which technique allows the surgeon to perform the best possible oncologic resection, taking into account the inherent challenges associated with both techniques? What is the impact of each technique on recurrence, both local and distant, and overall survival? While distant metastases are not likely under the control of the surgeon and are more likely related to tumor biology and nontechnical factors, tumor bed and peritoneal recurrence can quite plausibly be related to the surgeon's actions, respect for oncologic principles, and technical precision. This study evaluates the hypothesis that outcome is equivalent in patients undergoing LA compared to OA. Specifically, while we suspect that patients who undergo LA experience higher rates of incomplete resection and develop tumor bed or peritoneal recurrence significantly earlier and more often than patients who undergo OA, we have investigated the null hypothesis that the laparoscopic approach is not inferior.

METHODS

This study is a retrospective review of 217 patients (156 patients with stage I–III cancer) with ACC evaluated by the multidisciplinary adrenal clinic at the University of Michigan between July 2005 and November 2011. Outcomes of 88 stage I–III patients were reported in 2010,[6] and this current study allows for continued follow-up of those patients while adding 68 new patients. Patients with stage IV disease at diagnosis were excluded from recurrence analysis because any resection that might have been performed was for palliative reasons only. Demographics, European Network for the Study of Adrenal Tumors (ENSAT) stage at presentation using information from pre- and postoperative imaging, pathology reports, operative reports, pathology, adjuvant therapy received, and outcome data were collected and reviewed to compare patients who underwent LA versus OA for ACC. Specific aspects of surgical resection that were reviewed included the operative approach, recognition of violation of the tumor capsule, and findings of positive margins by pathologic review. Specific outcomes recorded included current disease status, time to first recurrence, site(s) of initial recurrence (tumor bed, peritoneal cavity, vascular, or lymphatic borne distant metastases), duration of follow-up, and time to death. Time to additional sites of recurrence after the initial recurrence was not recorded because treatment received for the initial recurrence could affect the subsequent disease course.

Outcomes were initially calculated for patients grouped by type of resection (LA or OA) and then broken down by stage and resection status. In addition, because a significant percentage of patients assumed to be stage II by preoperative imaging are found to be stage III by pathologic examination and documentation of microscopic periadrenal soft tissue invasion, this subgroup was also examined. This was an attempt to recreate everyday practice conditions faced by surgeons making decisions about operative approach for adrenalectomy in the setting of possible malignancy.

The final subgroup compares LA and OA patients with tumors <10 cm assumed to be stage II based on preoperative imaging and intraoperative findings, because at least 1 set of guidelines suggest that LA is equivalent to OA in presumed stage II ACC patients <10 cm.[7] All comparisons were made using the Student t and Fisher exact tests and the Kaplan–Meier method. $P \leq .05$ was considered statistically significant. The Predictive Analytics SoftWare package (version 18.0.3; IBM SPSS, Armonk, NY) was used for analysis.

RESULTS

Of 217 ACC patients, 156 were identified as having stage I–III cancer at the time of initial resection. Demographics are listed in Table I. Overall survival by stage is shown in Fig 1. LA was performed in 46 patients; 110 patients underwent OA. Initial resections performed at the University of Michigan accounted for 24 of 156 (15.4%) cases. The median tumor size of those undergoing LA was 7.4 cm (range, 3.2–16.5; median stage, II) compared to 12.0 cm (range, 5–28; median stage, III) for OA. Adjuvant mitotane administered to patients undergoing margin-negative (R0) resections was similar ($P = .15$), as was use of XRT ($P = .16$).

The review of radiologic characteristics concerning for malignancy revealed that 45 of 46 laparoscopically resected tumors were >4 cm.[8] When the size cut-off for concern of malignancy was increased, only 8 tumors resected laparoscopically were <6 cm. Tumor imaging characteristics, such as internal heterogeneity, were also reviewed, and

Table I. Demographics

		Adrenalectomy		
	Total	*Laparoscopic*	*Open*	P *value*
No. of patients	156	46	110	
Median age (yrs) (range)	47 (18–80)	50 (20–80)	47 (18–75)	.22
Female gender (%)	64	72	62	
No. of patients by stage undergoing intended curative resection				
I	4	4	0	
II	84	29	55	
III	68	13	55	
Tumor size (cm)				
Overall (range)	11.0	7.4 (3.2–16.5)	12.0 (5–28)	
Stage I	4.25	4.25	N/A	
Stage II	10.0	7.25	12.0	
Stage III	11.9	9.0	12.0	
Median duration of follow-up (mos) (range)	26.5 (1.1–188.5)	19 (1.11–145.9)	29.5 (0.9–188.5)	<.01

N/A, Not available.

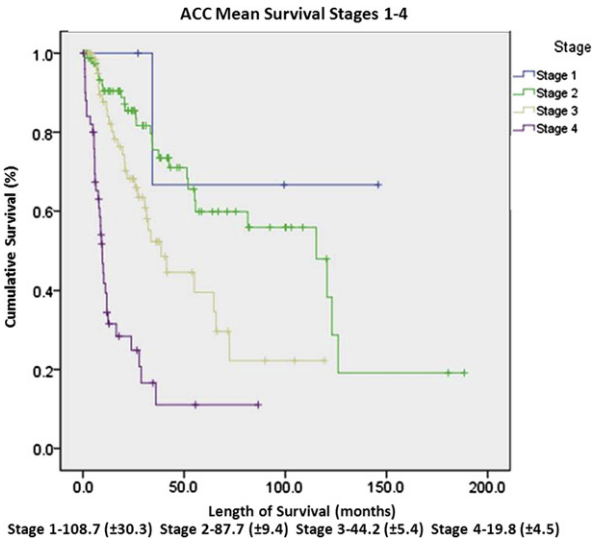

Fig 1. Overall mean survival of stage 1–4 adrenal cancer patients reported in months. *Hashmarks* indicate censored patients. (Color version of figure is available online.)

all laparoscopically resected tumors had varying degrees of concerning imaging characteristics.

No adjacent organs or vessels were resected in the entire LA group compared to 17 of 55 (31%) stage II and 34 of 55 (61%) stage III OA cases. The remaining 21 patients with stage III cancer had microscopic invasion noted on final pathology. Of those undergoing LA, 30% had positive margins or notation of intraoperative tumor spill (5 other pathology reports noted "close" or <1 mm margins) compared to 16% of OA ($P = .04$). When considering those who underwent an R0 resection, 18 of 26 (69%) LA patients recurred. Of these, 17 of 18 (94.5%) recurrences included the tumor bed or peritoneum at the time of initial recurrence. Of 72 patients undergoing R0 OA, 45 (62.5%) recurred during the follow-up period. Of all sites of R0 OA recurrence, 26 (58%) included the tumor bed or peritoneum at the time of initial recurrence. This does not take into account tumor stage or extent of resection (adrenalectomy versus adrenalectomy with adjacent organ[s]).

Occurrence of and time to initial visible recurrence in the tumor bed and peritoneum (TB/PER) was analyzed (Table II). The overall incidence of TB/PER recurrence at the time of initial recurrence for stage I–III cancers was 85.7% for LA and 40% for OA ($P = .07$), but this did not take into account the higher overall stage of OA patients or the resection status. Comparisons for recurrence and survival were not made for stage I because there were no OA patients with stage I cancer. Stage II percent initial recurrence in the TB/PER for the LA group was 55.2% vs 34% in the OA group. Mean time to recurrence in the TB/PER was significantly shorter in the LA group (11.7 months [standard deviation {SD}, ±2.1] LA vs 29.5 [SD, ±5.2] OA; $P = .002$; Fig 2). This difference persisted when examining R0 resections only (12.3 months [SD, ±2.1] LA vs 30.5 [SD, ±5.7] OA; $P = .002$). The same is found overall ($P = .001$) and for R0 resections ($P = .002$) when assessing time to first recurrence anywhere (Table III) in patients with stage II cancer. Stage III mean time to recurrence in the TB/PER was nearly significantly shorter in the R0 resection LA group (4.0 months [SD, ±2.4] LA vs 14.6 [SD, ±4.2] OA; $P = .06$). Time

Table II. Mean time to first recurrence tumor bed or peritoneal cavity (months ± standard error of the mean) according to postoperative stage (II or III) and resection status

	Time to first recurrence tumor bed or peritoneal cavity (mos)			
	Overall	*R0 resection*	*Positive margin*	P *value*
Stage II				
Overall	22.0 (±3.6)	22.5 (±3.7)	4.3 (±0.0)	UTC
LA	11.7 (±2.1)	12.3 (±2.1)	4.3 (±0.0)	UTC
OA	30.5 (±5.7)	30.5 (±5.7)	UTC	UTC
P value	.002	.002	UTC	—
Stage III				
Overall	11.7 (±3.5)	20.3 (±6.9)	4.4 (±1.0)	.005
LA	6.1 (±2.2)	0.7 (±0.0)	6.9 (±3.1)	UTC
OA	13.1 (±3.5)	22.1 (±7.3)	3.4 (±0.7)	.001
P value	.19	UTC	.19	—

LA, Laparoscopic adrenalectomy; *OA*, open adrenalectomy; *UTC*, unable to calculate.

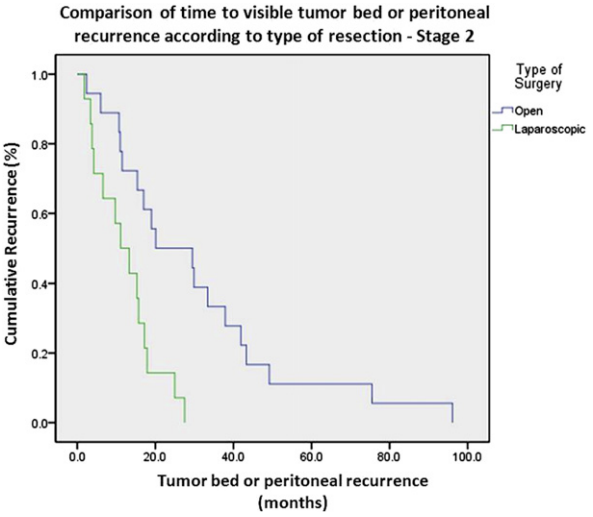

Fig 2. Time to visible tumor bed or peritoneal cavity recurrence in months for patients with stage 2 cancer undergoing laparoscopic adrenalectomy versus open adrenalectomy (P = .002). (Color version of figure is available online.)

to TB/PER recurrence and recurrence elsewhere was significantly shorter in those with positive margins versus R0 resections in stage III patients (P = .001 and P = .004, respectively), but were not significant in the other stage II or III subgroups.

Importantly, overall survival (Table IV) in stage II patients undergoing any type resection was significantly worse in those undergoing LA versus OA (50.9 months [SD, ±9.8] LA vs 103.1 [SD, ±10.9] OA; P = .002]). Broken down by resection status, survival remained significantly worse even when comparing LA and OA in those undergoing R0 resections (54.5 months [SD, ±11.3] LA vs 101.6 [SD, ±14.0] OA; P = .05). There was a trend toward improved survival in those undergoing OA who had positive margins compared to LA patients with positive margins (P = .09). Survival between groups in stage III was not different (P = .77).

In an effort to simulate the effect of the surgeon's pre- and intraoperative assessment on outcome based on the decision regarding operative approach, all pre- and intraoperative stage II tumors were compared to postoperative pathologic stage (Table V). Margin status was also evaluated. No stage I patients were upstaged. Of LA patients presumed to be stage II, 13 of 42 (30%) were upstaged to stage III only after pathologic examination. OA patients with preoperatively presumed stage II disease were found to have unsuspected stage III disease in 22 of 71 (31%) cases. In these unsuspected stage III patients, 8 of 12 (75%) LA had positive margins, with 3 others noted to have margins within 1 mm. One patient's margin status was not reported. In the OA group, 8 of 22 (36%) had positive margins, 1 was close, and 3 were unknown, suggesting that even when surgeons assume no periadrenal fat or adjacent organ invasion, there is a trend (P= .07) toward more complete resection of adjacent periadrenal tissue, which is better accomplished with OA.

Some groups suggest LA for ACCs <10 cm; however, when looking at this group in our patients, of 34 LA patients with tumors <10 cm, 8 were upstaged to stage III after surgery, 9 of 30 (30%) with specific comments about margin status had positive margins, an additional patient had intraoperative tumor spill, and 2 others had "close" margins. Of 36 OA patients, 7 of 15 stage III patients were upstaged only after resection. Of 29 patients with margin data, 9 were positive (3/9 had additional organs resected), there was no reported intraoperative tumor rupture, and 1 had "close" margins. The difference in mean size

Table III. Mean time to first recurrence anywhere distant (months ± standard error of the mean) according to postoperative stage (II or III) and resection status

	Time to first recurrence anywhere distant (mos)			
	Overall	*R0 resection*	*Positive margin*	P *value*
Stage II				
Overall	41.7 (±6.1)	37.1 (±6.6)	54.8 (±13.5)	.34
LA	17.6 (±3.0)	16.7 (±3.0)	18.5 (±6.9)	.70
OA	52.9 (±8.1)	46.7 (±9.0)	71.8 (±15.8)	.21
P value	.001	.002	.09	—
Stage III				
Overall	9.6 (±2.3)	13.2 (±3.7)	4.4 (±0.9)	.01
LA	5.0 (±1.8)	4.0 (±2.4)	5.7 (±2.6)	.33
OA	10.7 (±2.8)	14.6 (±4.2)	3.9 (±0.8)	.004
P value	.12	.06	.33	—

LA, Laparoscopic adrenalectomy; *OA*, open adrenalectomy.

Table IV. Mean length of survival (months ± standard error of the mean) according to postoperative stage (II or III) and resection status

	Length of survival (mos)			
	Overall	*R0 resection*	*Positive margin*	P *value*
Stage II				
Overall	87.7 (±9.4)	89.2 (±11.9)	77.6 (±16.0)	.92
LA	50.9 (±9.8)	54.5 (±11.3)	25.5 (±4.7)	.09
OA	103.1 (±10.9)	101.6 (±14.0)	103.4 (±22.1)	.87
P value	.002	.05	.09	—
Stage III				
Overall	44.2 (±5.4)	44.2 (±6.1)	38.8 (±6.6)	.81
LA	27.5 (±3.9)	27.2 (±7.2)	24.6 (±3.9)	.95
OA	43.7 (±5.6)	43.9 (±6.2)	38.8 (±6.6)	.77
P value	.77	.87	.53	—

LA, Laparoscopic adrenalectomy; *OA*, open adrenalectomy.

Table V. Change in patient stage based on preoperative imaging and intraoperative findings versus postoperative stage based on pathologic assessment

	Laparoscopic adrenalectomy	*Open adrenalectomy*
Stage II		
Preoperative	42	77
Postoperative	29	55
Stage III		
Preoperative	0	33
Postoperative	13	55
Percent upstaged	30% (13/42)	31% (22/71)

between LA and OA margin-positive specimens was 1 cm (LA, 7.4 cm; OA, 8.4 cm). A comparison of <10 cm stage II LA versus OA patients shows a shorter time to initial recurrence in the tumor bed in the LA group ($P = .03$), but time to distant recurrence as the initial site of recurrence and survival were not different ($P = .13$ and $P = .10$, respectively) possibly because of the smaller subgroup size.

DISCUSSION

This report evaluates the efficacy of 2 surgical techniques, separating TB/PER recurrences more likely related to the resection technique itself from more distant vascular and lymphatic-borne recurrences that are likely less influenced by surgical technique. This study also assesses outcome based on pre- and intraoperative judgement regarding tumor characteristics rather than staging patients solely based on postoperative pathologic results. The decision to perform OA for ACC is imperative. Starting a resection laparoscopically and assessing the tumor directly violates important oncologic principles of resection. In addition, pre- or intraoperative evaluation is insensitive for detection of many stage III tumors because of microscopic invasion, and therefore all known or suspected ACCs should be treated as if microscopic periadrenal invasion is present.

This study shows that OA is superior to LA. Overall time to initial recurrence (local and/or distant) and survival is improved in stage II patients when undergoing OA. These findings persist even when both LA and OA groups have undergone R0 resections, implying some type of inherent difference in the techniques. Stage III margin-negative resections were much higher among OA patients, and a true comparison of stage III patients who had R0 resections could not be made because only 1 stage III LA patient had a R0 resection.

Also concerning is the lack of appreciation of possible ACC based on radiologic characteristics resulting in a decision to proceed with LA. Significant effort should be extended to educating clinicians about recognizing the potential for ACC in order to make an appropriate choice regarding type of resection. Recently published guidelines from the European Society of Endocrine Surgeons suggest that laparoscopic resection is acceptable if imaging appears to suggest a stage I or II tumor ≤10 cm.[7,9] Based on our current data, including the inability to accurately identify stage III tumors requiring more extensive resections, we disagree with this position statement and suggest that these guidelines be re-evaluated.

While we have reported significant findings in this study that may have important implications for the future, we must consider this work in the context of its limitations. First, this was a retrospective study using a cohort of patients evaluated at a single institution. Despite this, it is one of the largest series comparing LA and OA in an extremely rare and lethal disease. It not only reviews data in a retrospective fashion, but also assesses outcome in a prospective fashion. Second, this study examines the role of surgical technique in disease outcome by evaluating initial failure in local control rather than using all sites of recurrence noted at any time during the disease course. Later recurrences could be influenced by metastatic tumor elsewhere rather than by the surgical technique, as well as potentially being affected by any treatments administered to manage the identified metastatic tumor. Third, laparoscopic resections for suspected ACC are not knowingly performed at our institution, and some have been critical of this approach as a limitation.[6] Because we see patients from all over the country at all different times during the disease process, our study population and results reflect broad practice patterns that help generalize our findings. Guidelines should be aimed at all providers privileged to perform these procedures, not just a select few, and therefore we do not see that the minority of initial operations performed at our institution is a limitation. While referral of patients with ACC to specialized centers would be optimal, this is not possible for many patients in a large country like the United States with long travel distances, economic disparities, and variable access to care for patients. Lastly, follow-up was significantly longer in the open group, and therefore even greater differences in recurrence and survival may be seen as follow-up time lengthens.

In a disease such as ACC, where little progress has been made in improving outcomes, optimal treatment of the disease must be approached in an incremental fashion—concentrating on factors that can be controlled rather than hoping that overall cure will be achieved with 1 type of operation or treatment alone. With any adrenal mass, it is imperative that the surgeon make a decision preoperatively regarding the potential for malignancy, and the operation should be conducted with that in mind. The quality of the resection performed must also be critically assessed because the patient's life depends on it. The surgeon must strive to achieve long-term local control of disease as the first step in having a long-term impact on disease outcome. One cannot assume that 2 surgical approaches are equivalent by only relying on similar overall survival, because tumor biology plays a significant role in distant metastases and survival. Studies should differentiate between TB/PER recurrence and metastases caused by vascular or lymphatic invasion. One must plan for the future when more successful chemotherapy or other modalities are available.

All previous studies comparing laparoscopic versus open resection for ACC have limitations, and some conclusions have been misleading. Of the larger studies published since the first International Adrenal Cancer Symposium was held in Ann Arbor, MI in 2003,[10] Porpiglia et al[2] reported in 2010 evidence that LA may be comparable to OA in patients with stage I and II ACC based on no significant difference in recurrence-free survival. A significant limitation of the reported series was that patients who had macroscopically incomplete resection, tumor capsule violation, conversion from laparoscopic to open surgery, and those found to have microscopic periadrenal fat invasion based on final pathology (stage III after surgery) were excluded from the study.

A study from the German Adrenocortical Carcinoma Registry Group reported no difference in survival, disease-free recurrence, tumor capsule violation, or peritoneal carcinomatosis among 117 patients undergoing OA and 35 patients undergoing LA for stage I–III ACCs <10 cm.[3] Patients

undergoing LA were also matched with a patient having undergone OA. While matching LA and OA patients is appropriate, the factors chosen lead to many additional questions of confounding factors. Three times as many patients in the OA group had stage III disease. Patients undergoing R1 or R2 resection should have been excluded in a subgroup analysis. Data was not available regarding resection status for 33% of OA and 26% of LA patients (32% of entire group). Resection status was unknown in 37% of OA matched controls.

Leboulleux et al[4] found that the only risk factor of peritoneal carcinomatosis occurring during follow-up for the entire study group was the surgical approach ($P = .016$).[4] Data reported from MD Anderson Cancer Center in 2005 revealed a high risk of peritoneal carcinomatosis after LA (83% [5/6]) vs 8% in 133 undergoing OA.[5] Future studies should consider the outcome based on what the suspected preoperative stage was and differentiate between recurrences most likely related to surgical technique rather than those more likely affected by tumor biology. Surgical technique must be optimized in anticipation of a time when additional, more efficacious therapies are available.

In conclusion, surgeons must carefully evaluate preoperative imaging to suspect ACC. An open approach for resection of ACC should be chosen and the operation should be conducted in an oncologically appropriate manner. Incomplete or flawed resection is significantly greater in patients undergoing LA. OA is superior to LA for ACC based on completeness of resection, site and timing of initial tumor recurrence, and survival in stage II patients. Pre- or intraoperative evaluation is insensitive for detection of stage III tumors. It is the surgeon's opportunity and responsibility to limit local and peritoneal recurrence, because distant metastases likely cannot be greatly influenced by type of surgery. Meticulous technique is imperative, because nonadherence to oncologic principles of resection will certainly lead to poor outcomes regardless of operative approach.

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DISCUSSION

Dr Quan-Yang Duh (San Francisco, CA): It is great that you follow up on your previous findings. I think the issue seems to come down to: is this a technical issue, or is this just tumor biology, as you mentioned?

What strikes me is that your laparoscopic group has a tumor size from 3.2 cm to 16.2 cm. In my mind, a 16.2-cm adrenal tumor that looked like a cancer probably will be obviously inappropriate. In that case, most likely that is a judgment mistake from the surgeon's standpoint.

On the other hand, if you are advocating that we should be removing 3.2-cm lesions open, there will be a lot of discussion about whether or not that is a sensible thing to do. As you know, the literature from colon cancer resection has gone full circle after about 15 years, with a prospective, randomized study, that it used to be said that you should never touch a colon cancer laparoscopically. Now, that is the only way you should touch a colon cancer.

My question for you is, what do you do with a 3-cm lesion that you are taking it out because you worry that it may be a cancer, as per the paper that was just discussed now?

Dr Barbra Miller (Ann Arbor, MI): When I look at these, we go based not only on size but also by imaging criteria. So it is not just the size; we will pick up small ACCs based on internal imaging characteristics alone.

I agree will with you that it is inappropriate to resect the 16-cm tumor laparoscopically. I do have an extra slide that talks about the imaging characteristics, because in all of the patients that had laparoscopic resections, there was concern for malignancy based on size and/or the criteria that we use for assessing internal imaging characteristics.

And so that is something where we need some more education, I think, in terms of helping our surgeons understand what to do when they think they are operating on an ACC. From my standpoint, to give that patient the best operation possible, that is done by an

open resection, because I can do certain things open from an oncologic standpoint that I cannot do laparoscopically. That includes packing off the rest of the abdomen.

All laparoscopic patients had concerning imaging characteristics based on just the internal imaging characteristics. But when we looked at size, using 4 cm as a cut-off, all but 1 were above this. Normally I say we do not take out tumors laparoscopically, but the 3.2-cm tumor was actually from our institution in 1998. That patient had nearly 50% washout and 1 single area of heterogeneity. And that, again, is one where we sit in tumor board and we say, what do we do with these? This part looks a little funny, but the rest looks fairly benign.

I think today PET scans can help you out quite a bit. And we do that frequently. So I jump to PET scan now if there are any questions. That helps me figure out which way to approach these tumors. But I would say from upfront, I decide am I treating this and taking it out because I think it is cancer? If I am, then I do that as an open resection. And that way, especially for these microscopically invasive tumors that turn out to be stage III, I am taking that entire area from the renal hilum to the diaphragm and from side wall to vena cava out, and there is nothing left, so that they get a good wide resection. They get a thorough exploration. Their liver is ultrasounded. I start that operation as a cancer operation. And if the tumor turns out to be benign, then that is the best thing for the patient. Approaching these tumors requires a certain mindset.

Dr Richard Hodin (Boston, MA): I guess I would just follow up on what Dr Duh was asking, and what you were just beginning to talk about, which is the technical aspects, which seem to be, really, the crux of the matter. And could I ask you a little bit more about what is different about your cancer resection? I am not talking about adjacent organ, that type of thing. Especially on the left side, it may be a little different between the left and the right—maybe you can comment on that?

But I feel like, when I have done a laparoscopic resection where I have any concern about cancer, it is as good as I can do open. But can you tell us what is different?

Dr Barbra Miller (Ann Arbor, MI): I certainly would prefer to do a laparoscopic operation because it is easier on the patient, and they are out of the hospital quickly. But I do not think, from an oncologic standpoint, it is anywhere close to what I do normally in an open operation. And this is such a biologically aggressive tumor that you cannot really rub up against it if at all possible. So I actually leave the anterior peritoneum over it. I do not open it up. And when people say I am going to start laparoscopically and see what happens and see what the tumor looks like, I think that is a completely wrong thing to do.

So I leave that anterior peritoneum on. I do not want to see that tumor. And I try to go basically from the upper half of the kidney, take all the fat off, and scoop that whole thing out from lateral to superior over to the medial aspect. I try not to see it at all. I want all the fat around it. I think greater pressure per square centimeter is exerted with laparoscopic instruments, and a hand is much gentler. Less ripping and tearing occurs. Packing off the rest of the abdomen is also more feasible.

Dr Richard Hodin (Boston, MA): But you can do that laparoscopically also.

Dr Barbra Miller (Ann Arbor, MI): Yes, some parts you can. But most people do not understand the aggressiveness of the tumor and so they basically try to shell it out. And I think that is the wrong thing to do because of those microscopic stage III tumors. The same thing can occur if you do an open procedure. That is why I am also saying, regardless, if you do a bad open operation, it is just as bad as doing a bad laparoscopic operation.

But I think the ability to touch that tumor as little as possible is important. We sit in there with those laparoscopic instruments, and we chopstick things away to get the tumor away from the vena cava or the aorta or the kidney. Trying to get down over the top of the renal hilum is hard to do, as well as trying to take out some lymph nodes. I think a lot of the lymph nodes come from around the renal hilum and around the SMA, which is difficult to obtain laparoscopically because of technical limitations of the instrumentation.

Dr Electron Kebebew (Baltimore, MD): I think the problem, in my mind, has changed, having to deal with a lot of these patients having had their disease resected laparoscopically.

The problem is, you still do not know the denominator. And having had such a large series of patients, have you at least been able to glean from their imaging studies additional imaging characteristics that are more specific for discriminating between ACC and benign adrenal tumors? What about specific SUVs on PET scan, where you could make some recommendation? Because I think, to go back to Dr Quan's comment, the denominator of patients that have benign disease is so large, I think it would really be helpful if you are able to go back and look at your data and clearly state a delayed washout of so much or PET SUV uptake of so much are associated with a higher risk of malignancy. Because these patients should get an adrenalectomy because of the risk of malignancy.

Dr Barbra Miller (Ann Arbor, MI): I just use what is in the literature, and there are several papers out on PET scan.

Dr Electron Kebebew (Baltimore, MD): But I do not think the literature is clear.

Dr Barbra Miller (Ann Arbor, MI): I mean, there are certainly PET-positive tumors that are benign. We have taken those out because of the concern for malignancy by an open approach. Imaging characteristics are not terribly specific and improvement is needed. But, again, it is making a decision preoperatively to say, "I am going to treat this as a cancer. I am not going to try to figure this out afterwards by pathology and say, 'Oh, now the patient has cancer that needs to be treated'"—that is game over for many of them.