Hypothesis: Outcome of patients with adrenocortical carcinoma (ACC) has improved with the advent of more widely available and higher quality imaging. Operative management strategies and use of adjuvant therapy have not changed.

Design: Retrospective review of patient histories, imaging studies, operative data, adjuvant therapy, and outcomes at a single institution. Follow-up was complete for a mean of 53 months. Data was compared with prior institutional experience.

Setting: Tertiary care referral center.

Patients: All patients undergoing operative management for ACC during the period from 1980 to 1996.

Main Outcome Measures: Determinants of recurrence, survival, and the effect of adjuvant therapy on overall outcome.

Results: Fifty-eight patients (30 men, 28 women) with a mean age of 53 years underwent primary operative management for ACC. Functional tumors were identified in 27 patients (47%). Mean tumor size was 12.5 cm. Stage according to the TNM staging system (AJCC Cancer Staging Manual) at presentation was I (n=0), II (n=30), III (n=7), and IV (n=21). Surgical management included curative resection in 41 (71%), noncurative resection in 14 (24%), and open biopsy in 3 (5%). Perioperative mortality was 5%. Recurrence occurred in 30 patients (73%) with a median time to recurrence of 17 months. Five-year survival by the Kaplan-Meier method was 37%. Prognostic factors (P<.05) included functional status, stage, and chemotherapy in stage III/IV patients. When compared with our prior institutional experience (1960-1980), current patients were more likely to present with stages I to II (52% vs 34%), have curative resections (71% vs 50%), and have improved 5-year survival (37% vs 16%).

Conclusions: (1) Surgical resection remains the principal treatment for stage I to III disease. (2) Adjuvant therapy may improve survival in patients with stage III or IV disease. (3) Current patients were more likely to present at an earlier stage, undergo curative resections, and have improved 5-year survival than institutional historical comparisons.

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From the Departments of Surgery (Drs Kendrick, Farley, Grant, Thompson, and van Heerden), Pathology (Drs Lloyd and Erickson), Endocrinology (Dr Young), and Statistics (Mr Rowland), Mayo Clinic, Rochester, Minn.

ADRENOCORTICAL carcinoma (ACC) is a rare endocrine malignancy typically associated with a poor prognosis. Determination of the optimal treatment of patients with ACC has proven extremely difficult given its infrequent occurrence; thus, good randomized prospective trials are lacking. Surgical resection improves survival and continues to be the mainstay of treatment. However, many trials of chemotherapy, with varied treatment regimens, have been performed in an attempt to improve outcome. The most commonly utilized chemotherapeutic agent o,p'-DDD (mitotane) has been at the forefront of adjuvant and nonsurgical management, yet debate continues whether its use significantly alters the outcome of patients with ACC when used in either a palliative or prophylactic fashion.1-5 We set out to determine whether the surgical and postoperative (adjuvant) management of patients with ACC has changed in our practice and whether this change has improved the outcome of patients with this challenging disease. With the more widely available and higher quality imaging, specifically computed tomography (CT), we speculated that patients might have ACC diagnosed at an earlier stage of the disease and therefore have improved outcome when compared with historical controls.
METHODS

We retrospectively reviewed all patients diagnosed with ACC who underwent surgical resection at our institution from 1980 to 1996. Additionally, we compared this group with similar patients at our institution treated from 1960 to 1980. Data evaluated included presurgical and postsurgical history; results of serum and urine chemical analyses and endocrine studies; imaging results; findings from pathologic examination; neoadjuvant or adjuvant treatment; and patient outcome.

PATHOLOGY

Adrenocortical carcinoma was diagnosed using established criteria. These included areas of confluent necrosis; mitoses, including atypical mitoses; vascular and capsular invasion; and nuclear atypia. Tumors were classified into 4 grades using the criteria given in Table 1. Mitoses were counted using light microscopy ×400 magnification. Tumors falling into grade 2 through 4 were relatively easy to diagnose. Grade 1 tumors were more difficult to classify because of the low mitotic activity, absence of necrosis, and atypical mitosis. These tumors were usually larger than 5 cm and weighed more than 100 g, but they invariably did not have many mitoses or malignant cytologic features. Within this group, the potential for an overlap between an “atypical” adenoma and a low-grade carcinoma exists. All surgical specimens underwent re-evaluation for histological grading at the time of this study, which was reconfirmed by 2 pathologists (R.L. and L.E.). Stage of disease was assigned according to the criteria of MacFarlane as modified by Sullivan et al (Table 2).

FOLLOW-UP

Data was obtained from the patients by telephone, return visits, or from follow-up generated by their primary physician. Follow-up was complete in all patients until death or completion of the study. Tumor endocrine functional status was determined either by serum or urinary endocrine studies and clinically when the medical history and physical examination were consistent with a diagnosis of Cushing syndrome (hypercortisolism), Conn syndrome (hyperaldosteronism), virilization, or feminization.

STATISTICAL ANALYSIS

Statistical evaluation was performed using the Wilcoxon rank sum test to assess differences in continuous measurements between groups, the χ² test to compare categorical variables between groups, and the log-rank test to compare distributions of survival. A multivariate analysis of survival end points was performed with the Cox proportional hazards model using a forward stepwise regression procedure.

RESULTS

CLINICAL CHARACTERISTICS

During the period of 1980 to 1996, 58 patients (30 men, 28 women) with a mean age of 53 years (range, 16-77 years) underwent surgical management of ACC. Abdominal pain was the presenting symptom in 28 patients (48%). Other presenting symptoms or signs included various manifestations of endocrine syndromes (47%), weight loss (16%), a palpable abdominal mass (7%), or back pain (3%). Functional tumors were identified in 27 patients (47%). Cortisol-secreting tumors were the most common functional tumors, comprising 67%, followed by mixed hormonal-secreting tumors in 15%, sex hormonal excess in 11%, and aldosterone-secreting tumors in 7%. The tumor was located on the right in 31, left in 26, and bilaterally in 1 patient.

SURGICAL MANAGEMENT

Surgical management consisted of curative resection (no gross residual disease) in 41 patients (71%), noncurative resection (gross residual disease) in 14 patients (24%), and open biopsy in 3 patients (5%). At operation the tumor was localized in 31 (53%), regionally metastatic in 10 (17%), and distantly metastatic in 17 (29%). In 11 patients (19%), tumor thrombus was identified in the renal vein or the inferior vena cava; 6 of these patients underwent complete resection with no gross residual disease.

PATHOLOGY

Surgical pathology was performed on all surgical specimens at the time of the original resection. Additionally,
at the time of this study, all specimens were reexamined to confirm the diagnosis and establish tumor grade. Grade 1 tumors were found in 7 patients, grade 2 in 15, grade 3 in 17, and grade 4 in 17. In 2 patients tumor grade could not be determined owing to inadequate material for review. Mean tumor diameter was 12.5 cm (range, 5-23 cm) and mean weight, 604 g (range, 32-3060 g). There were no patients identified with stage I disease. Stage II, III, and IV tumors were identified in 30, 7, and 21 patients, respectively.

ADJUVANT THERAPY

Patients were typically evaluated prior to hospital dismissal by a medical oncologist. Twenty patients (34%) received adjuvant therapy. In most patients, adjuvant treatment was initiated prior to hospital dismissal. Mitotane was initiated using 1 to 2 g per day and was advanced over the next few weeks to months as tolerated up to 10 g per day. The median dose of mitotane was 4.5 g per day (range, 1 to 10 g) for a median duration of 6.5 months (range, 1 to 131 months). Mitotane alone was used in 16 patients; mitotane plus etoposide and/or cisplatin, 1 patient; and a variety of agents excluding mitotane were utilized in 3 patients.

OUTCOME

Thirty-day perioperative mortality occurred in 3 patients (5%). Two patients died of sepsis with multiorgan system failure. One patient died 28 days postoperatively following hospital dismissal of a pulmonary embolus.

Recurrence occurred in 30 patients (73%) with a median time to recurrence of 17 months (range, 2-90 months). The cumulative probability of recurrence is shown in Figure 1. In 23 patients (74%), multiple sites were involved at the time of documented recurrence. Local or regional disease was the most common site of recurrence (65%), followed by lung (38%), liver (58%), and bone (29%). Recurrence was confined to local or regional involvement in only 4 patients and was distantly metastatic in 26. Thirteen patients with recurrence underwent subsequent surgical exploration with complete resection of gross disease. Currently, 4 of these patients—3 with isolated liver and 1 with lung metastases—are alive. Two of these patients are without evidence of disease (90 and 143 months from initial diagnosis), and 2 harbor recurrent ACC (88 and 166 months from initial diagnosis). Patients who underwent resection of recurrent disease had an improved survival over patients who did not, with a median survival of 29 months vs 11 months, respectively (P < .01), after documented recurrence.

Overall Kaplan-Meier 5-year survival in 58 patients was 37% with a median survival of 33 months (Figure 2). Median survival for curative compared with noncurative resection was 50.6 and 7.6 months, respectively.

Factors analyzed as prognostic indicators of survival are given in Table 3. Univariate analysis revealed significant (P < .05) factors for improved survival as low tumor grade, stage I to II, no tumor thrombus, and curative resection. On multivariate analysis however, only nonfunctional status, low tumor stage, and chemotherapy (in patients with stage III or IV disease) were predictors of longer survival. Survival by stage is shown in Figure 3. Factors analyzed for predictors of tumor recurrence are given in Table 4. On both univariate and multivariate analysis, age younger than 50 years and high tumor stage (III-IV) were predictive of recurrence.
multivariate analysis, adjusted for age, sex, grade, size, and stage at presentation. The results are as follows: 

- **Age at Diagnosis:**
  - Univariate: Risk Ratio 0.83, P = 0.05
  - Multivariate: Risk Ratio 0.83, P = 0.01

- **Sex:**
  - Univariate: Risk Ratio 1.0, P = 0.99
  - Multivariate: Risk Ratio 1.0, P = NS

- **Functionality:**
  - Univariate: Risk Ratio 1.74, P = 0.13
  - Multivariate: Risk Ratio 1.74, P = NS

- **Grade III or IV:**
  - Univariate: Risk Ratio 1.76, P = 0.14
  - Multivariate: Risk Ratio 1.76, P = NS

- **Stage III or IV:**
  - Univariate: Risk Ratio 2.17, P = 0.05
  - Multivariate: Risk Ratio 2.17, P = NS

- **Thrombus:**
  - Univariate: Risk Ratio 2.24, P = 0.07
  - Multivariate: Risk Ratio 2.24, P = NS

- **Chemotherapy:**
  - Univariate: Risk Ratio 0.83, P = 0.63
  - Multivariate: Risk Ratio 0.83, P = NS

**Table 4. Predictive Factors of Recurrence**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Risk Ratio</th>
<th>P</th>
<th>Risk Ratio</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥55 y</td>
<td>0.46</td>
<td>0.05</td>
<td>0.35</td>
<td>0.1</td>
</tr>
<tr>
<td>Female</td>
<td>1.0</td>
<td>NS</td>
<td>1.0</td>
<td>NS</td>
</tr>
<tr>
<td>Functional</td>
<td>1.74</td>
<td>0.13</td>
<td>1.74</td>
<td>NS</td>
</tr>
<tr>
<td>Grade 3 or 4</td>
<td>1.76</td>
<td>0.14</td>
<td>1.76</td>
<td>NS</td>
</tr>
<tr>
<td>Stage III or IV</td>
<td>2.17</td>
<td>0.05</td>
<td>2.17</td>
<td>0.02</td>
</tr>
<tr>
<td>Thrombus</td>
<td>2.24</td>
<td>0.07</td>
<td>2.24</td>
<td>NS</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>0.83</td>
<td>0.63</td>
<td>0.83</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Ellipses indicate not applicable; NS, not significant. Values in boldface are significant. Variable was not selected at .05 significance level in the forward stepwise model.

**Table 5. Historical Comparisons of Patients With Adrenocortical Carcinoma**

<table>
<thead>
<tr>
<th>Variable</th>
<th>1960-1980†</th>
<th>1980-1996‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>42</td>
<td>52</td>
</tr>
<tr>
<td>Female</td>
<td>58</td>
<td>47</td>
</tr>
<tr>
<td>Mean tumor size, cm</td>
<td>12.4</td>
<td>12.5</td>
</tr>
<tr>
<td>Tumor grade 3-4</td>
<td>37</td>
<td>58</td>
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<tr>
<td>Stage at presentation III-IV</td>
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<td>48</td>
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<tr>
<td>Curative resection</td>
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<td>71</td>
</tr>
<tr>
<td>Adjuvant treatment</td>
<td>58</td>
<td>34</td>
</tr>
<tr>
<td>Mitotane</td>
<td>39</td>
<td>29</td>
</tr>
<tr>
<td>Other</td>
<td>19</td>
<td>5</td>
</tr>
<tr>
<td>Kaplan-Meier 5-year survival analysis</td>
<td>16</td>
<td>37</td>
</tr>
</tbody>
</table>

* Values are given as percentages except where indicated. Ellipses indicate not applicable. Values in boldface are significant.
† According to Henley et al.6
‡ Comparing mitotane/other treatment among patients who received adjuvant treatment.
§ Comparing any adjuvant treatment/no adjuvant treatment.

**HISTORICAL COMPARISON**

Table 5 gives comparative data of the 2 time periods. When compared with our institutional experience from 1960 to 1980,6 current patients were more likely to present with higher grade yet lower stage tumors. They were also more likely to have a curative resection, but less likely to receive adjuvant chemotherapy. However, the decreased overall utilization of adjuvant therapy was largely due to less frequent use of non-mitotane chemotherapeutic agents. Overall, patients from the most recent era displayed an improved 5-year survival (37% vs 16%).

**COMMENT**

Adrenocortical carcinoma is a rare endocrine malignancy with an annual incidence of less than 2 cases per million.13,14 Equally rare is the ability to cure a patient with this disease as the overall 5-year survival ranges from 16% to 35% in large series.15,16

There are several intriguing yet unanswered questions pertaining to ACC. (1) Why do we continue to make the diagnosis so late? The mean tumor diameter remains greater than 12 cm at the time of diagnosis. (2) Is the surgical experience in the treatment of these patients improving, or are the outcomes status quo? (3) Is adjuvant therapy indicated with either a palliative or a prophylactic intent? If so, which agent or agents? (4) Do benign adenomas become malignant? (5) Should all incidentalomas, regardless of their size, be resected to detect the rare (but curable) small ACC? (6) Are all ACCs in fact ACCs, or are some atypical adenomas? This study, which is retrospective and comparative in design, does not and cannot answer any of these important questions with the possible exception of that pertaining to surgical results. We can only hope that answers to the remaining questions will be forthcoming.

Surgical resection has been the mainstay of treatment and improves survival. The world literature is inundated with retrospective and anecdotal reports regarding the role of chemotherapy and the adrenolytic agent α-β DDD (mitotane) in patients with ACC. Large retrospective studies exist, which tout of both success and failure of adjuvant therapy in affecting the outcome of these patients.1,4,6,17 However, no randomized prospective trials exist that validate or refute these data, and this debate will likely persist until a prospective randomized study is brought to fruition. Mitotane has been used predominantly as the agent of choice in treating patients with ACC, and one reason adequate studies are lacking is the frequently intolerable side effects and resulting compliance issues with this agent. More recently, evaluation of "low-dose" mitotane has surfaced, demonstrating greater patient compliance.4,18 By following serum mitotane levels, the lowest dose is given that achieves a "therapeutic" level of 14 mg/L. This serum level was derived from an observational study by van Slooten et al19 who observed that 7 of 8 patients with tumor regression had mitotane serum levels greater than this level, whereas 19 of 20 patients without tumor regression had mitotane serum levels lower than 14 mg/L. It should be noted however that mitotane has still not been definitively proven to improve survival or time to recurrence; thus, a specific serum level has little meaning at present. However, standardization of mitotane levels at doses that increase compliance will be helpful when a randomized study of the efficacy of mitotane materializes. Our patients did not have serum levels monitored.
tored but were encouraged to take the highest dose possible with tolerable side effects up to a dose of 10 g per day. The decision to institute adjuvant therapy was somewhat arbitrary. Of patients receiving mitotane, 65% were stage III or IV. Mitotane was thus used prophylactically (patients with curative resection) in 60% and with palliative intent in 40%. Adjuvant mitotane did not affect the time to recurrence in this study. Also, we observed no survival advantage with use of mitotane in patients with stage I or II disease. Our observation of an improved survival in patients with stage III or IV disease is similar to other reports. Although the numbers are small, this difference was apparent regardless of whether the resection was curative or not.

There is a desperate need for a prospective randomized trial evaluating the role of mitotane in patients who have undergone resection for cure. Because of the rarity of this disease, all of the current reports in the literature are limited by a small database. In an attempt to overcome this, the American College of Surgeons Oncology Group is currently in the process of preparing an international, prospective, randomized trial evaluating the role of adjuvant mitotane usage in ACC. Specifically, the proposal consists of the following: patients with stage I or II disease will be randomized to receive adjuvant mitotane or placebo. Patients with stage III or IV disease will be randomized to receive either mitotane or standard chemotherapy (cisplatin and etoposide). Finally, patients with stage IV and residual disease will be randomized to receive mitotane or standard chemotherapy. Such a trial is long overdue, and the surgical community anxiously awaits the results of this trial.

The surgical management of ACC has not evolved appreciably over time, and wide surgical resection remains the mainstay of treatment. With the advent of laparoscopic adrenalectomy, the question has risen regarding the appropriateness of laparoscopic resection in patients with known adrenal malignancies. Some advocate laparoscopic adrenalectomy in patients with small noninvasive malignancies; however, data supporting this are lacking. The pendulum, in our opinion, has swung too far in regard to the laparoscopic removal of adrenal tumors. More and more tumors that are subsequently found to be malignant are being removed laparoscopically. In our opinion, this is most unwise. The initial operation in patients with ACC is the most important one, and violation of surgical oncologic principles is unacceptable. In particular, the tumor should not be violated or morcellated. The senior author of this manuscript (J.A.V.) has personal experience now with 4 patients who underwent difficult laparoscopic adrenalectomy for tumors measuring less than 7 cm and who were subsequently found to have abdominal carcinomatosis secondary to tumor morcellation. Recently, Quan-Yang Duh, MD, and colleagues (unpublished data, 2000) at the University of California San Francisco reviewed their experience with 133 laparoscopic adrenalectomies. In 4 patients, ACC was identified, and all 4 had tumor recurrence. They suggested that laparoscopic adrenalectomy for ACC has a high recurrence rate and that this approach for ACC should be reconsidered; we emphatically agree.

In this study, we were able to identify only nonfunctioning tumors, early tumor stage, or use of chemotherapy treatment in patients with stage III or IV disease as predictive factors of longer survival. Whether resection of renal vein or inferior venocaval tumor thrombus improves survival is not known. We identified 11 patients who had either renal vein or inferior venocaval involvement, 7 of whom underwent complete resection of all gross disease. Although these patients clearly had a decreased median survival (18 months vs 33 months for all patients), this study was not designed to address whether a survival advantage exists following resection of tumor thrombus.

Re-resection for patients with recurrent disease has been reported to improve survival over patients forgoing an additional operation. Our study similarly confirmed a survival advantage to those patients with recurrence that underwent repeated resection (median of 29 vs 11 months, P<.01).

With the more widespread use of CT, the management of incidentalomas is an increasing dilemma for the surgeon. Recommendations for the size at which incidentalomas should be resected ranges from 3 to 6 cm. We previously addressed the likelihood of a malignancy in an incidentally found adrenal mass by evaluating 231 patients with incidentalomas who were treated nonsurgically and observed for a mean of 7 years. No patient in this group subsequently developed a hyperfunctioning tumor or adrenal malignancy. We continue to support the concept that most nonfunctioning adrenal incidentalomas can be observed safely. For tumors larger than 4 cm,
those with a suspicious imaging phenotype, evidence of endocrine hyperfunction, or those demonstrating increasing interval size, we strongly support adrenalectomy.

One additional area of concern regards a simple but valid question: are all ACCs really ACCs? Pathologic analysis of adrenal neoplasms in the absence of metastatic disease is an inexact science, especially when tumors are small (<7 cm) and are low grade (Figure 4). Although mitosis and malignant cytologic features may be sparse, a tumor that is larger than 5 cm and greater than 100 g is generally classified as ACC. Thus, are some of the long-term survivors patients with atypical adenomas rather than ACC?

With the improved availability and quality of imaging such as CT and magnetic resonance imaging, incidentalomas are more commonly identified. One might assume that this would also lead to earlier detection of “incidental” ACC. When comparing the 2 time periods at our institution however, we observed no difference in the size of adrenal carcinoma at the time of resection (Table 5). An intriguing question then, even in these 2 relatively small groups, is why are current patients more likely to present at an earlier stage, have an improved chance of curative resection, and have longer survival than the previous 2 decades of patients with similar-sized tumors? We cannot definitively explain this observation. It is possible that with greater awareness and improved imaging and functional studies that we are finding these tumors at an earlier stage, which may not be as closely related to size as previously thought. Another possibility is that our observations are owing to a referral bias in that patients with seemingly advanced stages may not be referred for surgical resection. However, we have not observed a decline in the number of patients with ACC undergoing resection.

Adrenocortical carcinoma remains a frustrating and challenging malignancy in terms of optimal treatment and patient survival. We support the call for a prospective trial regarding the role of adjuvant therapy to identify and optimize the management of what is currently a predominantly surgically treated disease.


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REFERENCES


Richard A. Prinz, MD, Chicago, Ill: I want to congratulate the authors for reviewing one of the largest single-institution experiences with adrenocortical carcinoma. Has there been any surgical progress made in this intervening time period? They do report an improved survival of 37% vs 16% in their earlier report, but is this just due to the presence of more favorable lesions in their current series? Stage for stage, has there been any change in the survival outcome of these patients? They have touched on the issue of whether some of these tumors are really adrenocortical carcinomas and not large atypical adenomas, which obviously are benign. Presumably, the latter would be grade 1 tumors. Did any of your 7 grade 1 tumors behave malignantly, or did these grade 1 lesions account for a substantial number of your long-term survivals? Only 20 patients in the series received adjuvant chemotherapy, even though you point to this improving survival. How was the decision made on who was to receive adjuvant chemotherapy, and how was the choice of agents that were used made? Local or regional disease was the most common site of recurrence. Have you used or considered using postoperative radiation therapy as an adjunct to your resection, especially for high-grade and locally invasive tumors? Eleven patients had tumor thrombus in the renal vein or inferior vena cava. How did your approach to these patients differ, and what techniques did you use to prevent tumor embolus? Thirteen of your patients had recurrence of disease and underwent subsequent resection of all gross disease. How did you decide that these patients had localized disease,

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and what would make a second resection reasonable in them? Have you used PET [positron-emission tomography] scanning or some other modality to do this? I appreciate your pointing out the challenges that still remain in this unusual cancer.

Donald L. Kaminski, MD, St Louis, Mo: I wonder if the authors could give us some insight into the opposite spectrum of this disease, for example, what percentage of these tumors were under 5 cm? Are there any patients in this series who might have been inappropriately observed with smaller tumors? Additionally, do they have any suggestions for us with regard to the management of incidental adrenal lesions that are found on CT scan? Should tumors under 5 cm be observed, or should they be removed?

Norman W. Thompson, MD, Ann Arbor, Mich: There are 2 issues that were not addressed. One was the use of fine-needle biopsy in adrenocortical lesions or in adrenal incidentalomas. How many of their patients had actually had a needle put into such a tumor, particularly a type 2, potentially curable tumor. It’s been our experience that far too many patients have had inappropriate needle biopsies that may obviate the chance for cure by implanting carcinoma cells outside the tumor capsule.

Secondly, I wonder if any of their patients had had laparoscopic procedures done for their adrenocortical cancers. This raises the issue of the incidentaloma and what size they are willing at the Mayo Clinic to say this is potentially a malignancy and therefore not a candidate for procedure. We think that either needle biopsy or laparoscopic procedure should absolutely be avoided in patients with adrenocortical carcinoma. Their pathologist, Rick Lloyd, when at the University of Michigan, stated that a cytologist could make the diagnosis based on the needle aspiration. The problem is many physicians are getting needle biopsies to differentiate benign from malignant adrenocortical tumors when it can’t be done to begin with. This needlessly breaks into a tumor and potentially loses the chance for cure as far as I’m concerned.

Mitchel P. Byrne, MD, Evanston, Ill: I wonder if the earlier presentation of these patients since your series in 1980 has anything to do with the type of testing such as ultrasound and CT being done for some other diagnosis much as we pick up aneurysms now on incidental scans being done for gallbladder problems and that type of thing.

Dr Farley: Dr Prinz asked about the surgical progress that we’ve made specifically per patient and in the operating room. Two differences in this study vs our historical controls: (1) There was lower mortality in the current study. We had 3 perioperative deaths from 1980 to 1990, and we had 6 patients die, 2 of them intraoperatively from blood loss, from 1960 to 1980. This lower operative mortality is important when we’re talking about small numbers of patients. Also, in the historical study, 23 patients developed recurrent disease; none of them went back for re-resection. It’s a tribute to Clive and John and others who have operated at Mayo on patients with adrenocortical carcinomas from 1980 to 1996. When 11 underwent re-resection and did well, they did far better than those that didn’t. Reexploration of an imaged lesion that looks resectable is valid and important. The second question related to patients with low-grade tumors. These tumors are bad actors whether they’re grade 1 or grade 4, and grade did not seem to make any difference in this newer study.

Dr Prinz also asked about when to use adjuvant therapy, mitotane or otherwise. We still don’t know the answer to that. We’re delighted that the American College of Surgeons Oncology Group has made it a priority to study this and will be forthcoming with an international study that’s randomized and prospective of adrenocortical carcinomas randomizing placebo and mitotane in stage I and II resectable lesions and then stage III and stage IV looking at mitotane and cisplatin and etoposide. We look forward to these results.

Dr Prinz asked about whether we used radiation therapy. It has not been a major portion of our practice. The historical group (1960-1980) had 10 patients who underwent radiation therapy, and only 1 of those patients showed a response. It would be nice to pull out all the guns, but not all the guns work with this disease.

Dr Prinz asked about surgical technique for tumor thrombus. Typical vascular control is necessary, but we have put a couple of people on veno-veno bypass when the clot does go up into the atrium. It’s clearly a challenging operation, to say the least. We have not used PET scanner in our 13 recurrences. We continue to use CT and MRI and have been happy with that at this point, but certainly would welcome the opportunity to look at that with the PET scanner.

Dr Kaminski asked if any of these lesions were under 5 cm in size, and indeed they were not. The smallest was 5.5 cm. The indication at the Mayo Clinic for removing an incidentaloma remains pretty much the same as it does elsewhere. I think in the United States, (1) if it’s a functional tumor, no matter what size it is, it needs to come out. (2) If it’s greater than 4 cm in size and the patient is fit for general anesthesia, it’s important to take that tumor out. (3) With high-resolution CT or MRI, if there’s a suspicion or a hint that this is potentially a malignant problem, then it should come out.

Dr Thompson asked about fine-needle aspiration, and we did have 8 patients of our 58 who had fine-needle aspiration. We do not recommend this. Five of the patients came to us by referral with percutaneous needle biopsy, and 3 of our own patients before surgical consultation was obtained had needle biopsy. Again, the outcome was no different, but we clearly do not recommend fine-needle aspiration in these patients. None of these patients underwent a laparoscopic exploration, and again, when in doubt the laparoscope should be put on the back table and an open celiotomy performed.

Dr Byrne asked about the use of CAT [computed axial tomography] scan and ultrasonography. Both were really not available for most portions of the study from 1960 to 1980, and we thought perhaps that we would have better survival because we found tumors earlier in this study. Size for size, tumors were exactly the same over the last 40 years.