PAPER

Selective Use of Steroid Replacement After Adrenalectomy

Lessons From 331 Consecutive Cases

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Hypothesis: Only selected patients require steroid replacement therapy following adrenalectomy.

Design: Retrospective review.

Settings: University tertiary care center and veterans' hospital.

Patients: A total of 331 patients who underwent adrenalectomy by 1 surgeon (Q.-Y.D.) between April 1, 1993, and August 31, 2005.

Interventions: Laparoscopic, open, and hand-assisted adrenalectomy. Steroid replacement therapy was administered using a standardized hydrocortisone taper protocol.

Main Outcome Measures: Indications for adrenalectomy, operative approach, requirement for postoperative steroid replacement, and episodes of acute adrenocortical insufficiency.

Results: Of the 331 adrenalectomies, 304 were laparoscopic, 23 were open, and 4 were hand assisted. There were 299 unilateral adrenalectomies and 32 bilateral adrenalectomies performed. Fifty-seven (17%) of the 331 patients required steroid replacement after adrenalectomy. Of the 57 patients requiring steroid replacement, 52 had Cushing syndrome and 5 had bilateral pheochromocytomas. The 52 patients with Cushing syndrome included 16 with pituitary tumors who had failed pituitary resection and/or medical therapy, 14 with unilateral adrenal adenomas, 9 with ectopic corticotropin-secreting tumors who had failed resection and/or medical therapy, 7 with incidentalomas and subclinical Cushing syndrome, 4 with macronodular hyperplasia, and 2 with adrenocortical carcinoma. No patients undergoing unilateral adrenalectomy for non-Cushing adrenal disease required steroid replacement. Four (7%) of the 57 patients receiving steroid replacement had episodes of acute adrenocortical insufficiency following operation and required increased steroid supplementation. There were no cases of acute adrenocortical insufficiency in the 274 patients who did not receive steroid replacement.

Conclusions: Steroid replacement therapy after adrenalectomy should be reserved for patients with Cushing syndrome (overt or subclinical) and patients undergoing bilateral adrenalectomy. Patients undergoing adrenalectomy for unilateral non-Cushing adrenal tumors do not require postoperative steroid replacement.

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THE PRACTICE OF PROVIDING perioperative glucocorticoid replacement therapy to prevent adrenal insufficiency in patients receiving steroids for inflammatory conditions is well established.[1,2] Since the early 1950s when the first articles[3,4] describing the dangers of postoperative adrenal insufficiency in steroid-dependent patients were published, the standard of care has been to treat these patients with physiologic or supraphysiologic doses of steroids during the perioperative period. Within the past 2 decades, there has been considerable debate regarding the amount of steroid replacement needed to provide adequate coverage for perioperative stress; the concept and practice of administering supraphysiologic, or "stress-dose," steroids has been called into question by several investigators,[5-8] and new guidelines for steroid-dependent patients undergoing operations have been proposed and used.[5-8]

Another population of patients who may require perioperative steroid supplementation consists of patients undergoing adrenalectomy for the spectrum of primary adrenal tumors or, less commonly, adrenal metastases or extra-adrenal hypersecretory conditions. However, few published guidelines exist for identifying precisely

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Table 1. Comparison of Patients Who Required Postoperative Steroid Supplementation vs Patients Who Did Not Require Postoperative Steroids

Characteristic	Patients Requiring Postoperative Steroids (n = 57)	Patients Not Requiring Postoperative Steroids (n = 274)
Episodes of adrenal insufficiency, No.	4	0*
Infectious complications, No.	4	0*
Length of hospital stay, mean ± SEM, d	2.6 ± 0.3	1.5 ± 0.1*

*$P<.05$.

which patients undergoing adrenalectomy require perioperative steroids. Not all patients undergoing adrenalectomy are at risk for postoperative adrenal insufficiency, and unnecessary steroid administration is associated with a host of deleterious effects, including poor wound healing, blood glucose level abnormalities, and other metabolic derangements. We therefore reviewed our experience with patients who underwent adrenalectomy during the past decade, with the goal of identifying which patients required perioperative steroid replacement. We aimed to provide rational guidelines for the administration of steroids in patients undergoing adrenalectomy and to highlight the subgroups of patients who are at highest risk for postoperative adrenal insufficiency.

METHODS

We reviewed the medical records of all of the patients who underwent adrenalectomy by 1 surgeon (Q.-Y.D.) between April 1, 1993, and August 31, 2005. Patients who underwent open, laparoscopic, or hand-assisted adrenalectomy were included. The clinical presentation and indications for operation were recorded for each patient. All of the operations were performed at the University of California, San Francisco, Medical Center, the San Francisco Veterans Affairs Medical Center, the University of California, San Francisco/Mt Zion Medical Center, or the San Francisco General Hospital.

All of the patients requiring postoperative steroid supplementation were identified, and their indications for and duration of steroid therapy were recorded. Steroid supplementation was administered using a standardized protocol established in conjunction with medical endocrinologists at our institution. Postoperative complications were noted, including all episodes of adrenal insufficiency requiring additional steroid supplementation and any complications related to hypercortisolism (including wound infections and other infectious complications). Episodes of adrenal insufficiency following operation were documented by either serum or urinary testing in patients with symptoms or signs of hypocortisolism. The duration of hospitalization was recorded. In our practice, all of the patients are seen for follow-up by the surgeon between 2 and 4 weeks after operation. If there are no persistent postoperative problems, subsequent follow-up is with the patient's endocrinologist or primary care physician. Episodes of delayed adrenal insufficiency, tumor recurrence, or other long-term complications either were reported directly to the surgeon or were identified during record reviews and follow-up telephone calls to referring physicians for this study.

RESULTS

Between April 1, 1993, and August 31, 2005, 331 patients underwent adrenalectomy by 1 surgeon (Q.-Y.D.) at the University of California, San Francisco, or one of its affiliated institutions. Of these 331 patients, 304 underwent laparoscopic adrenalectomy, 23 underwent open adrenalectomy, and 4 underwent hand-assisted laparoscopic adrenalectomy. Of the 23 open adrenalectomies, 4 were initially attempted laparoscopically but were converted to open adrenalectomy because of difficult dissection or intraoperative findings that may have been indicative of malignancy. The indications for operation for the 331 patients included aldosteronomas in 108 patients, pheochromocytomas in 71 patients (including bilateral pheochromocytomas in 5 patients), Cushing syndrome in 52 patients, nonfunctioning cortical adenomas in 34 patients, isolated adrenal metastases in 29 patients, adrenocortical carcinoma (not causing Cushing syndrome) in 5 patients, and a virilizing adrenal tumor in 1 patient. The remaining 31 patients who underwent adrenalectomy during this period had other types of unilateral nonfunctioning adrenal tumors (including myelolipomas, adrenal cysts, and adrenal hemorrhages).

Fifty-seven (17%) of 331 patients required steroid replacement following adrenalectomy; the remaining 274 patients did not require or receive any form of postoperative steroid supplementation. The 57 patients receiving steroids included 52 patients with Cushing syndrome and 5 with bilateral pheochromocytomas who underwent bilateral adrenalectomies. All of the 52 patients with Cushing syndrome were diagnosed preoperatively by biochemical testing either because of clinical features of hypercortisolism or as part of the routine workup of an incidentally discovered adrenal mass. The cause of glucocorticoid excess in the 52 patients with Cushing syndrome included functioning pituitary tumors in 16 patients who had failed pituitary resection and/or medical therapy; functioning unilateral adrenal cortical adenomas in 14 patients; ectopic corticotropin-secreting tumors in 9 patients who had failed resection and/or medical therapy; subclinical Cushing syndrome in 7 patients who had been diagnosed during biochemical workup of an incidentaloma; bilateral adrenal macronodular hyperplasia in 4 patients; and functioning adrenocortical carcinoma in 2 patients. The 5 patients with bilateral pheochromocytomas included 3 with multiple endocrine neoplasia type 2A or 2B, 1 with Osler-Weber-Rendu syndrome, and 1 with neurofibromatosis.

A comparison of postoperative complications in patients who received steroid supplementation and patients who did not receive steroids is provided in **Table 1**. The 57 patients who underwent steroid replacement included 4 who required additional steroid therapy because of signs and symptoms of addisonian crisis. Infectious complications developed in 4 patients undergoing steroid replacement therapy: 2 patients developed wound infections in trocar sites, necessitating bedside incision and drainage; 1 patient developed a subphrenic abscess requiring drainage by interventional radiology; and 1 patient developed severe postoperative pneumonia and a

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Table 2. Clinical Features of 4 Patients With Acute Adrenal Insufficiency After Adrenalectomy Despite Glucocorticoid Replacement

Age, y/Sex	Diagnosis	Operation	Time After Operation	Symptoms of Adrenal Insufficiency	Outcome
66/F	Cushing syndrome, ectopic corticotropin-secreting tumor	Laparoscopic bilateral adrenalectomy	2 d	Fever, nausea, failure to thrive	Improved, 5 d in hospital
51/F	Cushing syndrome, pituitary adenoma	Laparoscopic bilateral adrenalectomy	3 d	Hypotension, shock requiring intensive care unit care	Improved, 9 d in hospital
43/F	Subclinical Cushing syndrome, incidentaloma	Laparoscopic right adrenalectomy	1 y	Fatigue, nausea, dizziness during steroid taper	Improved, but recurrent episode during treatment for gallstones 1 y later
40/M	Cushing syndrome, bilateral macronodular hyperplasia	Laparoscopic bilateral adrenalectomy	2 y	Diarrhea, nausea, vomiting	Improved, no repeat hospitalization

urinary tract infection with subsequent extended hospitalization. In comparison, of the 274 patients who did not receive perioperative steroid replacement, only 1 developed an infectious complication after adrenalectomy ($P<.001$). Of the patients who underwent steroid replacement, 1 with adrenocortical carcinoma developed local recurrence requiring reoperation. One patient with multiple endocrine neoplasia type 2B and bilateral pheochromocytomas developed local recurrence requiring reoperation and died several months later of metastatic medullary thyroid carcinoma. There was 1 postoperative death in a patient with an ectopic corticotropin-secreting tumor who underwent emergent operation after developing acute multisystem failure despite aggressive medical therapy; this patient developed uncontrollable postoperative bleeding and died 1 day after operation.

The clinical features of the 4 patients who developed postoperative adrenal insufficiency despite glucocorticoid replacement are listed in **Table 2**. These 4 patients who required additional steroid supplementation included 2 patients who developed hypocortisolism in the immediate postoperative period and 2 patients who presented several months to years after their operations. The 2 immediate cases of addisonian crisis included 1 patient with pituitary Cushing syndrome who became critically hypotensive and required transfer to the intensive care unit on postoperative day 3 as well as 1 patient with an ectopic corticotropin-secreting tumor who developed fever, nausea, and failure to thrive on postoperative day 2. Both of these patients improved after additional supplemental steroid therapy. The 2 cases of delayed addisonian crisis included 1 patient with macronodular hyperplasia who had severe gastrointestinal distress 2 years after his bilateral adrenalectomy as well as 1 patient with subclinical Cushing syndrome who became acutely fatigued, nauseated, and dizzy while attempting to wean off of steroids 1 year after her adrenalectomy. These 2 patients with delayed symptoms of hypocortisolism showed improvement after additional supplemental steroid therapy; the patient with subclinical Cushing syndrome had another episode of addisonian crisis while being treated for cholecystitis 2 years after her adrenalectomy and required increased doses of steroids during this period.

The mean ± SEM length of hospitalization after adrenalectomy in the 57 patients who required perioperative steroid supplementation was 2.6 ± 0.3 days. The mean ± SEM length of postoperative hospitalization for the 274 patients who did not require steroid supplementation was 1.5 ± 0.1 days ($P=.002$).

COMMENT

In this study, we reviewed the clinical presentations and postoperative outcomes of 331 consecutive patients who underwent adrenalectomy during a 12-year period, and we identified factors that determined the requirement for perioperative steroid supplementation. The results of this investigation suggest that only patients with preoperatively diagnosed Cushing syndrome (either overt or subclinical) and patients undergoing bilateral adrenalectomy require perioperative steroid supplementation. In addition, patients receiving steroids for other medical conditions (eg, asthma, inflammatory bowel disease, rheumatoid arthritis) need to receive steroid coverage after adrenalectomy as they would with any operation. Patients undergoing unilateral adrenalectomy for non-Cushing adrenal tumors do not require perioperative steroid supplementation. The only cases of postoperative addisonian crisis that we encountered during this 12-year study period were in patients with Cushing syndrome. Overall, 4 (1%) of 331 patients undergoing adrenalectomy at our institution had an episode of postoperative hypocortisolism; this result is similar to that reported in other single-institution studies[9] of patients undergoing adrenalectomy. We also found that patients requiring perioperative steroid supplementation are at higher risk for postoperative infectious complications and have a significantly longer hospital stay than patients who do not require steroids.

In our practice, perioperative steroid replacement is administered according to a standardized protocol that was established with assistance from the medical endocrinologists at our institution. The protocol calls for 100 mg of intravenous hydrocortisone to be given prior to operation, followed by 100 mg of intravenous hydrocortisone every 8 hours for 1 day or an equivalent daily dose of oral prednisone, then a subsequent rapid 3-day taper to a maintenance dose of 25 mg twice daily of intravenous hydrocortisone or an equivalent dose of oral pred-

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nisone until the patient is seen in follow-up. Patients who undergo bilateral adrenalectomy will require lifelong steroid supplementation whereas those with Cushing syndrome who undergo unilateral adrenalectomy can usually be tapered off of all steroids within 6 months to 1 year.[10-14] In our practice, the referring endocrinologist or primary care physician determines the final tapering regimen for patients weaning off of steroids; all of the patients undergo repeat biochemical testing to confirm the integrity of the hypothalamic-pituitary axis prior to discontinuing steroid therapy. It is important to note that patients with Cushing syndrome may develop signs and symptoms of hypocortisolism months and even years after their adrenalectomy; 2 of the 4 patients with postoperative adrenal insufficiency in this study group presented within 1 to 2 years after operation.

Patients with subclinical Cushing syndrome represent an interesting subgroup of our study population. Subclinical Cushing syndrome is defined by autonomous secretion of glucocorticoids without overt clinical manifestations of Cushing syndrome. We identified 7 patients with this condition; these patients had incidentally discovered adrenal masses and no clinical features of hypercortisolism but were found to have elevated cortisol secretion on biochemical workup of their incidentalomas. These patients with subclinical Cushing syndrome are at risk for postoperative addisonian crisis and should receive steroid supplementation; 1 patient with subclinical Cushing syndrome in our study had 2 episodes of postoperative hypocortisolism despite steroid replacement. Other investigators[15,16] have reported cases of fatal adrenal insufficiency in patients with subclinical Cushing syndrome who did not receive glucocorticoid supplementation after adrenalectomy. As the frequency of incidentalomas continues to rise in conjunction with the increased use of abdominal computed tomographic scans and magnetic resonance images, it is of paramount importance that clinicians be aware of the existence of subclinical Cushing syndrome.[17,18] Up to 20% of patients with incidentally discovered adrenal masses will have evidence of glucocorticoid excess on biochemical testing.[17,18] All patients with an incidentally discovered adrenal mass should undergo biochemical testing to evaluate for hypersecretion of glucocorticoids and catecholamines, even if the patients are asymptomatic. For workup of hypercortisolism, our preference is to perform an overnight low-dose dexamethasone suppression test; in addition, we usually obtain a 24-hour urinary cortisol measurement since all of the patients undergo urinary testing for fractionated metanephrines and catecholamines to rule out pheochromocytoma.[19]

In conclusion, our review of 331 patients who underwent adrenalectomy during the past 12 years suggests that only patients with overt or subclinical Cushing syndrome and patients undergoing bilateral adrenalectomy require perioperative steroid supplementation. Patients undergoing unilateral adrenalectomy for non-Cushing adrenal tumors do not require steroid replacement. Patients who receive steroids for other medical conditions should continue their steroid regimen after adrenalectomy as they would after any other abdominal operation; the decision to give stress-dose steroids to these patients is dependent on patient history, extent of operation, and clinician judgment.

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DISCUSSION

Brett Sheppard, MD, Portland, Ore: This is a well-presented body of work that details a very extensive and rich experience in the surgical care of adrenal disease. These are outcomes that we can all be proud of and, as such, will provide us with a benchmark for adrenal surgery to refer to in years to come.

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The authors have made several important points which deserve reemphasis. First, superphysiologic or so-called stress doses of perioperative steroids are required only in a limited number of patient populations. In 1997 at our institution, Dr Loriaux previously reported in *Surgery* a randomized, double-blind study looking at steroid replacement in patients already on steroids undergoing surgery. He reported patients only required their normal dose of steroids around surgery and not supraphysiologic doses.

Today, Dr Duh has shown us that only 17% of patients undergoing adrenalectomy will require steroid replacement and that this population is confined to patients with depression of their hypothalamic-pituitary-adrenal axis from Cushing's syndrome or those patients undergoing bilateral adrenalectomy. These data and other studies should prompt all of us to reexamine the use of perioperative supraphysiologic doses of steroid replacement.

Second, the authors draw attention to the importance of subclinical Cushing's syndrome. As they point out, this diagnosis is becoming increasingly more important as we discover more incidentalomas with our imaging. In some series, the diagnosis of subclinical Cushing's syndrome is as high as 10%. When found early, patients may be spared the full expression of Cushing's syndrome. The authors describe the gold standard biochemical testing for this disease, but I am wondering if they have any experience with the use of midnight salivary cortisols and what utility this may have in the future.

Using a standardized protocol for steroid replacement, the authors have minimized the incidence of early addisonian crisis. However, I would like to ask if they have noted any difference in the response to their protocol or the need to deviate from their protocol in patients undergoing bilateral adrenalectomy for pheochromocytoma vs those undergoing the same operation for Cushing's syndrome.

Also, although the number of open cases was low, reflecting the current practice, was there any difference in the protocol administration between those patients undergoing an open adrenalectomy vs a laparoscopic adrenalectomy? Patients with florid Cushing's syndrome may also develop a prompt diuresis following a surgical cure. Do you have a protocol in place to address the fluid and electrolyte flux?

Drawing on our own experience in some 39 patients undergoing bilateral adrenalectomy for Cushing's syndrome, we found some patients could not be successfully weaned off to maintenance doses of steroids. We postulated this might be linked to the time and duration of disease. That is, these patients became accustomed to the loss of diurnal variation and require consistently higher levels of steroids. I am wondering if you have any experience with this and what your approach to this problem is.

In addition, in our patient population, patients self-report about a 45% incidence of 1 or more addisonian crises more than 1 year out from their bilateral adrenalectomy. We are unsure what this represents, whether it is related to steroid withdrawal or other causes. However, I am beginning to believe that our patients require long-term support to reap the full benefit from surgery. I am wondering what the approach at UCSF [University of California, San Francisco] is to this.

One final question. Patients with Cushing's syndrome often present very unique surgical challenges. They often will have BMIs [body mass indices] greater than 35 with central deposition of their fat and have other significant comorbidities. I am hoping you may share with us some clinical protocols you may have developed that have led to such good outcomes.

L. William Traverso, MD, Seattle, Wash: I would like to ask you [Dr Shen] and Dr Duh one additional twist to this. I have a patient in the hospital now who 10 years ago had a 5-cm adrenal cortisol-secreting tumor resected, and then a few months ago, she had a 22-unit bleed from a gut stromal tumor centered around the ampulla of Vater. Wednesday, I took that out with a Whipple procedure and now I can't keep her potassium up. Could you tell me what to do?

Philip I. Haigh, MD, Los Angeles, Calif: I just wanted to ask how the authors monitor these patients postoperatively, and it really relates to that 1 patient with subclinical Cushing's syndrome. Only 5% of the Cushing's patients with much more severe disease developed problems, so finding this 1 patient with subclinical Cushing's disease causing such prolonged adrenal insufficiency is fascinating. I am just wondering if it perhaps could have been an iatrogenic problem because of excess exogenous steroids given maybe for a longer time than was anticipated.

Rodney F. Pommier, MD, Portland: The adrenals get more metastases per gram of tissue than any other organ. We see adrenal insufficiency in our surgical oncology patients presenting with what appears to be a unilateral adrenal metastasis fairly often, presumably because the other gland is also affected. You did not, so I thought that was very interesting. Either you have carefully selected a group of patients with true unilateral adrenal metastases or the patients have aggressive tumors and are dying of other metastases before insufficiency occurs in the other adrenal gland. My questions are, what were the most common primary tumor histologies in these patients who had an adrenalectomy for a metastasis, and what was their median survival after the adrenalectomy?

Dr Duh: Midnight salivary cortisol levels are used by some people to diagnose Cushing's. We have not used it in our institution. It is supposed to be a good test, but we don't have any experience with it.

Do we use a different protocol or do we deviate from the protocol for those who undergo bilateral adrenalectomy for pheochromocytomas or for those who undergo open operations? No. We try to use the same protocol so people don't get confused. Of our 2 patients who had adrenal insufficiency immediately postoperatively, neither had pheochromocytoma. None of our open adrenal patients had adrenal insufficiency with this protocol. This means supraphysiologic doses beyond what we have in this protocol that you may expect are needed for patients who undergo open operation probably aren't necessary. So, I think our protocol works well in general. But, we need to keep in mind that despite using this protocol, we had 2 patients who had adrenal insufficiency on postoperative day 2 and day 3, so some patients may need more steroid or may need to be tapered more slowly.

Postoperative diuresis is a very interesting question. A frequently made mistake is to pull the Foley catheter immediately after the operation thinking that a simple laparoscopic adrenalectomy is like a laparoscopic cholecystectomy. These patients all have significant diuresis, not just the Cushing's patients. Because we operate with the patient in the lateral position, they tend to retain a lot of fluid, and when they are turned supine postoperatively, they diurese. Cushing's patients do diurese more, and we replace the fluid as needed. Since most patients are eating by the next day, fluid replacement is not a problem.

Difficulty in weaning patients off steroid is the most important issue. We begin weaning Cushing's patients several months postoperatively, and this is usually done by the endocrinologist. There is a very good study by Gerry Dougherty that showed the suppression of the pituitary-adrenal axis to last a median of 15 months. That is, more than a year after a unilateral adrenalectomy, half of the Cushing's patients still have trouble weaning off their steroids.

How do we support these patients? I think it is very important that these patients have a good endocrinologist and that they work very closely together. We have some excellent ad-

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renal endocrinologists at UC [University of California], and it is essentially their responsibility to follow and wean these patients. Some may be difficult to wean. For example, 1 of the 2 patients who had delayed adrenal insufficiency was a young patient who had subclinical Cushing's and couldn't get pregnant. We resected her 2-cm adrenal adenoma, but she could not be weaned for a couple of years. She got pregnant and during her pregnancy required more steroids. After her pregnancy, she had cholecystitis and needed a laparoscopic cholecystectomy. Again, she needed more steroids. She is now 4 to 5 years after adrenalectomy and is finally weaned off steroids. But, I am not sure that if she were to get diverticulitis or other problems, that she may again require steroids.

We do manage patients with Cushing's differently. They are the only patients to get perioperative antibiotics. We do not give perioperative antibiotics to other patients for adrenalectomy, only for those with Cushing's. Despite perioperative antibiotics, 4 Cushing's patients had infectious complications whereas those without Cushing's got no antibiotics and had no infections.

Dr Traverso, I don't know about the connection between adrenal insufficiency and GI [gastrointestinal] stromal tumors, but if I think the patient is addisonian, I would give the patient steroids. Although we are concerned about the complications of chronic steroid use, in situations like this, the risk of not giving the steroid is higher than the risk of giving a short course of steroids. To confirm the diagnosis, the endocrinologists like us to draw a cortisol level before treating the patient. You can also use dexamethasone, which does not cross-react in the assay for cortisol, so they can still under go a Cortrosyn stimulation test.

For Dr Haigh, how do we monitor these patients? Again, a good endocrinology colleague is very important. We talk to these patients before their operation so that they know they may have to deal with long-term issues related to adrenal insufficiency.

Dr Pommier brought up the subgroup of patients with adrenal metastasis. We had 29 patients in whom we resected adrenal metastasis. The adrenal gland is one of the most common sites for metastasis, but isolated adrenal metastases are quite rare. These can be resected safely. Surprisingly enough, we have not seen any local recurrence from laparoscopic resection of adrenal metastasis. Dr Kebebew presented our results at the Pacific Coast Surgical a few years ago. About a third of the patients subsequently had systemic recurrences, but two thirds had a long survival after resection of isolated adrenal metastases.

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