Quality of life after laparoscopic bilateral adrenalectomy for Cushing’s disease

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Background. Bilateral adrenalectomy to control symptoms of Cushing’s disease after failed transsphenoidal operation is effective. We examined surgical outcomes and quality of life after laparoscopic bilateral adrenalectomy for the treatment of Cushing’s disease.

Methods. Eighteen patients underwent laparoscopic bilateral adrenalectomy from November 1994 through December 2000. Patient data were obtained from chart reviews. Patients completed a follow-up survey including the SF-36 health survey (QualityMetric Inc, Lincoln, Neb).

Results. Laparoscopic bilateral adrenalectomy was accomplished in all 18 patients. There was 1 intraoperative complication of a colotomy, and 2 postoperative complications including 1 pancreatic pseudocyst and 1 hemorrhage. Three patients died at 12, 19, and 50 months after operation. At a median follow-up of 29 months, patients reported improvement in all Cushing’s-related symptoms. Nine of 11 patients who responded to the survey stated their health was improved after adrenalectomy. Results of the SF-36 health survey showed significantly lower scores in all 8 measured parameters when compared with the general population.

Conclusions: Results of laparoscopic bilateral adrenalectomy show this procedure is comparable with open adrenalectomy in controlling symptoms of Cushing’s disease. Despite patient reported improvement in health after adrenalectomy, this patient population continues to experience poor health as measured by the SF-36 when compared with the general population. (Surgery 2002;132:1064-9.)

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CUSHING’S DISEASE is both a physically and emotionally disabling disease. The sequelae of unopposed hypercortisolism include obesity, diabetes, hypertension, proximal muscle weakness, emotional lability, and hypogonadism. The mainstay of treatment for Cushing’s disease is transsphenoidal micro-operation of the pituitary adenoma.

A significant subset of patients fails transsphenoidal operation secondary to a pituitary macroadenoma or hyperplasia. For these patients, treatment options consist of repeated transsphenoidal operation, medical therapy with adrenolytic agents, radiation therapy to the pituitary gland, or bilateral adrenalectomy.

Adrenalectomy has been proven effective in reversing the effects of hypercortisolism in patients with persistent Cushing’s disease after transsphenoidal micro-operation. Laparoscopic adrenalectomy can be safely performed with less morbidity than the open procedure.1 The objective of this study was to examine the effectiveness of laparoscopic bilateral adrenalectomy on reversing the sequelae of hypercortisolism with an emphasis on patients’ quality of life after adrenalectomy for Cushing’s disease.

PATIENTS AND METHODS

A retrospective review of consecutive patients who underwent laparoscopic bilateral adrenalectomy for Cushing’s syndrome between November 1994 and December 2000 at Oregon Health and Science University was performed. The medical records were reviewed to assess patient demographics, operative parameters, and postoperative events. Follow-up consisted of a questionnaire regarding the resolution of their sequelae from Cushing’s syndrome, number and frequency of addisonian episodes, current corticosteroid replacement, and the development of Nelson’s syndrome. Patients were asked to rate the success of their operation in improving their health status. The SF-36 health survey (QualityMetric Inc, Lincoln, Neb) was also administered with the follow-up questionnaire to evaluate objectively their overall health status. Results from the SF-36 health survey were compared with published normative values for the US population using t tests.

Surgical technique. The procedure was performed with the patient in the lateral decubitus
position. Three to 4 trocars were used for the left side and 4 to 5 for the right side. Patients were repositioned between sides. Dissection was performed primarily with the harmonic scalpel with the exception of clips being placed on the right adrenal vein. Glands were removed in an endoscopically placed bag and the retroperitoneal beds were examined for completeness of gland removal.

Hydrocortisone replacement was started intraoperatively at the completion of the adrenalectomy. Patients were converted to oral hydrocortisone therapy once they were tolerating a clear liquid diet, and discharged when tolerating a regular diet and steroid replacement.

Six patients underwent confirmation of completeness of adrenalectomy. Postoperatively they were placed on dexamethasone replacement therapy and a serum cortisol level was measured the next morning. Undetectable serum cortisol levels confirmed absence of adrenal tissue. They were subsequently converted to standard hydrocortisone therapy before discharge.

RESULTS

Eighteen patients underwent laparoscopic bilateral adrenalectomy for Cushing’s syndrome during the study period. Demographic variables, duration of disease, and number of previous interventions are outlined in Table I. All patients had documented Cushing’s syndrome and increased 24-hour urinary free cortisol levels, mean 152 µg/dL (range, 47-366). Sixteen patients underwent transsphenoidal micro-operation at a median of 6.5 months (1-240 months) before adrenalectomy. One of the patients who underwent transsphenoidal operation was later diagnosed with bilateral adrenal dependent disease. Five patients underwent a second transsphenoidal micro-operation at a median of 18 months (3-29 months) before adrenalectomy. One patient who failed 2 transsphenoidal procedures also received γ-knife treatment 27 months before adrenalectomy.

Bilateral laparoscopic adrenalectomy was accomplished in all patients with a mean operative time of 296 minutes (160-420 minutes). The operative time includes repositioning and prepping the patient between sides, which added approximately 35 minutes on the basis of data available. The mean estimated blood loss for bilateral adrenalectomies was 218 mL (10-500 mL). There was 1 intraoperative complication of a colotomy secondary to adhesions from a previous appendectomy that was repaired through a limited open incision after completion of the adrenalectomy. There were 2 postoperative complications, 1 postoperative hemorrhage that was managed laparoscopically and resulted in a 1-U transfusion. The second complication of postoperative pancreatitis resulted in pseudocyst formation that has been managed conservatively. The median duration of stay was 3 days (range, 1-18 days). The patient who had the 18-day hospital stay was severely debilitated and had significant mental status changes secondary to her Cushing’s disease. She ultimately was discharged to a nursing home. Otherwise, all patients were discharged by postoperative day 5.

The mean combined adrenal weight was 30 g and ranged from 11 to 62 g with normal combined weight being 4 to 12 g. Documentation of completeness of adrenalectomy after the laparoscopic procedure was done in the initial 6 patients of this series. Dexamethasone was given for postoperative steroid replacement and serum cortisol was measured on postoperative day 1. All 6 patients had undetectable serum levels of cortisol confirming complete removal of both adrenal glands.

The median follow-up was 29 months. Three patients died at 12, 19, and 50 months after adrenalectomy from a cardiac event, stroke, and pneumonia, respectively. The age of these patients at death was 69, 73, and 74 years. Of the 15 patients available for follow-up, 14 were contacted by telephone to confirm their address and 11 returned the survey, for a 73% response rate. The effectiveness of adrenalectomy in reversing the sequelae of Cushing’s disease is shown in Table II. Hypertension, diabetes, and depression were defined by the requirement of medication for treatment of the disorder. The patients had a mean weight loss of 8 kg (3-19 kg).

### Table I. Patient demographics and disease characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Mean age (range)</td>
<td>47 y (18-72)</td>
</tr>
<tr>
<td>Female:Male</td>
<td>16:2</td>
</tr>
<tr>
<td>Pituitary dependent</td>
<td>15</td>
</tr>
<tr>
<td>Bilateral adrenal-dependent</td>
<td>3</td>
</tr>
<tr>
<td>Mean duration of disease</td>
<td>6.8 y (1-20)</td>
</tr>
<tr>
<td>Mean No. prior pituitary procedures</td>
<td>1.4 (1-3)</td>
</tr>
</tbody>
</table>

### Table II. Response of Cushing’s disease sequelae to adrenalectomy (N = 11)

<table>
<thead>
<tr>
<th>Sequela</th>
<th>Preoperative (%)</th>
<th>Postoperative (%)</th>
</tr>
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<tbody>
<tr>
<td>Hypertension</td>
<td>6 (55)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4 (36)</td>
<td>2 (18)</td>
</tr>
<tr>
<td>Depression</td>
<td>3 (27)</td>
<td>3 (27)</td>
</tr>
<tr>
<td>Hirsutism</td>
<td>6 (55)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Amenorrhea*</td>
<td>3 (38)</td>
<td>1 (13)</td>
</tr>
</tbody>
</table>

*Three patients were either postmenopausal or male.
All patients were discharged on hydrocortisone 15 mg twice a day and fludrocortisone acetate 0.1 mg/day. Between 6 and 18 months after operation, there was a decrease in the steroid replacement therapy to approximately 15 to 20 mg per day in divided doses. Seven of the 11 patients (64%) report seeking emergency care for steroid replacement at least once. Most of these events occurred during the first year after adrenalectomy and were related to vomiting and inability to take steroid replacement orally.

Ten of the 11 patients who responded to the questionnaire had pituitary dependent Cushing’s disease. One patient had Nelson’s syndrome develop 36 months after adrenalectomy and was treated with γ-knife irradiation. Six patients (60%) had disturbance in at least 1 other pituitary axis requiring treatment. Five had growth hormone deficiency, 2 had gonadal insufficiency, and 1 had permanent diabetes insipidus.

Four of the 11 patients are currently employed and returned to work between 1 and 5 months after adrenalectomy. Of the 7 who are not working, 3 stated that their current health status was preventing them from doing so. Nine patients (82%) state that their health is improved after adrenalectomy; 1, unchanged; and 1, worse. Results of the SF-36 health survey are displayed in Table III. Scores are transformed to a 0 to 100 scale with 100 representing the best perceived health. The 8 health concepts cover physical and emotional health, vitality, and perceived pain. Scores on all 8 parameters of the health survey are significantly lower than published normative scores for the general population.2

**DISCUSSION**

Transsphenoidal micro-operation is the treatment of choice for patients with Cushing’s disease. The success rate is 90% for pituitary microadenomas and falls to 65% for macroadenomas and 38% to 43% for recurrent or persistent disease.36 The treatment of patients who fail transsphenoidal micro-operation for the treatment of Cushing’s disease is a challenging clinical problem. Options include medical adrenalytic therapy, repeated transsphenoidal operation, γ-knife irradiation, and bilateral adrenalectomy.

Medical therapy is often poorly tolerated as a result of the side effects of chronic therapy. γ-Knife irradiation to the pituitary gland for the treatment of Cushing’s disease is effective in 63% to 83% of patients depending on the duration of follow-up.7,9 However, most patients don’t achieve normal cortisol levels until 6 to 18 months after treatment. Furthermore, the incidence of pituitary deficiencies in other axes after γ-knife therapy ranges from 17% to approximately 50%.7,8

Bilateral adrenalectomy is effective in reversing the signs and symptoms of Cushing’s disease.10-12 The introduction of the laparoscopic approach to adrenalectomy has decreased the operative morbidity of this procedure and several reports have confirmed that it is a feasible approach for patients with Cushing’s disease.13-16 Adrenalectomy renders patients dependent on steroid replacement therapy for the remainder of their lives. Previous reports have found that 9% to 20% of patients needed treatment for Addisonian episodes after adrenalectomy.10,17 We found that 63% of our patients sought emergency care for steroid deficiency. These are self-reported episodes and were not confirmed by obtaining medical records. Most patients stated that they sought care secondary to vomiting and inability to take their steroid replacement orally.

Bilateral adrenalectomy for pituitary dependent Cushing’s disease places the patient at risk for developing Nelson’s syndrome. The incidence of Nelson’s syndrome after adrenalectomy ranges from 15% to 30% depending on the duration of fol-
low-up.\textsuperscript{10,11,17,18} Prior pituitary irradiation is protective against the development of Nelson’s syndrome, factors that are associated with the development of the syndrome are subnormal or noncontinuous steroid replacement, female gender, pretreatment urinary cortisol level, and presence of a pituitary adenoma.\textsuperscript{10,18} One patient in our series had Nelson’s syndrome develop 35 months after adrenalectomy; however, our follow-up is relatively short.

Although 81\% of our patients who responded to this survey stated that their health was improved after adrenalectomy, they scored substantially lower on the SF-36 health survey when compared with the general population. The SF-36 is a generic health status survey that is not age-, disease-, or treatment-specific. It has been well-validated in measuring health status in multiple chronic diseases and the general population.\textsuperscript{2} The low scores in our patient population did not correlate with duration of follow-up, duration of disease before adrenalectomy, or preoperative urinary cortisol levels. We did not collect preoperative SF-36 data on our patients, and so we cannot measure specific changes in their health after adrenalectomy. We are now in the process of administering the survey before operation so that we can more effectively quantify our results in the future.

Other investigators have also found that patients with cured Cushing’s disease demonstrate marked impairment in both physical and mental health scores as measured by the SF-36.\textsuperscript{10,19} Persistent poor health after definitive treatment of Cushing’s disease is not limited to those patients who have undergone adrenalectomy.\textsuperscript{19} In a population-based study in Denmark, patients who were cured with initial pituitary operation still exhibited significantly poorer perceived health on several parameters of the SF-36 survey after more than 5 years of follow-up.\textsuperscript{19} The scores on the SF-36 were substantially worse when patients failed initial pituitary operation. The explanation for these findings seem to be more related to the long-standing sequelae of hypercortisolism rather than the treatment imposed. Our study does not define the reason for continued perception of poor health.

The natural history of untreated Cushing’s disease is poorly documented, but 1 study from 1952 reported a 5-year mortality rate that was greater than 50\%.\textsuperscript{20} Consistent with this, survival in patients with Cushing’s disease is much poorer for those patients who fail initial treatment with transsphenoidal operation.\textsuperscript{19} During our follow-up period, 3 of the 18 patients died from causes unrelated to operation. All 3 patients were more than age 65 years at the time of adrenalectomy, the remaining 15 patients were less than age 65 years (18-63). Of interest is that all 3 patients who died had poorly controlled hypertension before definitive treatment of their Cushing’s disease, despite being on 2 to 4 medications, whereas only 4 of the remaining 15 patients were on 2 or more medications.

This report confirms that laparoscopic bilateral adrenalectomy is effective in controlling the complications of Cushing’s disease. Patients enjoy improvement in their health status after definitive treatment of their disease; however, most continue to have poorer health than the general population. The sustained effects of Cushing’s disease appear to be more related to the disease process rather than the treatment imposed. We recommend laparoscopic bilateral adrenalectomy as the preferred treatment in patients who fail transsphenoidal pituitary operation. Adrenalectomy predictably and immediately reverses the hypercortisolic state in Cushing’s disease. Because of the frequent disturbances in other pituitary axes, we reserve \(\gamma\)knife radiation for those who have signs of developing Nelson’s syndrome.

REFERENCES

DISCUSSION

Dr Quan-Yang Duh (San Francisco, California). I want to say that I completely agree with you in terms of the recommendation that this is a treatment of choice for a patient who has a failed operation. You did state in your final conclusion that this may be a primary treatment for pituitary-dependent, adrenocorticotrophic hormone-dependent Cushing’s syndrome. Did I catch that correctly?

Dr Hawn. If I said that, then I misspoke. Adrenalectomy should be primary treatment for patients who have failed transphenoidal pituitary operation. And often the patients who have failed are patients with a very aggressive pituitary tumor, such as a macroadenoma. We recommend that they go on to adrenalectomy rather than a repeated transphenoidal procedure, and we recommend reserving the γ-knife for patients in whom signs or symptoms of Nelson’s syndrome develop.

Dr L. Michael Brunot (St. Louis Missouri). My question relates to the biochemical follow-up. There have been some cases reported which, with biochemical testing and adrenocorticotrophic hormone stimulation, there is evidence of some residual cortical function after bilateral adrenalectomy for patients who have been treated laparoscopically. I was just wondering if you have any long-term biochemical follow-up on these patients and if you carried out adrenocorticotrophic hormone stimulation testing in any of these patients or have you done 24-hour urine cortisol during long-term follow-up.

Dr Hawn. Approximately 8 of these patients continued to be followed-up at Oregon Health and Sciences University, by our study endocrinologist. To my knowledge, none of them have had long-term biochemical follow-up. But I agree that would be a nice addition to this study to confirm completeness of the adrenalectomy.

Dr Laurent Brunaud (San Francisco, California). My question is more related to the methodology you used. In your opinion, is an SF-36 questionnaire adequate or very accurate regarding the patient after laparoscopic adrenalectomy, especially when you have symptoms? Do you think that more specific tools than the ones you use are mandatory and better? And does this specific questionnaire validate previous studies?

Dr Hawn. The specific questionnaire that I used with regards to Cushing’s syndrome is not validated and was really trying to get at the resolution of the sequelae of Cushing’s disease. I think the 2 questionnaires are complementary. The SF-36 is well-validated in multiple chronic disease processes. Because this patient population is small, I think it will be challenging to get a well-validated, specific questionnaire for them.

The thing that I think is useful about the SF-36 is it addresses both physical and mental health, which are both affected by this disorder.

But I think a complementary disease-specific questionnaire is helpful to show that we do improve the symptoms related to Cushing’s despite the prolonged effect the disease has on patient health.

Dr William B. Inabnet, III (New York, New York). I agree 100% with your conclusions. When patients have failed pituitary-directed treatment for Cushing’s disease, they are given medical therapy and experience severe progression disease. When these patients are ultimately referred for adrenalectomy as a result of failure of medical therapy, they have multiple comorbidities from cortisol excess, which increases the perioperative complication rate.

In the 4 patients who had complications in your series, what was the interval from the failed pituitary treatment to adrenalectomy and did those patients undergo medical therapy? Was there a higher complication rate in patients who received medical therapy?

Dr Hawn. I don’t believe that any of the patients in our study underwent a prolonged attempt at medical therapy. The endocrinologist who we work with confirms the diagnosis quickly and refers them for operation. The median time between transphenoidal operation and adrenalectomy was 6 months in our study population. And to my knowledge (and I would have to look at the data more carefully) the duration of the disease did not correlate with morbidity.

Dr Inabnet. I think your conclusion of early surgical intervention is warranted and well-supported by your results.

Dr Janice L. Pasieka (Calgary, Alberta, Canada). Were all of your patients on the same dose of prednisone and fludrocortisone acetate after operation?

Dr Hawn. Yes, all patients were discharged on 30 mg of hydrocortisone in divided doses and 0.1 mg of...
Florinef. Most patients were then weaned to somewhere between 15 to 20 mg of hydrocortisone in divided doses within about 5 months after adrenalectomy.

Dr Thomas J. Fahey, III (New York, New York). Your data is excellent, and I think it confirms what many of us have seen in patients who have had bilateral adrenalectomy. I am wondering if you or your endocrinologist have made any proposals or adjustments in how to actually continue to improve these patients’ lives after bilateral adrenalectomy?

Dr Hawn. One of the things that we have found is because patients have had multiple previous transphenoidal procedures, they often had disturbances in other pituitary axises. And I think aggressive diagnosis and management of those axises has helped in improving their quality of life.