SCIENTIFIC PAPER

Laparoscopic Surgery for Malignant Adrenal Tumors

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ABSTRACT

Advances in imaging have improved early detection of primary and metastatic adrenal tumors. The laparoscopic approach, the gold standard for benign adrenal diseases, is controversial for malignant adrenal tumors. A prospective randomized study of the role of laparoscopic surgery in adrenal cancer is not feasible because of the rarity of the disease. A review of the literature demonstrates the safety and efficacy of laparoscopic adrenalectomy for solitary adrenal tumors. In primary adrenal malignancies, the laparoscopic approach should be considered cautiously, only when it can achieve complete tumor resection with an intact adrenal capsule. Conversion to an open procedure should be an early decision, prior to tumor morcellation or fracture of the tumor capsule. Patients who have local invasion, tumors that are too large, or require organ resection require an open procedure.

Key Words: Laparoscopic adrenalectomy, Malignancy, Malignant tumors.

INTRODUCTION

Advances in biochemistry and imaging have led to earlier diagnosis and enrichment of adrenal pathology. Development of endocrinology and laparoscopic surgery has lowered the morbidity of adrenal operations. Laparoscopic adrenalectomy is one of the successful applications of minimally invasive surgical techniques. Since the first laparoscopic adrenalectomy was performed in 1992,[1] this approach has been adopted quickly as the procedure of choice to treat benign functioning and nonfunctioning adrenal tumors. It is widely accepted that the laparoscopic approach provides better visualization of anatomically complex areas through smaller and less painful incisions. Several series[2,3] have documented that laparoscopic adrenalectomy is followed by lower complication rates, less operative blood loss, and less need for transfusion, less postoperative pain, earlier return to activity and diet, better cosmetic results, shorter hospital stay, and lower overall costs.

In the era of advanced laparoscopic surgery, laparoscopic adrenalectomy has gained popularity, and several institutions have expanded indications for this procedure. Potentially malignant primary adrenal tumors and solitary adrenal metastases, once considered contraindications for the laparoscopic approach, are now being removed laparoscopically in some centers.[4–8] The suitability of the laparoscopic approach to primary adrenal carcinomas remains the focus of debate. A curative laparoscopic resection incorporates the oncologic principles of the open technique, avoiding fracture of the tumor capsule.

Malignant tumors of the adrenal gland are categorized into those arising from the cortex or medulla and metastatic ones from known primary origin.

ADRENAL CORTICAL CARCINOMA

An adrenal cortical carcinoma (ACC) is a rare, highly malignant endocrine neoplasm with few effective therapeutic options apart from surgical resection.[9–11] It has a worldwide incidence of approximately 2 per million population per year.[12] It represents 0.2% of all cases of cancer. Regardless of size, approximately 1 per 1500 adrenal tumors is malignant.[13] The incidence rate of malignancy is

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small in all adrenal masses that are <4 cm. In series with tumors >5 cm, carcinoma may be found in as many as 7% of patients.[14] About 60% of these tumors are functioning and may secrete excess cortisol, androgens, estrogens, aldosterone, or a combination of those.[15,16] ACCs may occur sporadically or rarely as a component of multiple endocrine neoplasia type I (MEN I), Beckwith-Wiedemann syndrome, and Li-Fraumeni syndrome.[17,18]

Adequate imaging is essential for staging of the disease and operative planning. Both CT and MRI are useful for evaluating the primary tumor and especially for detecting regional disease, vascular disease, lymphadenopathy, and liver and lung metastases. ACCs are usually >6 cm, with heterogeneity, irregular margins, hemorrhage, necrosis, calcifications, or adjacent lymphadenopathy. Metastases and local invasion into adjacent organs or the vena cava are possible radiographic features of ACC.[19] Radiocholesterol scintigraphy, using 131 I-6-beta-iodomethylnorcholesterol (NP-59) has been used to determine whether an adrenal cortical tumor is benign. Decreased or no uptake of NP-59 is more likely in a cancer and the majority of ACCs have no NP-59 uptake.[20]

Local disease at diagnosis and complete tumor resection constitute the 2 most important factors for improved survival. Five-year survival for patients with ACCs ranges from 16% to 60%. Even patients who undergo complete resection may have recurrence, metastatic disease, or both. Approximately two-thirds of patients develop recurrence within 2 years, and about 85% eventually develop local recurrence or distant metastases. Resection of the primary tumor in the presence of metastatic disease can improve local symptoms but rarely affects overall survival.[21]

MALIGNANT PHEOCHROMOCYTOMA

Pheochromocytomas are rare catecholamine-secreting tumors deriving from chromaffin cells. The incidence of pheochromocytoma is 1 to 2/100 000 adults per year.[22] About 10% of pheochromocytomas were thought to be hereditary, but recently it has been shown that approximately 25% of patients with sporadic pheochromocytoma and no family history have germ-line mutations in 1 of 4 susceptible genes for pheochromocytoma. These mutations may be seen in isolation or as part of a syndrome, such as multiple endocrine neoplasia (MEN) IIA and IIB, and various neuroectodermal disorders including neurofibromatosis, von Hippel-Lindau syndrome, Sturge-Weber syndrome, and Carney triad, the latter being associated with multifocal extraadrenal pheochromocytomas.[23] When these tumors are found in patients with familial syndromes, they are more likely to be bilateral or multifocal and benign unless there is a family history of malignant pheochromocytoma.[24] A diagnosis of malignant pheochromocytoma can only be made reliably by the findings of local invasion or nodal and distant metastases. CT and MRI are very useful for the recognition of these tumors and so is scintigraphy with I-131-meta-iodo-benzyl-gouanidine (MIBG 131), which is a functional imaging test especially important for tumors that cannot be detected by CT or MRI for extraadrenal, multifocal, or metastatic disease, for MEN syndromes and for the early detection of disease relapse.[25–27] Malignant pheochromocytoma may recur early or late (even 20 years) after the initial resection.[28–31] Unfortunately, no accurate histologic criteria exist to establish the diagnosis, and 5% to 26% of pheochromocytomas are malignant.[32–35]

METASTATIC TUMORS

Solitary adrenal metastases are quite common and normally do not cause symptoms. Primary localization of metastatic tumors is lung (the most common), breast, kidney, bowel, stomach, lymphoma, and melanoma. In a patient with a history of an extraadrenal primary malignancy, an adrenal incidentaloma represents metastatic disease in 32% to 73% of cases. Detection of metastases is becoming increasingly common with the widespread use of cross-sectional imaging (CT or MRI) and with 28-fluorodeoxyglucose positron-emission tomography.[36] Adrenal metastases are in most cases confined within the capsule of the organ, which suggests that simple adrenalectomy may be sufficient to achieve negative margins.[37–38] Many studies[39–41] advocate that resection of isolated metachronous adrenal metastases from various primary cancers may improve survival. These studies demonstrate median survival between 20 months and 30 months after adrenal metastasectomy, compared with 6 months to 8 months in cases with unresected adrenal metastases.

LAPAROSCOPIC SURGERY IN MALIGNANCY

Laparoscopic surgery can be an accepted method in the surgical management of cancer if it fulfils a number of parameters. First of all, there should be evidence drawn by operative morbidity and mortality that laparoscopic surgery is equally safe or even safer than conventional open surgery is. Moreover, it should be as radical as conventional open surgery.

The role of laparoscopic surgery for malignant adrenal tumors is controversial, because there are small series in

the literature for a rare disease. Furthermore, there have been concerns regarding local recurrences and port-site metastasis after potentially curative resections.[42] The pathogenesis of port-site metastasis remains unknown but is probably multifactorial. Direct wound implantation of tumor cells plays a major role in the development of port-site metastasis. However, this does not explain the development of metastasis at nonextraction port sites. Other causal factors are contamination of instruments, aerolization of tumor cells, the chimney effect, poor surgical technique, improper handling of the tumor, pneumoperitoneum, hematogenous spread, effect of the carbon dioxide on tumor cells, and lack of preventive measures of local recurrence and port-site metastasis. Several strategies have been proposed to prevent port-site metastasis. To achieve better results, strictly oncologic techniques should be followed as in open surgery. Moreover, additional techniques like wound protectors, evacuation of the pneumoperitoneum through the port, and peritoneal wound closure have been proposed and applied successfully.[43–46]

Three cases of diffuse peritoneal dissemination and death of patients who underwent laparoscopic adrenalectomy for adrenal cancer have been reported.[46] Moreover in a study of 13 patients (6 with adrenal cortical carcinoma and 7 with metastasis),[47] the mean size of the malignant lesions was 5.9cm. The mean follow-up was 30 months, during which 3 patients died, one due to endoperitoneal and trocar port-site seeding. In another study,[48] 31 patients underwent 33 laparoscopic adrenalectomies, 26 for metastatic cancer and 7 for primary adrenal malignancy. Follow-up was 26 months, during which 15 patients died. Local recurrence was noted in 7 patients. However, no port-site metastasis occurred. Five-year survival reached 40%.

LAPAROSCOPIC RESECTION OF SOLITARY ADRENAL METASTASES

Surgical excision in cases of solitary adrenal metastases is advantageous to the patient in terms of disease-free and overall survival. Solitary adrenal metastasis does not mean systemic disease, and studies have shown that these patients may be treated with laparoscopic surgery. Moreover, it has been suggested that patients who have a metachronous metastasis from any of a variety of primary tumors may benefit, as they will suffer less morbidity than with open surgery.

Heniford and colleagues[49] in a review of 10 patients with metastatic adrenal tumors and 1 patient with adrenocortical carcinoma reported no local or port-site recurrence at a mean follow-up of 8.3 months. Another study[50] has focused on solitary adrenal gland metastasis in patients who have been formerly operated on for non-small cell lung cancer. There were 11 patients with solitary adrenal metastases. All of them underwent laparoscopic adrenalectomy. Three were still alive and well 37 months to 80 months after the lung resection. One patient (who underwent bilateral adrenalectomy) was still alive 44 months later but with local relapse. Two patients died of other causes 5 months and 6 months after the adrenalectomy, one after 14 months of local and systemic relapse and the remaining 3 after 12 to 38 months of systemic relapse.

LAPAROSCOPIC SURGERY IN PRIMARY ADRENAL MALIGNANCY

Malignant pheochromocytomas and ACCs must be approached cautiously. Peri-adrenal invasion is common, and the possibility of tumor fragmentation and abdominal dissemination is significant. The surgeon must mobilize the tumor and surrounding adipose tissue without grasping the tumor or gland. The ultrasonically activated scalpel should be carefully used so that it does not divide tumor surface or adrenal tissue and thus create fragmentation and malignant cell dissemination.

Lombardi et al[51] reported complete laparoscopic excision of 3 ACCs and 2 malignant pheochromocytomas, both well-encapsulated macroscopically. Unfortunately, one patient with ACC presented with pelvic recurrence 6 months later, and one patient with malignant pheochromocytoma developed intraabdominal recurrence 1 year after laparoscopic surgery. Li and colleagues[52] have reported 3 cases of pheochromocytomatosis following laparoscopic adrenalectomy; however, it is not clear whether it was malignant dissemination or spillage of a benign tumor due to bad technique. Additionally, laparoscopic adrenalectomy for clinically unsuspected adrenocortical cancer was associated with a high recurrence rate.[53] Despite the several hundreds of laparoscopically resected pheochromocytomas reported in the literature, data are lacking on the long-term follow-up of patients who have undergone laparoscopic adrenalectomy for malignant pheochromocytoma.[54,55] The natural history of the resected malignant pheochromocytoma is still unknown. Recurrence has been reported more often 6 years to 7 years following curative surgery, but it can occur as late as after 24 years.[55]

With regard to malignant adrenal cortical tumors, it appears from literature data **(Table 1)** that the risk of locore-

Table 1.
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Author	Journal	Tumor Size (cm)	Patients Number	Abdominal Dissemination
Heniford BT	Semin Surg Oncol 1999;16:293	1.8–12	11 (10 metastatic, 1 ACC)	(-) 0.5 -19 months
Henry J	World J Surg 2000;24:1342	3.5–4	4 metastatic	(-) 12 months
Valeri A	Surg Endosc 2001;15:90	2.5–6	6 metastatic	(-) 3 -18 months
Clark OH	Arch Surg 2002;137:948–951	7–12	6 primary	3 local recurrences
Clark OH	Arch Surg 2002;137:948–951	2.5–12	13 metastatic	65% disease free survival in 3.3 years
Henry JF	World J Surg 2002;26:1043	>6	6	6 months liver metastasis
Rassweijer J	J UroI 2003;169:2072	-	11	1 local recurrence, 1 port-site metastasis
Lombardi CP	Tumori 2003;89:255	-	9	(-)
Giraudo G	Minerva Chir 2004;59(1):1–5	-	4 primary, 4 metastatic	(-) 9–72 months
Porpiglia F	BJU Int 2004;94(7):1026–1029	Mean 5.9	6 primary, 7 metastatic	1 port-site metastasis
Kerher	Ann Surg 2004;241(6):919–928	-	2	(-) 21.4 months
Lucchi M	Eur J Cardiothorac Surg 2005;27(5):753–756	-	11 metastatic, 4 primary	1 local relapse, 4 systemic relapses

gional recurrence and tumor dissemination is unclear. In spite of several reports of locoregional recurrence following laparoscopic adrenalectomy, data are insufficient to attribute the recurrences to the laparoscopy per se or to bad surgical technique with erratic patient selection. Furthermore, in most reports of laparoscopic adrenalectomy for ACC, a cancer diagnosis was not established or suspected preoperatively. Because the ACCs in these reports were localized tumors, possibly representing less aggressive disease, or potentially malignant tumors, results may not reflect the true survival and risk of local recurrence.[54]

Given that no reliable and accurate preoperative diagnostic test to confirm the diagnosis of primary malignant adrenal tumor or local invasion exists, it is often difficult to determine whether the laparoscopic approach can achieve a curative resection.

The role of the laparoscopic approach for large tumors is still controversial. There are not many reports of patients with malignancies >8 cm; however, a review of the literature shows that these patients may undergo laparoscopic surgery. The overall morbidity and mortality is independent of the size of the tumor,[53] and the mean operative time is not significantly different. Conversion to open surgery is necessary more often with larger tumors, due to invasion of adjacent tissues or organs or due to capsular disruption. Lesion sizes of 12 cm to 14 cm have been cited as the upper limit for laparoscopic adrenalectomy in most of the studies.[56]

At present, laparoscopic adrenalectomy is contraindicated for invasive malignant tumors.[57] En-block extensive resections like nephrectomy, hepatectomy, pancreatectomy, and splenectomy are not well suited to the laparoscopic technique.[58–63]

CONCLUSION

A prospective randomized study of the role of laparoscopic surgery in adrenal cancer is not feasible because of the rarity of primary and metastatic adrenal malignancies. It seems that metastatic lesions in the adrenal gland are more favorable for the laparoscopic approach than is primary malignant disease. Laparoscopy should be the initial step in the surgical approach to localized primary tumors as well as to solitary metastasis. Nevertheless, laparoscopic mobilization of the tumor with the minimum "handling," without grasping the tumor should be the second step. Laparoscopic adrenalectomy should be performed only when it can achieve complete tumor resec-

tion with an intact adrenal capsule. This is very important, as complete resection constitutes the only possibility of curing patients, and it should be taken into account that even small tumors may rarely be malignant. The principles of oncologic surgery should be routine for all adrenal tumors. If a complete resection cannot be performed safely, the operation should not be continued laparoscopically. Conversion to an open procedure should be an early decision, prior to tumor morcellation or fracture of the tumor capsule. Patients who have local invasion, tumors that are too large, or require organ resection require an open procedure.

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