

## CLINICAL STUDY

# Adrenocortical carcinoma: is the surgical approach a risk factor of peritoneal carcinomatosis?

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## Abstract

**Context:** Peritoneal carcinomatosis (PC) is a rare site of distant metastases in patients with adrenocortical cancer (ACC). One preliminary study suggests an increased risk of PC after laparoscopic adrenalectomy (LA) for ACC.

**Objective:** The objective of the study was to search for risk factors of PC including surgical approach.

**Design:** This was a retrospective cohort study conducted in an institutional practice.

**Patients:** Sixty-four consecutive patients with ACC seen at our institution between 2003 and 2009 were included. Mean tumor size was 132 mm. Patients had stage I disease in 2 cases, stage II disease in 32 cases, stage III disease in 7 cases, stage IV disease in 21 cases, and unknown stage disease in 2 cases. Surgery was open in 58 cases and laparoscopic in 6 cases.

**Main outcome:** The main outcome was the risk factors of PC.

**Results:** PC occurred in 18 (28%) patients. It was present at initial diagnosis in three cases and occurred during follow-up in 15 cases. The only risk factor of PC occurring during follow-up was the surgical approach with a 4-year rate of PC of 67% (95% confidence interval (CI), 30–90%) for LA and 27% (95% CI, 15–44%) for open adrenalectomy ( $P=0.016$ ). Neither tumor size, stage, functional status, completeness of surgery, nor plasma level of op'DDD was associated with the occurrence of PC.

**Conclusion:** We found an increased risk of PC after LA for ACC. Whether this is related to an inappropriate surgical approach or to insufficient experience in ACC surgery should be clarified by a prospective program.

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## Introduction

Peritoneal carcinomatosis (PC) in adrenocortical carcinoma (ACC) is unusual and was reported in 4–15% of the patients (1–4). Peritoneal dissemination occurs essentially through tumor cells spread across the peritoneal cavity before surgery, but it can also be caused by iatrogenic dissemination during the operation itself. Gonzalez *et al.* (5) reported an 8% risk of PC in patients treated through open adrenalectomy (OA) and an 83% risk of PC in patients treated through laparoscopic adrenalectomy (LA). Classically, OA allows a maximal exposure, a vascular control of the inferior vena cava and renal vessels, and lymphadenectomy. LA was first introduced for the resection of small, presumably benign tumors and of pheochromocytoma (6). Studies have documented its superiority over OA in terms of postoperative recovery, length of hospital stay,

and overall costs (7–11). It has therefore become the treatment of choice for benign lesions with a diameter of <6 cm, whereas OA remains the standard treatment for ACC with invasion of adjacent organs, inferior vena cava thrombosis, enlarged regional lymph nodes, or tumors larger than 10–12 cm in size (12, 13). Because of the excellent results of LA, several authors proposed it for larger and malignant adrenal tumors (14–20). However, these reports derived from centers with very large experience in laparoscopic surgery included a limited number of ACC patients and had a short follow-up. The risks of tumor spillage and of local recurrence after LA for ACC remain unknown.

We therefore performed a retrospective study to search for factors associated with PC in consecutive ACC patients treated with adrenalectomy and referred to our tertiary care referral center for postoperative treatment and follow-up.

## Patients and methods

### Patients

Approval from our institutional review board was obtained for the study. Files of all patients between November 2003 and April 2009 were reviewed. Inclusion criteria were as follows: i) patients treated with adrenalectomy, ii) confirmed pathological diagnosis of malignancy (defined with a Weiss score of 3 or more), and iii) postoperative imaging performed within 2 months of surgery.

At initial diagnosis, clinically functional tumors were confirmed by appropriate hormonal tests. Otherwise, biological tests included measurement of potassium level, plasma and/or urinary excretion of cortisol, plasma testosterone and/or androstenedione and/or dehydroepiandrosterone sulfate (3).

### Methods

All patients underwent a postoperative thoraco-abdomino-pelvic computed tomography (TAP-CT) with i.v. injection of iodinated contrast medium (21). Complete surgery was defined by a R0 resection and a normal TAP-CT performed within 2 months after surgery. Initial staging was based on the Revised TNM Classification of the European Network for the Study of Adrenal Tumors (22). PC diagnosed within 2 months after initial surgery was considered as being present since initial diagnosis. Some patients also underwent fluorodeoxyglucose positron emission tomography (FDG-PET) either postoperatively (13 cases) or during follow-up (26 cases).

PC was diagnosed on postoperative CT in case of parietal peritoneal thickening, parietal peritoneal enhancement, and enhancing nodules (23). Recurrences in the adrenal bed, stuck to the peritoneum, were classified as local recurrences. PC on FDG-PET/CT was suspected in cases of intense peritoneal focal uptake, nodular or curvilinear uptake along the liver or left subphrenic space (23). All PC diagnosed on FDG-PET were confirmed on a subsequent guided TAP-CT. All PC diagnosed on CT and on FDG-PET/CT were confirmed by one experienced radiologist and one experienced nuclear medicine physician respectively. The standard basis for diagnosis of PC was confirmed by tumor pathology in four cases and by progression on follow-up TAP-CT in the other cases.

### Statistical analysis

The time to PC was defined as the time between surgery and occurrence of PC or last follow-up for patients who did not experience PC. Time to PC and time to local relapse were estimated with the Kaplan–Meier method. The 95% confidence intervals (95% CIs) of the actuarial rates were calculated using the Rothman method (24).

Risk factor analysis was performed by log-rank test with the following parameters: type of surgery (OA versus LP), completeness of resection, tumor size ( $\leq 5$  cm, 5–10 cm, or  $> 10$  cm), stage, and functional status. The occurrence of PC was compared between patients who received op'DDD with effective therapeutic plasma levels and those who did not reach effective therapeutic level or who did not receive op'DDD at all. Because obtaining the therapeutic level was not a baseline characteristic but occurred during follow-up, analysis was performed using a Cox's model with the achievement of therapeutic level as a time-dependent covariate.

## Results

### Patients

Seven patients were excluded because of unknown surgical procedure (two cases), absence of adrenal surgery due to large tumor burden with distant metastases (one case), and absence of postoperative imaging study (four cases). Functioning tumors were identified in 35 patients (55%), among whom 18 disclosed mixed hormone productions. Sixty-four patients (28 males and 36 females; median age: 54 years; range: 23–79) were therefore included, and they form the basis of this study.

ACC sizes were available in all cases except two. The mean size was 132 mm (range: 35–330; median: 130). Patients were classified as stage I in 2 cases, stage II in 32 cases, stage III in 7 cases, stage IV in 21 cases, and unknown stage in 2 cases (unknown size of ACC and no distant metastases). Among patients with stage IV disease, 11 disclosed more than one site of distant metastases.

Fifty-eight patients had undergone OA, and six underwent an LA. The two patients with unknown primary tumor size underwent OA. LA was performed by five different surgeons in five hospitals, and OA was performed by 46 different surgeons in 41 hospitals. A lymph node dissection was performed in 16 cases. Mean size of the tumors treated with LA was 69 mm (range: 35–90; median 70), and mean size of the tumors treated with OA was 137 mm (range: 40–330; median: 140) ( $P=0.006$ ). Tumors treated with LA were stage II in five cases and stage IV in one case. In this last case, lung and bone metastases were diagnosed postoperatively, which explains why LA was performed despite a stage IV tumor. Tumors treated with OA were stage I in 2 cases, stage II in 27 cases, stage III in 7 cases, stage IV in 20 cases, and unknown in 2 cases. Complete R0 surgery was achieved in 42 cases (5 cases of LA and 37 cases of OA).

Postoperative adjuvant external beam radiation on the adrenal bed was performed in six cases, in one case treated with LA, and in five cases with OA.

Op'DDD was given postoperatively to 61 patients. Effective therapeutic levels of plasma op'DDD were obtained in 42 patients. Median follow-up of the cohort was 35 months (range: 1–372).

### PC at diagnosis and recurrence

PC was diagnosed in 18 patients (28%) and was asymptomatic in all cases except one (Fig. 1 and Table 1). It was present at initial diagnosis in three patients and occurred during follow-up in 15 cases. PC was part of the first recurrence of ACC in ten of these patients. Median interval of time between initial surgery and the occurrence of PC in these 15 patients was 20 months (range: 6–332; mean 43). PC occurring during follow-up was isolated in four cases, associated with a local recurrence only in three cases, associated with abdominal lymph nodes only in one case, associated with a local recurrence and abdominal lymph nodes in one case, and associated with multiple distant metastases in six cases.

The only factor associated with the occurrence of PC was the type of surgery (Table 2). PC occurred in four of the six patients treated with LA and in 11 of the 55 patients treated with OA. The 4-year rate of PC was 67%

(95% CI, 30–90%) for LA and 27% (95% CI, 15–44%) for OA ( $P=0.016$ , hazard ratio=3.8 (95% CI, 1.2–12.3)). Taking into account only patients operated with a curative intent, PC occurred in three of the five patients treated with LA and in 9 of the 36 patients treated with OA. In these patients, the 4-year rate of PC was 60% (95% CI, 23–88%) for LA and 25% (95% CI, 13–42%) for OA ( $P=0.08$ , hazard ratio=3.1 (95% CI, 0.81–11.8)).

Among patients with PC after surgery, mean size of the primary tumor was 77 mm (range: 70–90; median 75) for the four patients treated with LA and 135 mm (range: 50–250; median 145) for the 11 patients treated with OA. The two patients treated with LA without PC during follow-up had initial primary tumors of 35 and 70 mm respectively. Median interval of time between initial surgery and diagnosis of PC was 20 months (range: 16–22; mean 20 months) for the four patients treated with LA and 20 months (range: 6–332; mean 52) for the 11 patients treated with OA.

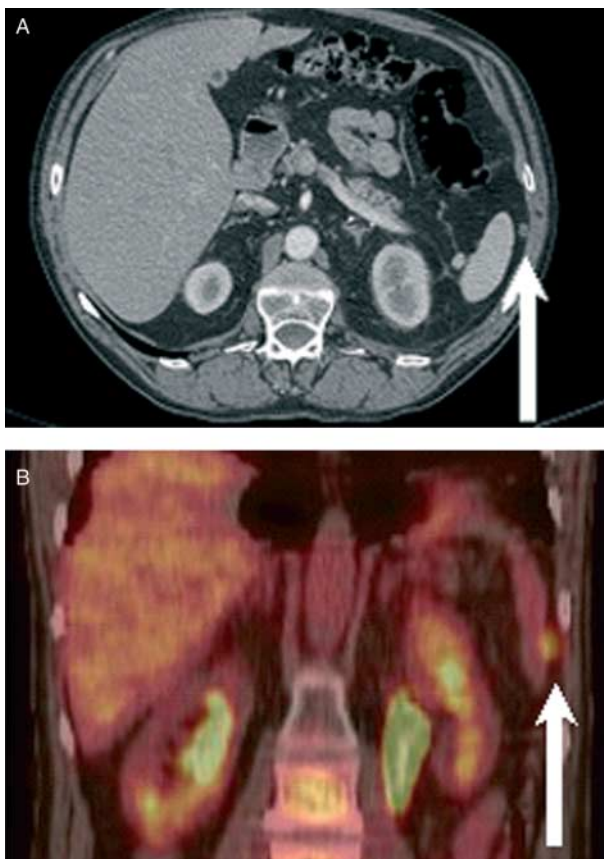
Among the six patients who underwent adjuvant postoperative external beam radiation, PC occurred in one patient treated with LA and did not occur in the five patients treated with OA. Overall, op'DDD effective therapeutic levels were obtained in four (67%) of the patients treated with LA and 38 (69%) of the patients treated with OA. Among the 15 patients who disclosed PC during follow-up, plasma op'DDD levels reached the therapeutic target in 10 (67%) patients. However, the therapeutic level was reached before the occurrence of PC in only six patients. Among patients who did not disclose PC, plasma op'DDD levels reached the therapeutic target in 32 (69%).

Ten of the 15 patients (67%) with PC occurring during follow-up died. They had been treated with LA in three cases and with OA in seven cases. The median survival after the diagnosis of PC was 32 months (range: 1–47), being 5 months (range: 4–6) for patients treated with LA and 38 months for patients treated with OA (range: 1–47).

Furthermore, the 1- and 2-year local relapse-free survivals were 33 and 66% respectively in patients treated with LA, and 10 and 28% respectively in patients treated with OA ( $P=0.07$ ).

### Discussion

ACC is a rare disease with a poor prognosis mainly depending on stage and quality of initial surgery. The five-year survival ranges from 16 to 60%, but is close to 35% in most studies (4, 25–32). Surgery (in patient with localized disease or limited resectable distant metastases) is the only potentially curative treatment (4, 27, 33). Recurrence however occurs in 37–87% of the patients (27, 28, 33). They most often consist of distant metastases and less frequently of local recurrence only (28, 29, 33). All efforts should therefore be



**Figure 1** CT (A) and PET/CT (B) showing peritoneal carcinomatosis (white arrow).

**Table 1** Clinical characteristics of patients with PC.

	Sex/age at diagnosis of ACC	Primary tumor size (mm)/side	Stage	Secretion	Surgical approach for adrenalectomy	R0 obtained after surgery	Interval of time between diagnosis of ACC and PC (months)	Other organ involved at the time of PC diagnosis	External beam radiation on adrenal bed before occurrence of PC	Op'DDD treatment before occurrence of PC/therapeutic range reached before occurrence of PC
1	F/29	70/R	II	Yes (cortisol-androgens)	Laparoscopic	Yes	17	Liver, abdominal LN, mediastinal LN, and local relapse	No	Yes/no
2	F/68	70/L	II	Yes (cortisol-androgens)	Laparoscopic	Yes	18	Liver, lung, and bone	No	Yes/yes
3	M/52	80/G	II	No	Laparoscopic	Yes	22	None	Yes	Yes/no
4	F/59	90/L	IV	No	Laparoscopic	No	23	Liver, bone, and local relapse	No	Yes/yes
5	F/43	NA/G	NA	No	Open	Yes	338	Abdominal LN	No	Yes/no
6	M/61	50/R	I	No	Open	Yes	17	Local relapse	No	Yes/no (simultaneously)
7	F/56	80/R	II	Yes (cortisol-androgens)	Open	No	49	None	No	Yes/yes
8	M/56	90/L	IV	No	Open	No	0	None	No	No/no
9	F/70	90/L	II	Yes (cortisol-androgens)	Open	Yes	10	Liver, lung, abdominal LN, and local relapse	No	Yes/yes
10	F/45	120/R	II	No	Open	Yes	17	Abdominal LN and local relapse	Yes	Yes/no (simultaneously)
11	M/74	140/G	II	No	Open	Yes	27	Local relapse	No	Yes/no
12	F/40	150/R	II	Yes (cortisol)	Open	Yes	28	None	No	Yes/no
13	F/67	150/R	III	No	Open	Yes	6	Liver, lung, bone, and local relapse	No	Yes/no (simultaneously)
14	F/59	160/L	II	Yes (cortisol-androgens)	Open	Yes	14	Local relapse	No	Yes/no
15	F/69	160/R	II	No	Open	Yes	41	None	No	Yes/yes
16	M/67	190/L	IV	No	Open	No	0	Liver and abdominal LN	No	No/no
17	M/59	220/L	IV	No	Open	No	0	Liver, lung, abdominal LN, mediastinal LN, and bone	No	No/no
18	F/34	250/L	IV	Yes (cortisol-androgens)	Open	No	20	Liver, lung, abdominal LN, and mediastinal LN	No	Yes/yes

ACC, adrenocortical carcinoma; PC, peritoneal carcinomatosis; L, left; R, right; LN, lymph node; NA, not available.



**Table 2** Predicting factors of peritoneal carcinomatosis (PC) occurrence.

	<i>n</i>	4-year PC rate	<i>P</i> (log-rank test)
<b>Surgery</b>			
Laparoscopic adrenalectomy	6	66.7%	0.016
Open adrenalectomy	55	26.8%	
<b>Size</b>			
≤5 cm	3	33.3%	0.97
5–10 cm	21	43.8%	
>10 cm	35	31.1%	
<b>Stage at initial diagnosis</b>			
I	2	50.0%	0.75
II	32	38.2%	
III	7	16.7%	
IV	18	20.0%	
Complete surgery (R0)	42	29.3%	0.94
Incomplete surgery	19	46.7%	
Secretion	35	29.9%	0.66
No secretion	26	34.6%	
Therapeutic plasma op'DDD		N/a*	0.55**
Obtained	42		
Not obtained	19		

\*N/a because therapeutic plasma op'DDD is a time-dependent variable.

\*\*Cox model with time-dependent variable.

made to perform a complete initial surgery. Owing to the scarcity of ACC, the high frequency of adrenal incidentaloma, the absence of absolute preoperative criteria of malignancy, and the increased quality of life brought by LA, a shift is being made toward minimally invasive surgery of adrenal tumors, including malignant tumors (14–16, 19, 34). These studies however only included a limited number of ACC patients.

In this retrospective study, we found a 5% incidence of PC at diagnosis and a 25% incidence of PC during follow-up, which is much higher than previously reported (1–4). This figure might simply be related to the focus brought on PC in this study and also to the use of FDG-PET/CT in some patients. PC did not occur preferentially at the port sites. This does not preclude the technical approach from taking part into the increased risk of PC. Insufflations performed during LA may allow fluid movements and cell dispersion in the peritoneal cavity.

We found that the surgical approach was the only significant factor associated with PC: with a 4-year PC recurrence rate of 67% in patients treated with LA and 27% in patients treated with OP. These results are in accordance with those of Gonzales *et al.* (5). We also found a tendency toward a higher risk of local recurrence after LA compared with OA. Of course, our study is limited by the low number of ACC patients who underwent LA. But since this approach is not routinely recommended in such patients, we could not expect a large number of patients. Even taking only into account patients treated with RO complete surgery, the occurrence of PC was more frequent in patients treated with

LA. The difference was not statistically significant, but we are limited by the low number of patients treated with LA. A second limitation of this study is that patients were essentially referred to our center for postoperative follow-up and treatment either for recurrence or for high risk of recurrence. The number of patients treated successfully by LA or OA is in fact unknown precluding the determination of the true risk factor of PC in ACC.

We were not able to distinguish the risk of PC due to an inappropriate surgical approach from the risk of ACC due to difficult surgery or surgery performed in non-experienced centers. The avoidance of tumor capsular rupture during surgery is, in fact, mandatory in ACC treatment, and is both dependent of tumor characteristics and surgeon skill. However, none of the surgical reports of LA mentioned tumor rupture. Furthermore, both OA and LA were performed in various centers. In the literature, besides the study from Gonzalez *et al.* (5), only one retrospective study did not observe an increase in PC after LA of adrenal malignancies (16). They however did not compare open surgery to laparoscopic surgery, and only included four ACC patients among whom one needed a conversion to an open procedure and one developed a pelvic 18-cm recurrence 6 months after initial surgery that was compatible with PC. Of note, clinical cases of PC occurring in ACC patients after LA were recently reported (35–37).

Tumors operated with LA were smaller than those operated with OA (mean size 69 vs 137 mm) but disclosed more often PC. Interestingly, the smallest tumor which disclosed PC had a 50-mm diameter, and was operated through an OA. These results suggest that the risk of PC is not limited to large tumors, and that caution should be applied to adrenal tumors bearing suspicious preoperative features of malignancy at imaging, including size, elevated spontaneous density on CT scan, contrast enhancement in tumor with spontaneous density above 10UH, presence of lymphadenopathy, and FDG uptake (38, 39).

Strikingly, one-third of the PC observed during follow-up was isolated suggesting that avoiding PC would be a major issue in patients with ACC whether operated through a LA or an OA. Furthermore, in 20% of other cases, PC was only associated with a local recurrence which might have been resectable. Intraperitoneal rupture of the primary tumor causing tumor spillage during surgery is indeed a major cause of PC. In our study, surgery was performed by many surgeons, and the occurrence of PC was not associated with a particular surgeon.

Whether PC has an impact on prognosis remains to be proven. PC is indeed regarded as a lethal entity. However, the hypothesis that ACC recurrence is a major prognostic event is reasonable. Indeed, the first recurrence is known to be highly predictive for further recurrences with a shorter interval of time between recurrences (40). Of note, in our study, the

median interval of time between initial surgery and the occurrence of PC was 20 months, similar in patients treated with LA or OA and close to the median 10–30 months reported median time between initial surgery and first recurrence (1, 29, 31, 33, 40, 41).

In conclusion, our results suggest that there may be an increased risk of PC after laparoscopic surgery of malignant ACC. Whether the increased risk of PC is related to an inappropriate surgical approach or to insufficient experience in ACC surgery should to be clarified by prospective program set up by international ACC network.

### Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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