Adrenocortical carcinoma: effect of hospital volume on patient outcome

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Purpose

Optimal management of adrenocortical carcinoma (ACC) involves a detailed diagnostic workup, radical surgery, and appropriate adjuvant therapy. However, due to the rarity of this disease, adequate expertise is necessary to ensure optimal patient care. We evaluated if the experience of a treating center influences the outcome of ACC.

Methods

Two hundred sixty-three patients who underwent adrenalectomy for ACC were included in a multi-institutional surgical survey and divided into 2 groups: “high-volume center” (HVC) ($\geq$10 adrenalectomies for ACC) and “low-volume center” (LVC) (<10 adrenalectomies for ACC). A comparative analysis was performed.

Results

One hundred seventy-two patients underwent adrenalectomy at HVC and 91 at LVC. The two groups were homogeneous for age, sex, clinical presentation, and stage. The mean lesions size of ACC was higher in HVC than in LVC (104.1 ± 54.6 vs 82.8 ± 41.3 mm; $P < 0.001$). A significantly higher rate of lymph node dissection ($P < 0.01$) and of multiorgan resection ($P < 0.01$) was accomplished in HVC. The number of patients who underwent adjuvant therapy was significantly higher in HVC ($P < 0.001$). Local recurrence rate was lower in patients treated at HVC (6% vs 18.5%; P = NS). Mean time to recurrence was significantly longer in HVC than in LVC (25.2 ± 28.1 vs 10.1 ± 7.5; $P < 0.01$).

Conclusion

The expertise of dedicated centers had a positive impact on the outcome of patients with ACC, resulting in a lower recurrence rate and improved mean time to recurrence. The improved patient outcome could be related not only to the appropriateness of the surgical procedure, but also to a more adequate multidisciplinary approach.

Keywords

Adrenocortical carcinomaPatient volumeOncologic outcomeAdrenal tumor
This paper is based on a work that has been presented as an oral presentation at the ESES Workshop in Lyon, France, 12–14 May 2011.

Introduction

Adrenocortical carcinoma (ACC) is a rare and highly aggressive endocrine neoplasm that is associated with a dismal prognosis [1–5]. Indeed, the overall 5-year survival rate has been reported to range from 16% to 44% [6–11]. Prognosis is stage-dependent and, in localized disease, complete surgical resection remains the only potential curative treatment that is effective also in the case of recurrent disease [7, 11, 12]. For cases involving advanced stages of the disease, the administration of adjuvant mitotane or chemotherapy has shown some efficacy, although significant side effects are associated with these treatments [3]. With the increased availability of imaging studies, it has been hypothesized that ACC could be diagnosed in its earlier stages and, therefore, more amenable to complete resection [13]. However, published studies failed to demonstrate an unequivocal improvement in survival rates for ACC in recent years [14]. Indeed, even in patients with localized disease (stages I and II ACC) who underwent surgery with curative intent, recurrence was common [13, 15]. In addition, for stage II patients, the 5-year survival rate ranges from 38% to 61% [1, 6–8, 13].

On the other hand, as with other rare diseases, ACC patients often encounter physicians with no prior experience with this rare disease. As a result, increased uncertainty regarding the necessary diagnostic and therapeutic measures required occurs [16]. Recently, a significantly improved survival rate was reported for patients with localized ACC who were followed up prospectively in specialized centers [13]. An improved survival rate was also reported for a large series of ACC patients treated at a single tertiary care referral center where patients underwent surgeries that achieved a complete resection of all gross disease [12]. Additional studies have also clearly demonstrated that increased surgeon

and hospital volume are positively associated with improved patient outcomes following adrenalectomy [17, 18]. As a consequence, we can argue a similar advantage in terms of oncologic outcome, including improved disease-free survival (DFS) and overall survival (OS) rates, for ACC patients who receive early specialized care at high-volume centers (HVC).

In 2003, we proposed an Italian multi-institutional surgical survey on ACC. The aim of this study was to evaluate whether the quality of medical care for patients with ACC, evaluated in terms of oncologic outcome, are influenced by the volume of patients treated.

Material and methods

Based on the previous Italian Registry for ACC [6, 11], a new Italian multi-institutional surgical survey was initiated in December 2003. Following contact with the heads of various Italian surgical divisions and their agreement to participate in this survey, a structured patient form was specifically developed for this study and distributed. The goal was to obtain comprehensive information regarding the diagnostic procedures, treatment, and follow-up of patients receiving treatment for ACC. Completed forms were returned to a specific e-mail address (surrene@rm.unicatt.it) established specifically for this survey. Patient forms addressed patient demography, primary diagnosis (including functional status), imaging study data, operative and pathologic data, adjuvant treatment(s), and patient follow-up data. Participating centers were asked to fill out a form for each enrolled patient and to provide additional follow-up information every 6 months regarding any relevant changes in the course of disease for each enrolled patient. Recruitment and follow-up data for the enrolled patients were closed at the end of July 2010. All data collected were then entered into a specifically designated database (Microsoft Excel®, Microsoft Corporation, Redmond, WA, USA) by trained medical personnel.

Study design

Participating centers were grouped into quartiles basing on the number of patients observed and recruited for this survey. Centers in the upper quartile were considered as HVC [17]. Centers fell in the upper quartile if they recruited at least 10 ACC patients.

Therefore, for the purpose of this study, the participating centers were considered as HVC if they recruited 10 ACC patients or more and as low-volume centers (LVC) if they recruited <10 ACC patients. Since the recruitment period was different among the different centers, the annual case load of ACC was calculated for each center (number of ACC recruited/recruitment period in years). A comparative analysis between the two groups was performed in order to evaluate the oncologic outcome. Comparison included the following parameters: patients' demographics, preoperative diagnosis, functional status, tumor size, type of surgical procedure (laparoscopic vs conventional), extent of surgery (biopsy, adrenalectomy, multiorgan resection, and lymph node dissection), completeness of surgery, postoperative stage, adjuvant therapy, and follow-up results.

Definitions

Assessments of preoperative workup were based on treatment guidelines provided by the National Institutes of Health (e.g., NIH State-of-the-Science Statement on Management of Clinically Unapparent Adrenal Mass ("Incidentaloma")) [19] and recommendations from the European Network for the Study of the Adrenal Tumors on the care of ACC patients (http://www.ensat.org/acc.htm) [16], which do not fundamentally differ from earlier recommendations [20].

Computed tomography (CT) or magnetic resonance imaging of the abdomen and CT of the thorax were recommended for a complete radiological evaluation [4, 16, 19, 20]. In the latter case, this imaging was recommended due to the lung being the most common site for metastasis in cases of ACC [16].

The extent of surgery was designed as adrenalectomy alone vs multiorgan resection (adrenal plus at least one or more adjacent organs removed and demonstrated at histological examination). Completeness of the resection performed was reported as grossly complete (R0), incomplete (R1), or undetermined (Rx) based on operative reports. Postoperative stage was determined based on criteria proposed by MacFarlane [21] and revised by Sullivan et al. [22]. The period of OS for the study population was calculated from the date of diagnosis to the date of death or to the date of the last follow-up evaluation for surviving patients. In addition, the period of DFS was calculated from the date of diagnosis to the date of diagnosis of tumor recurrence or the date of last follow-up evaluation for patients without recurrence. Disease recurrence was diagnosed based on

clinical, laboratory results, and radiological evidence. Histological confirmation of recurrence was not required.

Statistical analysis

Statistical analyses were performed using a commercially available statistical software package (SPSS 10.0 for Windows; SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as the median ± standard deviation (SD), followed by the range. The χ^2 test was used for categorical variables, and analysis of variance was used for continuous variables. OS and DFS curves were calculated according to the Kaplan–Meier method and were compared by means of the log-rank test. A P value <0.05 was considered significant in all cases, regardless of the test used.

Results

When the database for this study was closed (July 2010), 278 patients were included: 181 patients had been treated for ACC at participating HVC and 97 patients had been treated for ACC at participating LVC. Correspondingly, the mean number of patients (range) treated per center was 20.1 ± 8.6 (10–34) and 4.0 ± 2.6 (1–8), respectively. Moreover, the annual ACC case load was significantly higher for the HVC (0.8 ± 0.3 cases per year) than for the LVC (0.2 ± 0.2 cases per year; $P < 0.001$). Fifteen patients were excluded from this study since they did not undergo surgical resection of the primary tumor. These included five patients in both the HVC and LVC groups who presented with extensive metastatic disease and four patients in the HVC group and one patient in the LVC group who presented with locally advanced, unresectable primary tumors. As a result, 172 HVC patients and 91 LVC patients were included in the analyses performed.

Patient characteristics for this survey are listed in Table 1. The HVC and LVC groups were found to exhibit similar distributions of patient age, gender, preoperative diagnosis, and postoperative stage (P = NS; Table 1). However, the mean histological lesion size for ACC treated at HVC was significantly larger than those treated at LVC (104.1 ± 54.6 vs 82.8 ± 41.3 mm, respectively; $P < 0.001$). Moreover, the number of patients who underwent laparoscopic resection of their primary tumor was significantly higher at LVC (18 out of 91, 19.7%) than at HVC (15 out of 172, 8.7%; $P < 0.05$). However, the gross resection status was found to be similar for both groups (P = NS). Associated lymph node dissection was

also performed significantly more often at HVC (38 out of 172, 22%) than at LVC (7 out of 91, 7.7%; $P < 0.01$). Similarly, multiorgan resection (e.g., adrenal plus at least one or more additional adjacent organs) was performed in 24% (41 out of 172) of ACC cases treated at HVC and in 8% (7 out of 91) of ACC cases treated at LVC ($P < 0.01$).

Table 1

Patient characteristics and comparative analysis of patients treated at HVC vs LVC

	All the patients	HVC	LVC	*P* value[a]
No. of patients	278	181	97	
Gender (male/female)	113/165	72/109	41/56	N.S.
Median age in years ± SD (range)	49.5 ± 16.0 (10–81)	49.2 ± 15.6 (10–81)	50.2 ± 16.9 (10–81)	N.S.
Preoperative diagnosis				
Symptomatic nonfunctioning lesions	37	23	14	N.S.
Functioning lesions	103	69	34	
Incidentalomas	138	89	49	
Type of surgery performed				
Laparoscopic	33	15	18	<0.05
Laparotomic	230	157	73	
Histological median tumor size in mm ± SD (range)	104.1 ± 54.6 (30–340)	104.1 ± 54.6 (30–340)	82.8 ± 41.3 (30–200)	<0.001
Resections status				
R0	193	123	70	N.S.
R1	52	37	15	
Rx	18	12	6	
Associate lymph node dissection	45	38	7	<0.01
N0	26	23	3	N.S.
N+	19	15	4	
Multiorgan resection	48	41	7	<0.01

	All the patients	HVC	LVC	*P* value[a]
Tumor stage				
I	33	22	11	
II	123	80	43	N.S.
III	66	43	23	
IV	41	27	14	
No. of cases with follow-up data	229	148	81	N.S.
Mean follow-up time in months ± SD (range)	34.4 ± 36.1 (1–221)	36.5 ± 38.7 (1–221)	30.5 ± 30.4 (1–120)	N.S.
Adjuvant therapy				
Mitotane	26	23	3	<0.001
Polychemotherapy (PCT)	19	10	9	
Mitotane + PCT	25	24	1	
Recurrence				
Local	24	9	15	<0.05
Distant	53	39	14	
Both	8	6	2	
Mean time of recurrence in months ± SD (range)	22.4 ± 26.2 (3–115)	25.2 ± 28.1 (3–115)	10.1 ± 7.5 (3–39)	<0.01
OS				
Mean (months)	60	63	32	N.S.
5-year rate	48.8%	52.9%	44.4%	
DFS				
Mean (months)	16	24	15	N.S.
5-year rate	29.9%	31.8%	26.5%	

N.S. not significant

[a]Comparative analysis performed between HVC patients and LVC patients

Patient follow-up data were available for 148 out of 172 (86%) cases treated at HVC and for 81 out of 91 (89%) cases treated at LVC (P = NS), with associated mean follow-up times being 36.5 ± 38.7 months (range, 1–221 months) and 30.5 ± 30.4 months (range, 1–120 months), respectively (P = NS). The rate of patients who underwent adjuvant therapy was significantly higher in HVC (67 out of 148, 45.2%) than in LVC (13 out of 81, 16%; $P < 0.001$). Moreover, the rate of local recurrence was 6% (9 out of 148) for the HVC group and 18.5% (15 out of 81) for the LVC group. The rate of distant metastasis was 26.3% (39 out of 148) for the HVC group and 17.2% (14 out of 81) for the LVC group, and a combined pattern of recurrent disease (e.g., local recurrence + distant metastasis) was observed in 4.0% (6 out of 148) of HVC patients vs 2.5% (2 out of 81) of LVC patients ($P < 0.05$). The mean time to recurrence was significantly longer for the HVC group (25.2 ± 28.1 months; range, 3–115 months) than the LVC group (10.1 ± 7.5 months; range, 3–28 months; $P < 0.001$).

When this survey was closed to further data, 53% (121 out of 229) of the patients enrolled had died, including 81 out of 148 (55%) HVC patients and 40 out of 81 (49%) LVC patients (P = NS). Moreover, the median DFS period was 63 months for the HVC group and 32 months for the LVC group (P = NS), and the median OS period was 24 and 15 months, respectively (P = NS). The 5-year OS (Fig. 1) and DFS (Fig. 2) rates were found to be similar for the two groups (P = NS).

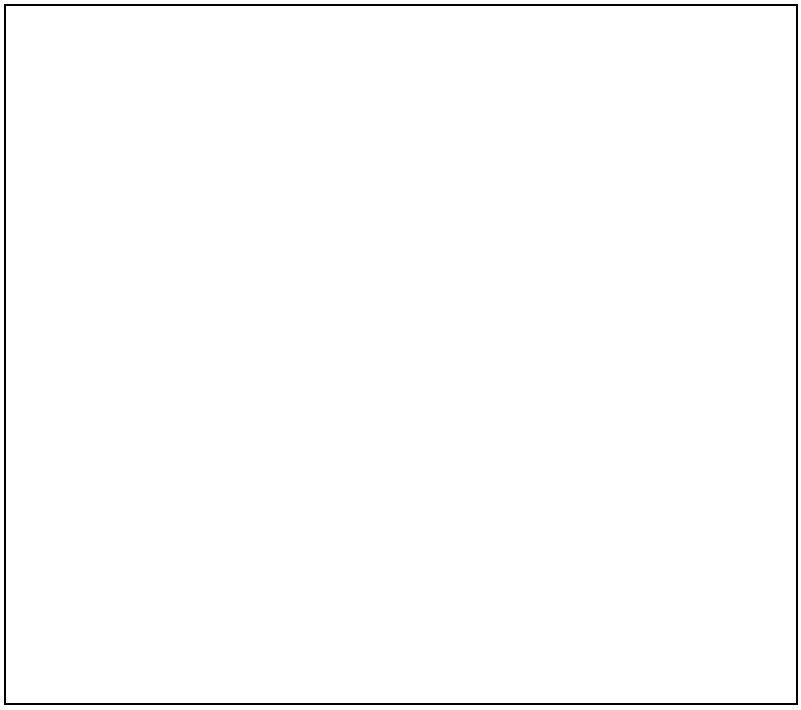

Fig. 1

Kaplan–Meier OS curves for HVC and LVC patients

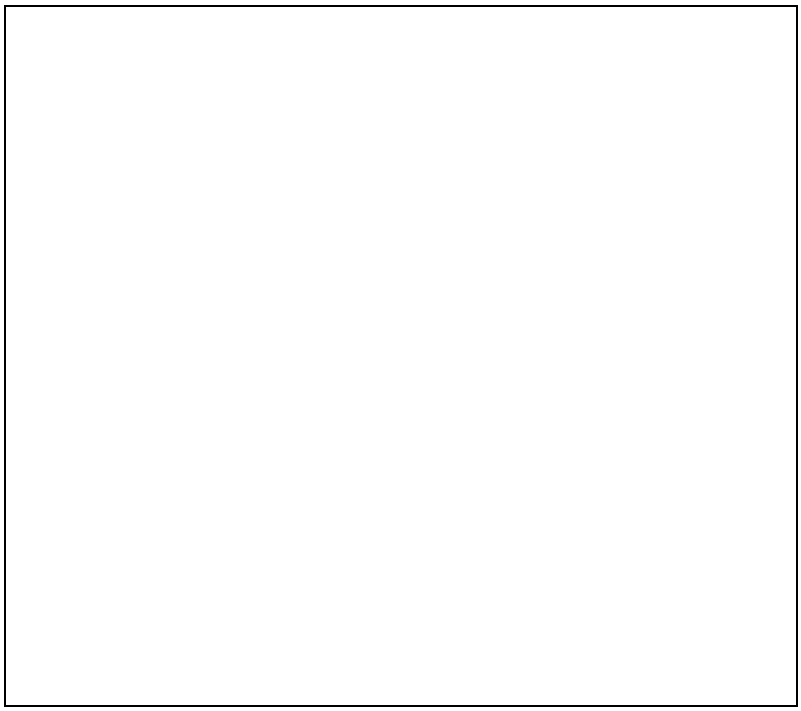

Fig. 2
Kaplan–Meier DFS curves for HVC and LVC patients

Discussion

ACC is a rare malignancy associated with a dismal prognosis. Moreover, a significant proportion of patients (30–85%) have distant metastasis at the time of their initial presentation [1–5]. Correspondingly, the 5-year OS rate for cases of ACC is poor and has been reported to range from 16% to 44% [6–11]. Despite several prognostic factors associated with long-term survival being reported in the published literature, the most consistently reported factors associated with a poor outcome are an advanced stage of disease and incomplete surgical resection [14]. Accordingly, adequate resection during the initial surgery for ACC patients is of utmost importance for oncologic outcome [12, 23]. Furthermore, in a recently published single-center cohort study, it appeared evident that patients operated on and treated at a larger cancer center had a better outcome, both in terms of DFS and OS, compared to patients that underwent surgery at another center and then were referred to the same large cancer center for adjuvant treatment and follow-up [12]. The main reason for such results should be searched in the higher proportions of incomplete resections and positive margins. In addition, patients who underwent surgery at the referral centers more frequently underwent procedures involving multiorgan resection and lymph node dissection [12].

In addition to the importance of the initial surgical treatment in the treatment of ACC, patients who are referred to specialized centers early in their diagnosis have a greater opportunity to receive more frequent adjuvant therapy, as well as regularly scheduled and closely monitored follow-up visits [13]. As a result, an early diagnosis and treatment (surgery) for recurrent disease can be achieved [13]. These observations were made in a large multicenter cohort analysis of ACC case data maintained by the German ACC registry involving stage II ACC patients who received early specialized care and experienced improved survival [13]. Therefore, theoretically, differences in patient outcome between the various series that have been published are related to the quality and completeness of the primary surgical resection performed [12] and differences in post-surgical care involving follow-up regimens and adjuvant (mitotane) treatments [13].

Of note, it has also been reported that about one half of the adrenalectomies performed in the US are performed at community hospitals, rather than academic or specialized cancer centers [23]. This is a significant consideration given the results of a recent cohort analysis of 3,144 adrenalectomies performed where the surgeon volume was found to be an independent predictor of postoperative complications [17]. These results were further confirmed in a Spanish national survey where surgeons and center volume were found to be major factors in the outcome of adrenal surgery [18].

Unfortunately, despite many large, nationwide multi-institutional series (i.e., French, Italian, German) [5, 6, 8, 11, 13, 15] conducted over the last two decades involving centers with different volumes of treated ACC patients, there has not been a study to address the impact of center volume on oncologic outcome. Therefore, the goal of this study was to evaluate the impact of center volume on the oncologic outcome of a large cohort of ACC patients. One of the first challenges experienced in this study was how to define the cutoff number used to identify high-volume vs low-volume treatment centers, especially with ACC being a rare disease. Eventually, we chose to define center volume based on the number of patients recruited for this multi-institutional survey, with HVC having 10 or more recruited patients [17]. However, it may have been more appropriate to consider the overall annual case load of adrenal disease as an indicator of center volume. Unfortunately, though, it was not possible to calculate the case load of adrenalectomies for each center since the survey only obtained information regarding ACC cases and not patients with benign adrenal disease that were treated. While this could be considered a limitation of the present study and representative of the multi-institutional nature of the study, the annual case load of ACC for each department was still calculated and the mean

annual case load for HVC was found to be significantly higher than that of the LVC (0.8 vs 0.2 cases per year). Accordingly, the HVC had significantly greater experience with the treatment of ACC than LVC.

For the HVC included in this study, a more aggressive surgical approach was applied to cases of ACC. Correspondingly, a significantly higher rate of lymph node dissection and multiorgan resection was observed (Table 1). This partially explains why, in the absence of significant differences in terms of tumor stage, patients treated at HVC had lower rates of local recurrence than patients treated at LVC (6% vs 18.5%, respectively). Moreover, patients treated at LVC experienced earlier recurrences than patients treated at HVC. In contrast, mean lesion size was significantly larger for patients treated at HVC, possibly suggesting that more complex and difficult cases are referred to HVC. Moreover, larger tumor sizes (e.g., >12 cm) have been associated with poorer outcomes following complete surgical resection [2].

In this survey, it was observed that significantly more patients underwent a laparoscopic adrenalectomy at LVC than at HVC. Based on this observation, it would appear that, at LVC, a diagnosis of ACC is frequently based on histology performed following an operation for adrenal incidentaloma and that preoperative workups are less accurate at LVCs, as previously suggested [23]. Nonetheless, despite laparoscopic adrenalectomies being considered hazardous in cases of ACC due to the higher risk of local recurrence and peritoneal carcinomatosis associated with this approach, mainly due to higher rates of positive resection margins [23], increasing evidence suggests that a laparoscopic adrenalectomy can be as adequate as conventional surgery in patients with localized ACC (e.g., stages I and II) [24, 25].

Moreover, the mean follow-up time, even if not significant, was longer for patients treated at HVC. This finding suggests that the follow-up at HVC is more consistent. One could expect that, with longer follow-up time, the risk of disease recurrence increases.

In a large retrospective analysis of patient data from an Italian–German multicenter study, the risk for recurrence and death due to ACC was observed to be significantly higher for patients who did not receive adjuvant mitotane [26]. Despite the fact that, in the present series, only a small percentage of patients underwent postoperative adjuvant treatment due to a referral bias, the patients treated in HVC benefit from a significantly more frequent use of adjuvant therapy than those treated in LVC. This difference could partially be responsible for the reduced local recurrence rate associated with HVC. Moreover, this finding confirms that a better outcome is not only associated with the appropriateness of

the surgical procedure performed for cases of ACC, but also involves a more adequate, multidisciplinary approach with dedicated surgeons, endocrinologists, radiologists, and oncologists.

Conclusions

The results of this study are consistent with previous reports that ACC remains a rare disease with a dismal prognosis. However, patients that underwent surgery at HVC experienced a better oncologic outcome, with a significantly longer time to recurrence and a lower rate of local recurrence observed. We propose that this observation is mainly due to the more comprehensive and multidisciplinary approach applied at HVC as a result of the increased availability of surgeons, endocrinologists, radiologists, and oncologists, as well as to the more aggressive surgical approaches and post-surgical adjuvant treatment strategies received by ACC patients at HVC.

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