Outcome of multidisciplinary management of adrenocortical carcinoma: a retrospective study

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Abstract

Background: Adrenocortical Carcinoma (ACC) is a rare and highly malignant tumor with a high recurrence rate. Reoperation to attain negative resection margin is recommended for selected patients. However, there is limited data on the outcome of unresectable recurrent tumor treated with palliative radiotherapy (RT) and transhepatic arterial embolization (TAE).

Method: A retrospective analysis of the Peking Union Medical College Hospital was conducted. Patients with pathologically confirmed ACC were included.

Result: Ninety-two patients fulfilled the criteria. The 5-year, 3-year, 1-year overall survival (OS) rates were 27.2%, 44.6% and 71.7% respectively, and median OS was 32.1 months. Age < 50 years, ENSAT stage I/II, surgery and negative surgical margin were associated with improved OS (all P <0.05). A Ki67 index < 20% was a predictor of better disease-free interval (P =0.011). Of 51 patients with recurrent ACC, local treatment (reoperation, palliative RT and TAE) improved OS after recurrence from 14.5 months to 41.6 months. Local therapy and mitotane were both prognostic factors for improved OS after recurrence.

Conclusion: multidisciplinary treatment is the major therapeutic approach for ACC. Resectable cases should receive complete resection to attain negative margin. Local treatment such as palliative RT and TAE may extend OS for unresectable recurrence.

Introduction

Adrenocortical carcinoma (ACC) is a rare and highly aggressive malignancy with a median overall survival of 35.2 months [1]. Women develop ACCs more often than men with female/male ratio 1.5 to 2.5 :1 [2, 3]. In spite of low annual incidence of 1-2 case per million population [4], most tumors are diagnosed at an advanced stage with invasion of adjacent organs or metastatic disease [5]. Based on the tumor staging classification suggested by the European Network for Study of Adrenal Tumors (ENSAT), the estimated 5-year overall survival of stage I, II, III and IV are 82%, 61%, 50% and 13%, respectively [6].

The mainstay of treatment for primary ACC is complete radical resection to attain negative surgical margins [7]. However, local recurrence and metastasis rates remain high, with up to 85% patients in previously reported cohort experiencing local recurrence [8]. Adjuvant therapy such as mitotane and radiotherapy were suggested for patients with a high risk of recurrence, despite inconsistent results in published studies [9, 10].

There is no consistent agreement in the management of recurrent ACC and few effective chemotherapy regimens can be offered for these recurrent ACC patients. Mitotane monotherapy is recommended for unresectable patients, but not all of these patients can achieve longer survival time [11]. As for isolated recurrent ACC, if complete resection is possible, aggressive surgical resection seems to be the best method to prolong survival. Some studies have proved that the median survival after recurrence could be more than 60 months in patients receiving reoperation[5]. For patients with resectable liver metastases,

surgical resection should be considered with a 5-year overall survival of 39% [12]. There is limited data about palliative radiotherapy (RT), transhepatic arterial embolization (TAE) and radiofrequency ablation (RFA) in the management of recurrent ACC patients. These available researches supported the benefit of palliative RT for unresectable locally or distant metastatic disease, such as in bone or lung [13].

In the present study, based on ACC patients treated in Peking Union Medical College Hospital (PUMCH) for 30 years, we analyzed the predictive clinicopathologic and therapeutic factors associated with the prognosis and survival of ACC patients. Furthermore, we evaluated the benefit of reoperation, palliative radiotherapy and TAE in local recurrence or distant metastases.

Methods

The clinical data of all patients with ACC treated at PUMCH over a 30-year period from February 1, 1990 to January 1, 2019 were retrospectively collected. Medical records at PUMCH were retrospectively reviewed for demographic data, clinical and histo-pathologic information, and treatment parameters. Dates of death, cancer recurrence and metastasis were confirmed by either querying the medical records or making telephone interviews. Data of 98 patients having pathological diagnosis could be included. One patient with early postoperative mortality (<30 days) and 5 patients with inadequate clinical records were excluded.

The last time of follow-up for this study was October 1, 2019. Overall survival (OS) was defined as the interval from the date of diagnosis to the date of death by ACC or the final follow-up, with patients alive at last follow up censored on that date. Disease-free interval (DFI) was defined as the interval from the date of the initial treatment to the date of first relapse or metastasis by ACC or the final follow-up, with patients censored on the date of last follow up if alive without disease progression on that date. For tumor stage, we used the European Network for the Study of Adrenal Tumors (ENSAT) [14] staging system to evaluate the ACC stage. Stage and stage II were combined and classified as the reference.

Continuous variables were described with medians and interquartile range (IQR), and Mann–Whitney U tests were used to compare the differences between the groups. Survival analysis was conducted using Kaplan-Meier methods and log-rank tests. Multivariate analysis was carried out using Cox proportional hazards regression methods. *P* values <0.05 were considered statistically significant. All analyses were performed using SPSS 23.0.

Results

Overall survival in whole group

Of 92 patients, 46 were female, with a female/male ratio of 1:1, which was contradicted with previous reported studies. The median age at first diagnosis of ACC diagnosis was 43.5 years old (IQR: 37.0-57.0), and all the patients were adults except for a 2-year child. 66.3% patients were <50 years and 33.7% were ≥50 years. According to the ENSAT staging system, 10.9% patients presented with stage I, 47.8% with

stage II, 26.1% with stage III and 15.2% with stage IV. In terms of the location of primary tumor occurrence, 56.5% occurred in the right adrenal gland and 43.5% in the left. In terms of clinical symptoms, 35.9% patients had endocrine symptoms (20 with Cushing's syndrome, 9 with sex hormone abnormality and 4 with primary hyperaldosteronism), 27.2% had tumor-related symptoms, and 36.9% didn't show any clinical symptoms. Demographic characteristics of the studied population are summarized in Table 1.

Of all patients, 81.5% underwent surgery, 39.1% received chemotherapy, and 26.1% received radiotherapy. In patients who received chemotherapy, 86.1% included mitotane as monotherapy or a part of their regimen. In patients who received radiotherapy, 50% received adjuvant radiation after resection, with a median dose of 56 Gy (range, 40-60) in a median of 28 fractions (range, 20-30 fractions). All adjuvant RT were external radiation including Tomotherapy, IMRT and VMAT, using a linear accelerator of 6MV to 18MV. In general, adjuvant RT was well tolerated, with reports of mild to moderate nausea (n=6), fatigue (n=4), abdominal pain (n=1). The total course of RT was not interrupted due to side effects.

The follow-up for the whole series ranged from 1.2 to 201.9 months, with a follow-up rate of 90.2%. Median OS were 32.1 months (IQR: 10.7-65.0) (Fig. 1). The 5-year, 3-year, 1-year OS rates were 27.2%, 44.6% and 71.7%, respectively. Fifty-one patients died in the cohort. DFI was available in 70 patients with initial resection and record of recurrence, and the median DFI was 16.2 months (IQR: 9.3-37.2) (Fig. 1). The 5-year, 3-year and 1-year DFI rate were 12.9%, 25.7% and 62.9%, respectively.

We evaluated the significance of various clinical and treatment factors that may influence the prognosis and survival. In the entire group, age < 50 years old, ENSAT stage I/II, Ki-67<20%, surgery and negative surgical margin were all associated with superior OS by univariate analysis. However, those who received any form of chemotherapy only demonstrated an insignificant survival benefit compared with those who did not receive chemotherapy. The local recurrence rate of adjuvant RT patients was significantly lower than that of non-RT patients (16.7% vs. 51.7%, p = 0.027), but the latter had a tendency to prolong OS (23.13 vs. 44.40, p= 0.61). Multivariate analysis of above variate showed that age < 50 years, ENSAT stage I/II and negative surgical margin were independent predictors of prolonged overall survival (P < 0.05).

All the characteristics mentioned above were re-evaluated on DFI (Table 2). Negative surgical margin and Ki67 index<20% were associated with improved DFI (P < 0.05). ACC in left side, ENSAT stage I/II and postoperative adjuvant radiotherapy tended to improve DFI. In multivariate analysis, negative surgical margins (P = 0.001) and Ki67 index<20% (P = 0.008) were still independent predictors of improved DFI.

Overall survival after recurrence

We further analyzed the 51 patents who recurred after the initial operative resection. Among them, 37 had negative margins, 9 had positive margins and 5 were unknown. According to the initial ENSAT stage, 10 patients presented with stage I, 27 with stage II, and 14 with stage III. The median interval from primary operation to first recurrence was 14.2 months (IQR: 8.8-28.5). Thirty-two patients had local recurrence and 29 patients had distant metastases, 10 patients had both local recurrence and distant metastases.

According to the primary treatment after recurrence, these patients were divided into local treatment group (n=29) and expectant treatment group (n=22).

Therapy modality of the local treatment group included reoperation (n=17), palliative RT (n=8) and TAE (n=4) (Fig. 3&4). All the 17 operated patients had locoregional resection: 7 had resection of only the tumor bed, and 10 had resection of adjacent organs (6 radical nephrectomies, 2 partial nephrectomies, 2 partial hepatectomy, 1 cholecystectomy and 1 segmental colectomy). No death occurred within 30 days after operation. Of the 8 patients received palliative RT, the median dose was 45 Gy (range 24-60Gy) in a median of 12 fractions (range 6-30 times). The sites of the treated regions were the adrenal tumor bed (n=3), bone metastasis (n=2), lung metastasis (n=1), abdominal mass (n=1) and psoas major metastasis (n=1). All patients obtained either symptom relief or tumor shrinkage through imaging assessment after RT. In terms of TAE, the 4 patients underwent 2, 3, 11 and 13 courses respectively. The median diameter of hepatic metastases was 6.3cm (range, 3.9-17.8). Through imaging assessment, their tumor sizes did not enlarge significantly for at least half a year after receiving treatment. Besides, all these patients could tolerate with TAE.

Demographic characteristics of the two groups are summarized in Table 3. There were no statistically significant differences in age, gender, clinical manifestation, tumor distribution, primary surgical approach, surgical margin and mitotane use between the two groups. In the local treatment group, the proportion of patients with initial ENSAT stage I/II (stage I: 21.4% vs. 17.4%, stage II: 64.3% vs. 39.1%, p = 0.033), local recurrence (75% vs. 47.8%, p=0.048) and DFI>12 (75% vs.47.8%, p=0.048) is significantly higher than that of the expectant treatment group. Median OS after recurrence of the local treatment group was 41.6 months (IQR: 27.4-66.1), while it was 14.5 months (IQR: 5.7-24.9) of the expectant group (P=0.001) (Fig. 2). There was no difference in OS after recurrence among these patients who received reoperation, palliative RT and TAE (41.9 months [27.4-69.1], 41.5 months [21.9-63.7], 40.1 months [26.5-97.8], respectively).

In univariate analysis, independent prognostic factors for higher OS were female, original ENSAT stage I/II, local treatment for recurrence, chemotherapy (All P<0.05). Age <50 years old (P=0.073), liver metastases (P=0.093), DFI >12 months between the initial resection and the diagnosis of recurrence (P=0.079) tended to improve OS after recurrence (Table 4). The original tumor size, ENSAT stage, Ki67 index, and the primary surgical technique were not predictive factors for OS after recurrence. In multivariate analysis, local therapy for recurrence, mitotane use and female were independently factors for improved OS after recurrence (P <0.05).

Discussion

ACC constitutes very rare and aggressive malignancies that leads to highly recurrence and metastasis. It is really challengeable to assess the management about this disease. Consequently, relevant studies are generally of reports from Europe and North America. In this retrospective study, with the largest sample size in Asia population, we analyzed the clinicopathologic and therapeutic factors associated with the

prognosis and survival of ACC. And we further compared two groups with recurrent disease: the first group received local therapy for recurrence, and the second group had expectant therapy. We demonstrated a significant survival advantage of local treatment (reoperation, palliative RT, TAE) in recurrent ACC.

Previous studies have proved that tumor stage, surgical resection margin, mitotic index, Ki67 index, age and overproduction of cortisol were associated with prognosis [7, 15-17]. The results of this study indicated that age <50 years old, ENSAT stage I/II, negative resection margin were significant factors with better prognosis of ACC. The tumor size and clinical symptoms had no obvious impact on the prognosis, which could be explained partly by our small sample size. Although some previous studies [18, 19] and our study found that laparotomy and laparoscopy had similar impact on OS, most researchers believed that laparoscopy for ACC resection would lead to more frequent and earlier recurrence [9, 19, 20]. Therefore, most guidelines recommend laparotomy as a standard surgical treatment for ACC method [19].

In addition to surgical resection margin, Ki67 index is also an important factor to evaluate the risk of recurrence. It has been used to select patients for adjuvant chemotherapy [16]. The cutoff value of Ki67 index for high and low recurrence risk of ACC has not yet been determined [21]. However, a high-grade ACC defined partly by a high mitotic rate (and/or Ki67 score> 20%) has a higher risk of recurrence [22] when compared with a low-grade ACC. A recent study showed that patients with a Ki67 index <10% had an OS after initial surgery of 181 months, while patients with a Ki67 index ≥20% had on OS of only 42 months[16]. In our study, patients with Ki67 index ≥20% also had a shorter OS (32.2 vs. 44.3 months, P =0.023) and recurred more quickly after initial surgery (DFI: 10.8 vs. 16.4 months; P = 0.016) than patients with Ki67 index <20%. Therefore, ACC patients with Ki67 index ≥20% may need to take more active measures to prevent recurrence. And it was interesting to note that patient with right ACC had a shorter DFI and a higher distant metastasis rate at initial recurrence (62.5% vs. 26.7%, p=0.003). There are several reasons for this observation. First, right adrenocortical tumors are in a narrower space among liver, inferior vena cava and kidney with a higher potential of invasion compared with left tumors. Second, resection of left organs (kidney, spleen, pancreas) is easier than resection of right organs (liver, inferior vena cava). Third, there is only one venous return of the right adrenal gland, which is more likely to rupture under the compression of the tumor, increasing the risk of tumor cells entering the blood vessels.

Locally recurrent or distant metastatic ACC is currently uncurable. If complete surgical resection is possible, surgical treatment should be performed to obtain a negative resection margin [23]. Reoperation can significantly improve the prognosis when the recurrence can be completely removed, especially in patients with a disease-free survival (DFI) >12 months. Simon et al included 59 patients who recurred after initial operative resection, and the OS of 29 reoperated patients was significantly better than that of the 30 non-operated patients (91m vs. 15m, p <0.001) [5]. Baur et al reported 43 patients who underwent liver metastases resection with a 5-year survival rate of 51.3% and a median OS of 76.1 months [12]. The prognosis of 17 reoperated patients in our study was also better than that of patients in expectant treatment group. Furthermore, 6 patients underwent ³2 reoperations achieving with an OS of 80.5 months.

This indicated that repeated operative resection for recurrent ACC could achieve long-term survival in selected patients.

Mitotane has been used in the treatment of unresectable and recurrent ACC, but the results were not exactly the same [10, 24]. Mitotane acts on adrenocortical cell mitochondria to inhibit CYP11B1 and CYP11A1 causing necrosis of adrenocortical cells [25]. The toxicity profile of mitotane limits tolerability and requires frequent drug monitoring. It should be noted that the results of surgery cannot be achieved with mitotane monotherapy and combined chemotherapy [26]. Most patients with unresectable metastases die within 1 year making it urgent to find a way to extend their lives. Therefore, more and more attention has been put on local palliative treatment such as RT and RFA with deeper understanding.

ACC was once thought to be radiation-resistant in previous small studies [27, 28]. However, with the application of modern radiation techniques, more and more retrospective studies showed that postoperative adjuvant RT can reduce the local recurrence rate. Sabolch et al [29] performed a case-control analysis on 20 patients who received adjuvant RT with a median irradiation dose was 55Gy. The local recurrence rate of adjuvant RT group was significantly reduced to 5% vs. 60% of non-RT group, although there was no difference in OS. The largest study [30] on this subject included 39 patients with a median irradiation does of 55Gy, and found that adjuvant RT significantly improved the local recurrence (33.3% vs. 71.8%) and OS (77.7% vs. 48.6% at 3 years). In the present study, only 16.7% patients in adjuvant RT group experienced local recurrences, which was significantly lower than 51.7% in non-RT group. Large-scale prospective randomized studies are needed to better understand the role of adjuvant radiotherapy in the management of ACC, especially to figure out whether the reduction in the local recurrence rate would accompany with better OS.

There is limited evidence to support the use of palliative RT for unresectable ACC. Polat et al [13] reported 51 of 91 patients gained benefit (ie, pain relief, reduction in paresthesia or paralysis) from palliative RT for advanced ACC. Ho et al [31] reported 10 of 12 patients had either a clinical or radiographic response after palliative RT, although the long-term effect is unknown. Our study also showed that 8 patients gained benefit after palliative RT with an improved median OS of 73.8 months. This could be partly explained by the active local treatment of these 8 patients, of which 2 patients received ³3 times of palliative RT and 1 patient received RFA after second recurrence. By the way, the patients in our study received more precise and advanced RT technology, including IMRT, VAMT and Tomotherapy.

In the case of metastatic ACC, liver is one of the most commonly involved organs beside the lung [12]. Liver resection in the case of liver metastases can achieve long-term survival, while the OS of patients with unresected hepatic metastases was only 10.1 months. RFA may provide short-term local control for small liver metastases with a 5-year OS rate of 29% [32, 33]. TAE is frequently used in the treatment of unresectable liver cancer and metastases. However, the number of patients receiving TAE for hepatic metastases of ACC is small due to its rarity. In our study, 4 patients received TAE for unresectable liver metastases after initial recurrence, two of whom had more than 10 courses of embolization. The median OS of these 4 patients was 76.5m, indicating repeated TAE can achieve long-term control of unresectable

liver metastases of ACC, although there may be selection bias, which is a common problem in the study of this disease.

The main limitations of this study are its retrospective, non-random design and inconsistency in treatment management due to the long-time span. The number of patients was small and not all patients were thoroughly followed because some of them were treated and managed in several different hospitals. Most of the current researches are retrospective studies, and the heterogeneity of treatment preference in different institutions is relatively large. Prospective studies will help understand the potential role of local treatment such as palliative RT and TAE in the treatment of recurrent ACC.

In summary, multidisciplinary treatment is the major therapeutic approach for ACC. Physicians need to choose the most appropriate local and systemic treatment for each individual patient according to the physical condition and tumor characteristics. Resectable cases should receive complete resection to attain negative margin for both primary and recurrent ACC. In terms of unresectable recurrence, whether locally recurrent or distant metastatic, local treatment such as palliative RT and TAE may not only relieve symptoms, but also extend OS through repeated treatment.

Abbreviations

ACC: Adrenocortical carcinoma; RT: Radiotherapy; TAE: Transhepatic arterial embolization; ENSAT: European Network for Study of Adrenal Tumours; ;OS: Overall survival; DFI: Disease-free interval; RFA: Radiofrequency ablation.

Declarations

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Availability of data and materials

Owing to data privacy policy at our facility, publication of patient-related raw data is not possible.

Author Contributions: JW.Z and ZY.Z collected, analyzed, and interpreted the data; wrote the manuscript. Jing.S, X.L, Z.M and FQ.Z reviewed and edited the manuscript. Jie.S designed the study, interpreted the data, critically reviewed the manuscript, and supervised the study. Jie.S has full access to all the data in the study and final responsibility for the decision to submit for publication. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This retrospective study was approved by the Institutional Review Board of The PUMCH.

Consent for publication

No applicable, as no individual patient data has been published.

Competing interests

The authors have no conflict of interest to disclose.

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Tables

Table 1. Demographic and treatment features with associated OS

Variables	N (%)	Univariate		Multivariate	
		Median OS (mo)	*P* value	Hazard ratio	*P* value
Age at diagnosis					
≥50 years	31 (33.7)	23.00	<0.001	1	
< 50 years	61 (66.3)	40.38		0.149	<0.001
Sex					
Male	46 (50.0)	31.62	0.137		
Female	46 (50.0)	33.13			
Tumor site					
Right	52 (56.5)	32.64	0.439		
Left	40 (43.5)	34.07			
Clinical symptoms					
Tumor symptoms	25 (27.2)	18.83	0.823		
Endocrine symptoms	33 (35.9)	28.71			
No symptoms	34 (36.9)	39.62			
Tumor stage					
I	10 (10.9)	49.61	<0.001	1	0.014
II	44 (47.8)	51.60		0.306	0.014
III	24 (26.1)	19.19		0.705	0.533
IV	14 (15.2)	4.75		1.091	0.892
Ki-67%					
<20	24 (26.1)	20.47	0.046	1	0.349
≥20	24 (26.1)	25.74		0.880	0.814
Unknown	44 (47.8)	39.47		0.593	0.207
Number of operations					
0	17 (18.5)	5.75	<0.001	1	0.881
1	57 (61.9)	32.92		0.026	0.959
≥2	18 (19.6)	61.49		0.032	0.961
Operative approach					
Laparotomy	53 (57.6)	40.38	0.821		
Laparoscopy	22 (23.9)	44.04			
Margin status					
Negative	53 (57.6)	55.46	<0.001	1	0.001
Positive	13 (14.1)	13.57		11.653	<0.001
Unknown	8 (8.7)	29.32		2.475	0.177
Biopsy only	18 (19.6)	5.03		0.103	0.974
Radiotherapy					
Adjuvant	12 (13.0)	23.13	0.218		
Palliative	13 (14.1)	81.51			
No	67 (72.8)	32.36			
Mitotane					
Yes	34 (37.0)	35.71	0.433		
No	58 (63.0)	32.64			
Chemotherapy					
Yes	40 (43.5)	35.71	0.477		
No	52 (56.5)	27.79			

Table 2. Demographic and treatment features with associated DFI

Variables	N (%)	Univariate		Multivariate	
		Median DFI (mo)	*P* value	Hazard ratio	*P* value
Age at diagnosis					
≥50 years	19 (27.1)	11.01	0.752		
< 50 years	51 (72.9)	17.51			
Sex					
Female	37 (52.9)	14.23	0.503		
Male	33 (47.1)	23.33			
Tumor side					
Left	30 (42.9)	21.39	0.058		
Right	40 (57.1)	12.98			
Clinical symptoms					
Tumor symptoms	19 (27.1)	11.01	0.997		
Endocrine symptoms	23 (32.9)	13.96			
No symptoms	28 (40.0)	18.18			
Tumor stage					
I	10 (14.3)	22.00	0.099		
II	37 (52.9)	20.17			
III	19 (27.1)	9.49			
IV	4 (5.7)	5.01			
Ki-67%					
<20	18 (25.7)	16.41	0.001	1	0.011
≥20	21 (30.0)	10.84		2.314	0.042
Unknown	31 (44.3)	29.67		0.788	0.511
Operative approach					
Laparotomy	48 (68.6)	15.44	0.339		
Laparoscopy	22 (31.4)	16.23			
Margin status					
Negative	53 (75.7)	20.67	<0.001	1	<0.001
Positive	11 (15.7)	5.95		7.757	<0.001
Unknown	6 (8.6)	14.42		1.778	0.280
Adjuvant radiotherapy					
Yes	12 (17.1)	9.45	0.071		
No	58 (72.9)	18.46			

Table 3. Demographic and treatment features in relapsed patients

	Local treatment (n=29)	Expectant treatment (n=22)	P value
Age at first diagnosis (median, IQR)	41.0 [35.0-45.0]	42.0 [31.5-61.3]	0.293
Sex			0.477
Male	13 (44.8%)	13 (59.1%)	
Female	16 (55.2%)	9 (40.9%)	
Clinical presentation			0.362
Endocrine symptom	10 (34.5%)	6 (27.3%)	
Tumor symptom	7 (24.1%)	6 (27.3%)	
No	12 (41.4%)	10 (45.4%)	
Tumor side			0.139
Right	15 (51.7%)	17 (77.3%)	
Left	14 (48.3%)	5 (22.7%)	
Initial operative approach			0.115
Laparotomy	17 (58.6%)	17 (77.3%)	
Laparoscopy	12 (41.4%)	5 (22.7%)	
Tumor size (median, IQR, cm)	7.5 (6.3-9.5)	8.7 (5.6-15.1)	0.053
Margin status			0.147
Negative	24 (82.8%)	13 (59.1%)	
Positive	2 (6.9%)	7 (31.8%)	
Unknown	3 (10.3%)	2 (9.1%)	
ENSAT stage of original neoplasm			0.033
I	6 (20.7%)	4 (18.2%)	
II	18 (62.1%)	9 (40.9%)	
III	5 (17.2%)	9 (40.9%)	
Site of recurrence			
Adrenalectomy	21 (72.4%)	11 (50.0%)	0.048
Metastasis	12 (44.8%)	16 (72.7%)	0.027
Liver	7 (24.1%)	1 (4.5%)	0.046
Lung	3 (10.3%)	10 (45.5%)	0.008
Bone	3 (10.3%)	0	0.109
Other sites	1 (3.4%)	3 (13.6%)	0.215
DFI > 12mo	21 (72.4%)	11 (50,0%)	0.048
Chemotherapy	15 (51.7%)	11 (50.0%)	0.835
Mitotane	13 (44.8%)	10 (45.5%)	0.790

Table 4. Demographic and treatment features with associated OS after recurrence

Variables	N (%)	Univariate		Multivariate	
		Median OS (mo)	*P* value	Hazard ratio	*P* value
Age at diagnosis					
≥50 years	12 (23.5)	17.41	0.073		
< 50 years	39 (76.5)	32.43			
Sex					
Male	26 (51.0)	19.61	0.017	1	
Female	25 (49.0)	32.82		0.424	0.032
Original tumor size					
<10 cm	34 (66.7)	26.00	0.743		
≥10 cm	17 (33.3)	31.47			
Original ENSAT stage					
I/II	37 (72.5)	36.47	0.006	1	
III	14 (27.5)	13.52		2.209	0.086
Site of recurrence					
Adrenalectomy	32 (62.7)	31.95	0.359		
Liver	8 (15.7)	37.42	0.093		
Lung	13 (25.5)	25.40	0.696		
Bone	3 (5.9)	21.91	0.208		
Local recurrence only					
No	29 (56.9)	21.91	0.561		
Yes	22 (43.1)	37.17			
Site of recurrence >1					
No	36 (70.4)	29.93	0.807		
Yes	15 (29.4)	20.63			
DFI					
>12mo	32 (62.7)	34.64	0.079		
≤12mo	19 (37.3)	14.39			
Ki-67%					
<20	12 (23.5)	39.46	0.228		
≥20	17 (33.3)	19.09			
Unknown	22 (43.1)	31.95			
Reoperation					
No	34 (66.7)	19.86	0.377		
Yes	17 (33.3)	42.45			
Local treatment					
No	22 (43.1)	14.78	<0.001	1	
Yes	29 (56.9)	41.86		0.319	0.005
Mitotane					
No	28 (54.9)	24.67	0.020	1	
Yes	23 (45.1)	27.07		0.448	0.046

Figures

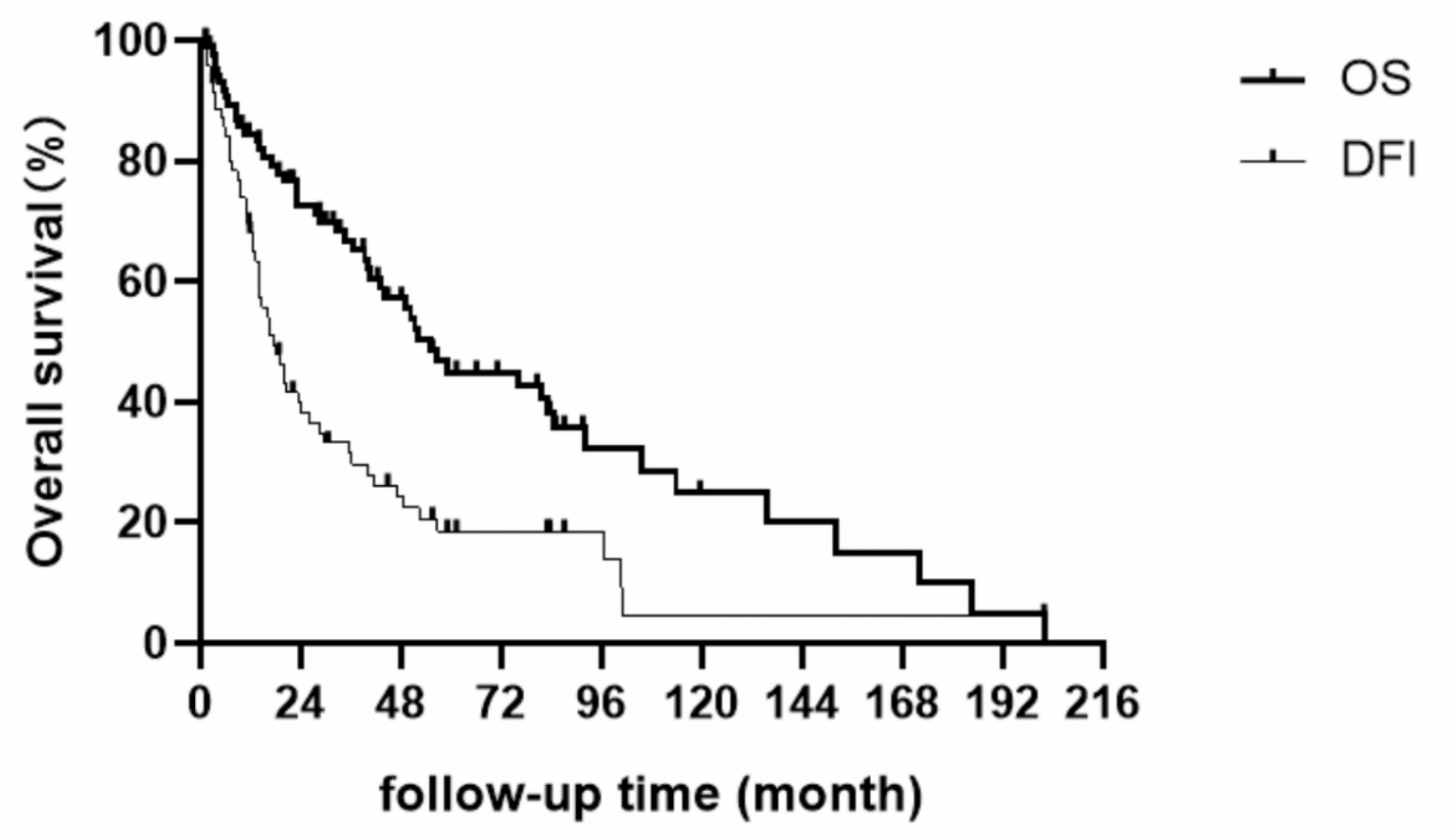

Figure 1

Overall survival and disease-free interval of the entire series

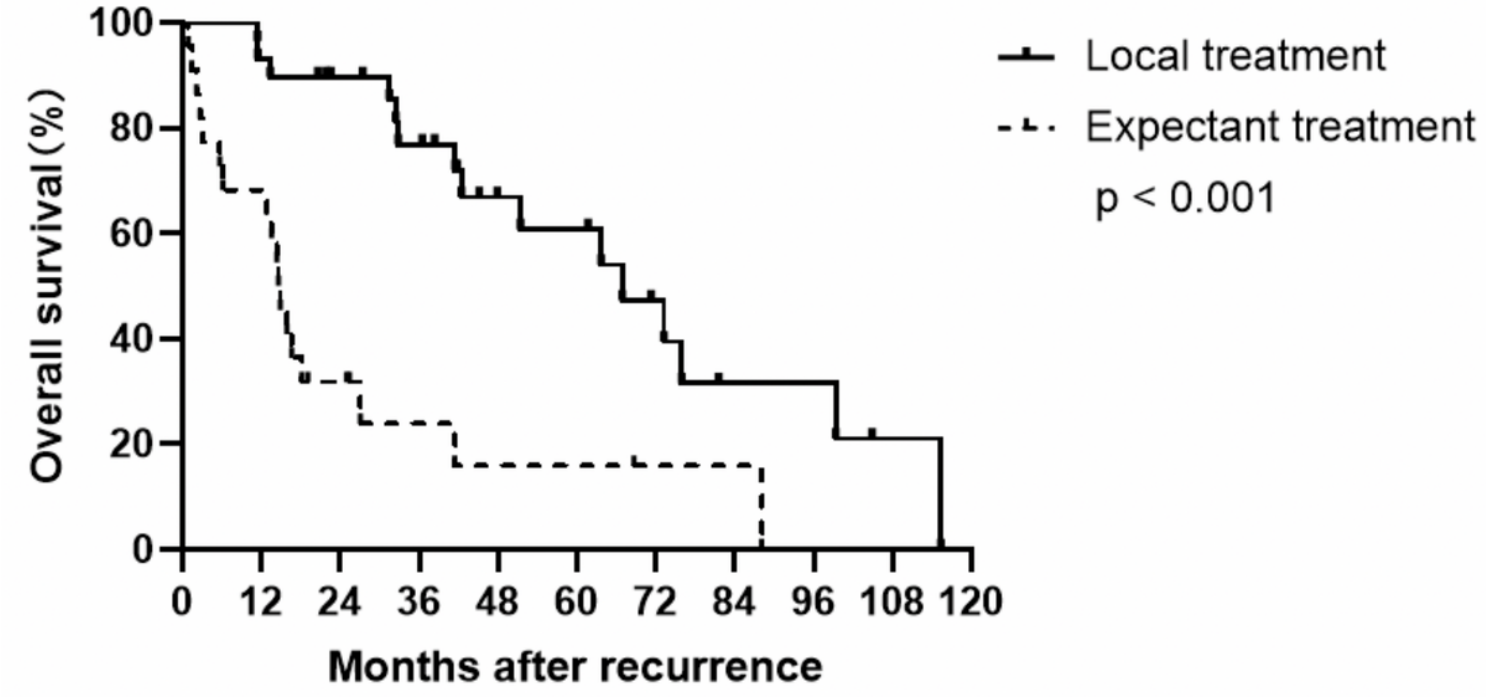

Figure 2

Overall survival of recurrent ACC patients according to the treatment

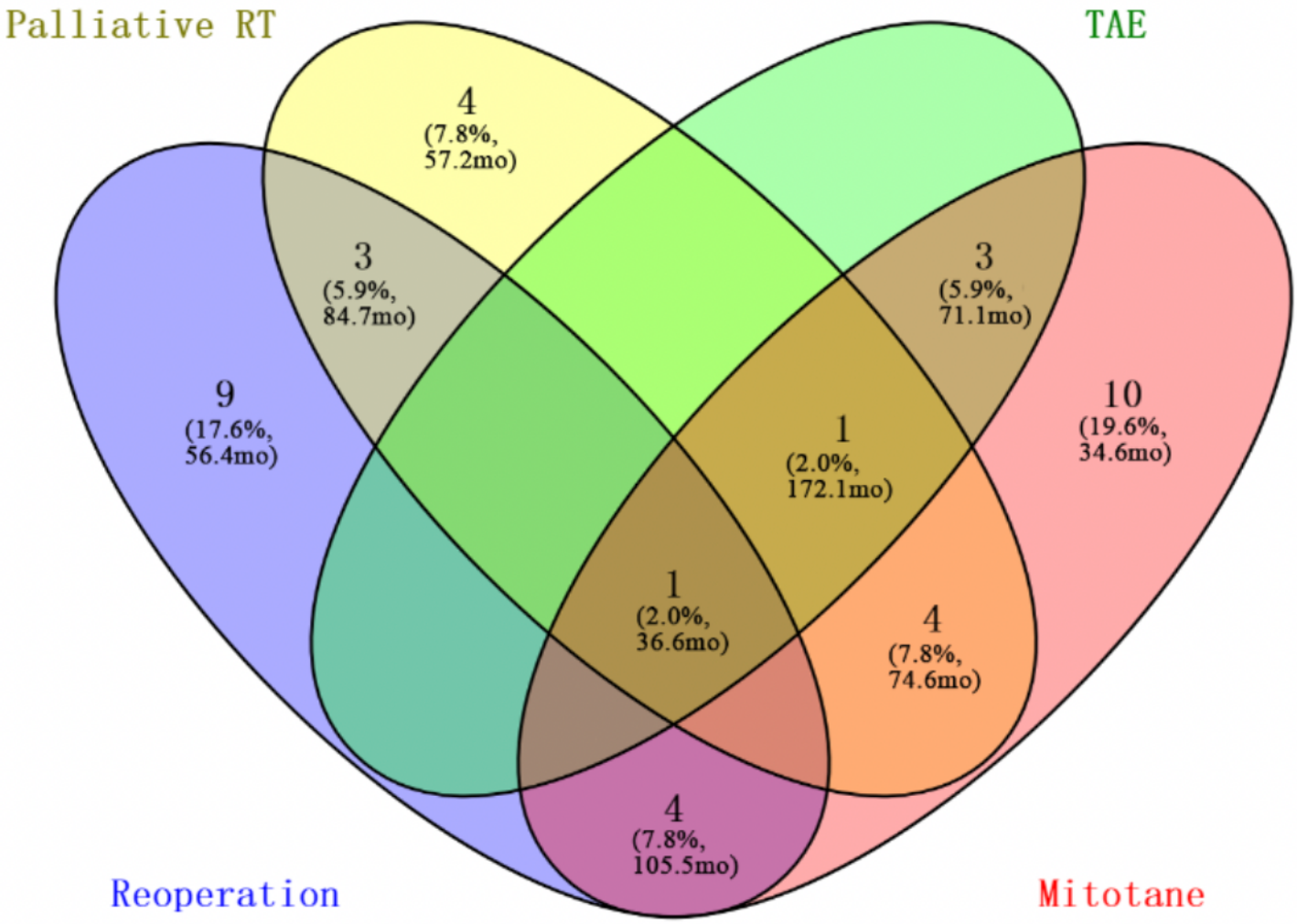

Figure 3

Treatment selection and OS of recurrent ACC patients

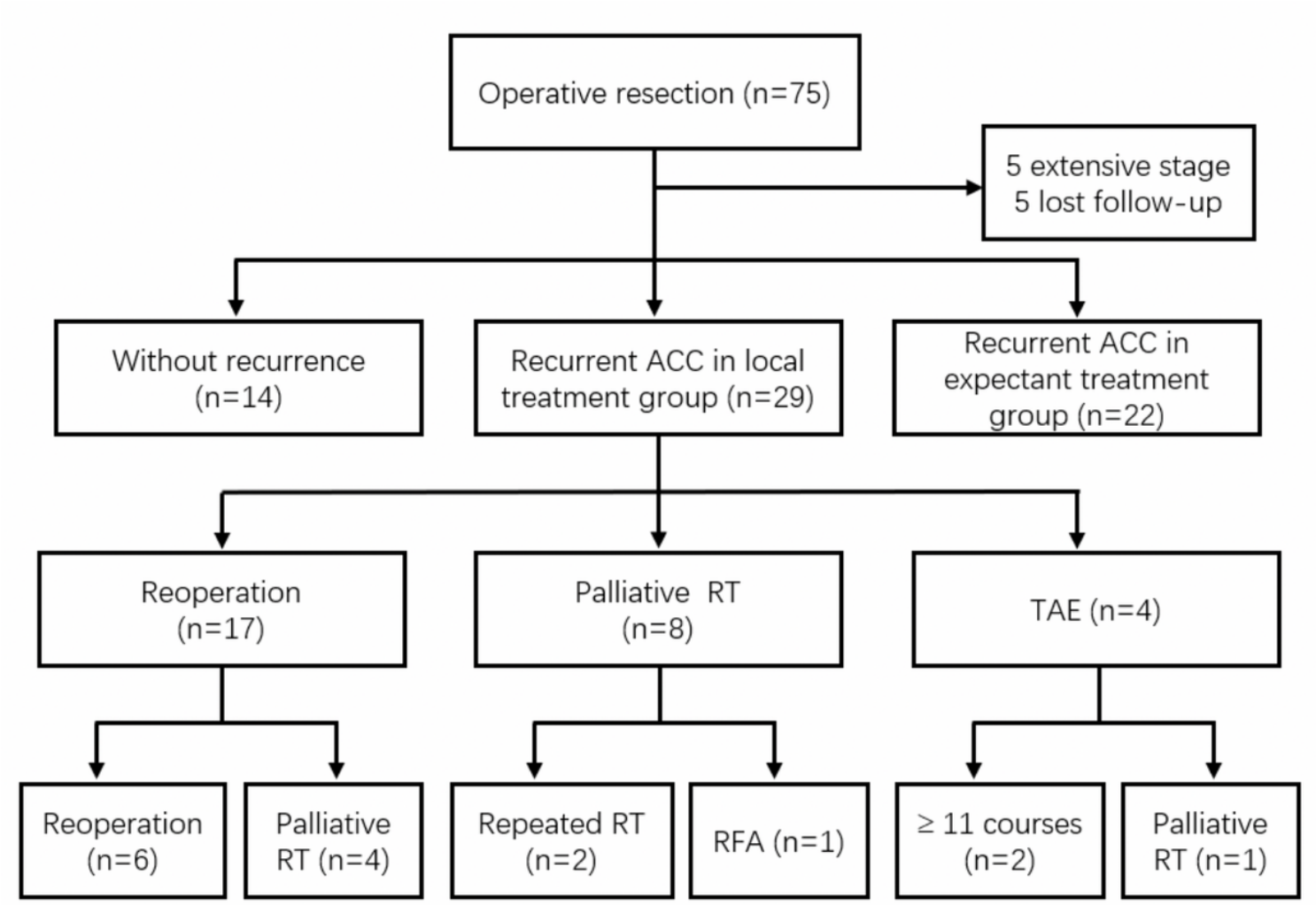

Figure 4

Treatment flowchart of operative patients