Surgery Versus Nonsurgical Therapy for Recurrent Adrenocortical Carcinoma

31

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Abstract

Adrenocortical carcinoma is a rare endocrine neoplasm associated with poor prognosis. Complete surgical resection is the only potential cure for the disease. Unfortunately, a significant number of patients develop disease relapse and present with local or systemic recurrence. Close follow-up with regular clinical examination aided by radiological imaging and blood investigations is crucial for the early detection of recurrent disease. The best treatment options for recurrent disease remain unclear and these include surgery, chemotherapy, and radiotherapy, in addition to new and upcoming treatments. This chapter will focus on the treatment of recurrent ACC including a discussion of surgical and non-surgical therapy options.

Keywords

Adrenocortical carcinoma · Recurrence · Surgery · Mitotane · Chemotherapy · Radiotherapy · Radiofrequency ablation · Treatment

Introduction

Adrenocortical carcinoma (ACC) is a rare and aggressive endocrine malignancy. Approximately 0.7–2.0 per million individuals are diagnosed with ACC each year [1, 2]. The prognosis of patients with ACC is poor, with an overall 5-year

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survival of less than 35% [3–5]. Patients with stage IV ACC have a 5-year survival rate of less than 15% [6, 7]. A bimodal age distribution is described, with a peak frequency at ages younger than 5 years and a second peak most commonly in the fourth and fifth decades [1, 3]. Females are slightly more frequently affected than males [1].

This chapter will focus on the treatment of recurrent ACC including a discussion of surgical and non-surgical therapy options (Table 31.1).

Adrenocortical carcinomas present as a functional tumor related to excess adrenal hormone production, as a result of mass effect most often in cases of a non-functional tumor, or found incidentally on radiological imaging. Up to 60% of patients present with the hormonal symptoms of the functional tumor (most commonly Cushing's syndrome) [8]. Unfortunately, when these tumors are non-functional, they may not be detected until they develop into a large mass that may invade into adjacent structures with possible metastases.

The etiology of ACC is unclear, but smoking and the use of oral contraceptives have been described as risk factors [9]. The majority of ACCs are sporadic. Familial association has been shown in patients with Li-Fraumeni syndrome [10]. Progress is being made in recent years in the understanding of the molecular mechanisms of ACC tumor development and genetic profiling [11].

Historically, the McFarlane classification as modified by Sullivan was used for staging in ACC (Table 31.2) [12, 13]. Subsequent modifications restricted stage IV disease to include patients with metastatic disease. Current classifications include the World Health Organization and the Union for International Cancer Control classification which is based on the McFarlane/Sullivan system and the European Network for the Study of Adrenal Tumor (ENSAT) classification (Tables 31.3 and 31.4) [14, 15].

The management of patients with ACC requires a multi-disciplinary approach. Surgical resection of disease is the main treatment modality in patients with limited disease. Adjuvant therapy includes chemotherapy and/or radiation. Although complete surgical resection offers the best chance of cure in patients who present with localized disease, recurrence following surgery is common. Unfortunately, up to 75–85% of patients with ACC develop local and/or distant metastases, despite initial pathological evidence of a complete R0 resection [16, 17]. Disease recurrence is most common within the first 2 years following surgery, with 40% of patients recurring within this time period [18]. Unfortunately, tumor recurrence is likely to be followed by further relapses, with a shortened disease-free interval (DFI) between these episodes. Literature on the treatment of recurrent ACC is scarce, and level I evidence is lacking. Treatment can be broadly divided into surgical or non-surgical options. Non-surgical treatment encompasses chemotherapy, radiation therapy, radiofrequency ablation and cryosurgery. This chapter will focus on the treatment options for the treatment of recurrent ACC. The available evidence for these treatment modalities will be discussed (Table 31.5).

Table 31.1 PICO table

*P*opulation	Patients with recurrent adrenocortical carcinoma
*I*ntervention	Surgical resection
*C*omparator	Chemotherapy, radiotherapy, tumor ablation, targeted therapies
*O*utcomes	Surgical resection is recommended for patients with recurrent adrenocortical carcinoma who are suitable for further intervention and who develop a recurrence after 6–12 months of initial treatment. Treatment with chemotherapy and/or radiotherapy may be of benefit following surgery

Table 31.2 The MacFarlane classification modified by Sullivan for staging adrenocortical carcinoma

Stage	Size	Lymph nodes	Local invasion	Metastases	TNM
I	<5 cm	–	–	–	T1, N0, M0
II	>5 cm	–	–	–	T2, N0, M0
III	Any size	+	+	–	T1–2, N1, M0
IV	Any size	+	+	+	T1–2, N1, M1

Table 31.3 Union for International Cancer Control (UICC)/World Health Organization (WHO) 2004 staging system for adrenocortical carcinoma, derived from the MacFarlane classification as modified by Sullivan

Stage	UICC/WHO
I	T1, N0, M0
II	T2, N0, M0
III	T1–2, N1, M0 or T3, N0, M1
IV	T4, N0, M0 or T3, N1,M0 or T1–4, N0–1, M1

T1 tumor ≤5 cm, *T2* tumor >5 cm, *T3* tumor infiltration locally reaching neighboring organs, *T4* tumor invasion of neighboring organs, *N0* no positive lymph nodes, *N1* positive lymph nodes, *M0* no distant metastases, *M1* distant metastasis

Table 31.4 European Network for the Study of Adrenal Tumors (ENSAT) 2008 staging system for adrenocortical carcinoma

Stage	ENSAT
I	T1, N0, M0
II	T2, N0, M0
III	T1–2, N1, M0 or T3–4, N0–1, M0
IV	T1–4, N0–1, M1

T1 tumor ≤5 cm, *T2* tumor >5 cm, *T3* tumor infiltration into surrounding tissue, *T4* tumor invasion into adjacent organs or venous tumor thrombus in vena cava or adrenal vein, *N0* no positive lymph nodes, *N1* positive lymph nodes, *M0* no distant metastases, *M1* distant metastasis

Table 31.5 Studies reporting treatment of recurrent adrenocortical carcinoma

First author	Year	Type	Number of patients included with recurrent disease	Treatment modality	Outcome
Linos [19]	1986	Retrospective case series	1	Surgical resection	– Alive at 16 months follow-up
Decker [20]	1991	Retrospective case series	Includes patients treated for primary disease, recurrence both local and distant	Surgical resection and/or mitotane	– Resection for local recurrence may prolong survival
Jensen [21]	1991	Retrospective case series	15 patients treated with surgical resection plus chemotherapy and 18 patients treated with chemotherapy alone	Surgical resection plus chemotherapy	– Improved survival in the surgical group compared with chemotherapy alone – 5 patients (33%) were alive at 5-year follow-up
Icard [6]	1992	Retrospective case series	Includes patients treated for primary disease, recurrence both local and distant	Surgery and/or medical therapy	– 5-year survival 27% with reoperation – Mitotane improved the survival rate only in patients with metastases who received it after operation (vs non-mitotane-treated patients)
Pommier [16]	1992	Retrospective case series	45 treated for recurrent disease (19 treated medically and 26 surgically)	Surgical resection or chemotherapy	– 5-year survival 47% with complete resection – Mean survival of 56 months for patients who underwent reoperation compared with 19 months for patients treated medically – Mitotane had a 24% partial response rate. Other chemotherapeutic agents were ineffective – Surgery superior to medical treatment
Van Aalderen [22]	1992	Case report	1	Mitotane	Long term survival noted
Ahlman [23]	1993	Retrospective case series	2	Surgical resection	

Haak [24]	1994	Retrospective case series	Includes patients treated for primary disease and recurrence 38 with recurrence	26 patients treated with mitotane at recurrence	Tumor response was only observed in patients with high maintenance mitotane levels. Five of these patients had a complete remission lasting 2–120 months at the time of reporting
Sakamoto [25]	1995	Case report	1	Surgical resection	Alive at 18 years follow-up
Crucitti [18]	1996	Retrospective case series	Includes patients treated for primary disease, recurrence both local and distant	Surgery and/or medical therapy	– Re-operated patients experienced better survival (mean, 41.5 months) than non-re-operated cases (mean, 15.6 months)
Bellantone [26]	1997	Retrospective case series	52 patients with recurrence (20 treated with surgical resection)	Surgery or no surgery for recurrence	– Mean survival in 20 patients who underwent reoperation was significantly higher (15.85 ± 14.9 months) than in non-reoperated cases (3.2 ± 2.9 months) – 5-year actuarial survival in re-operated patients is significantly better than in nonreoperated patients (49.7% versus 8.3%, respectively)
Khorram-Manesh [27]	1998	Retrospective case series	5	Surgery	Positive correlation between DFI and survival after repeat surgery
Schulick [28]	1999	Retrospective case series	47	Surgery	– Median survival of 47 months with complete second resection and 16 months with incomplete second resection – 5-year survival 57% with complete resection and 0% for incomplete resection
Seki [29]	1999	Case report	1	Mitotane at recurrence	Recurrence 2 years after mitotane for first recurrence and death 4 months later
Langer [30]	2000	Retrospective case series	1	Surgical resection	Surgery is recommended for recurrent disease if resectable
Ilias [31]	2001	Retrospective case series	One treated with surgery followed by mitotane and second treated with mitotane	One patient who had surgery followed by mitotane and a second treated with mitotane	First patients alive at 16 years and second patient alive at 14 year
Fujii [32]	2003	Case report	1	Radiotherapy, chemotherapy then surgery	Alive at 5-year follow-up

(continued)

Table 31.5 (continued)

First author	Year	Type	Number of patients included with recurrent disease	Treatment modality	Outcome
Tauchmanova [33]	2004	Retrospective case series	2	Surgical resection and chemotherapy	Overall survival was 96 months for one patients and 39 months for the second
Matsumoto [34]	2005	Case report	1	Surgery then chemotherapy	Alive at 3-year follow-up
Palazzo [35]	2006	Retrospective case series	1	Surgery	Outcome following surgery not reported
Schlamp [36]	2007	Case report	1	Surgery followed by radiotherapy and chemotherapy	Alive at 21 month
Tan [37]	2009	Retrospective case series	2	Surgery followed by chemotherapy and radiotherapy	– Outcome for first patient not reported – Second patient overall survival of 35 months
Sabolch [38]	2011	Retrospective case series	27 (out of a total of 58 patients studied)	Surgery alone (n = 8), surgery with radiotherapy (n = 7), radiotherapy alone (n = 12)	– Overall results reported (primary and recurrent) – Local failure occurred in 16 of the 48 instances of treatment with surgery alone, in 2 of the 10 instances of surgery plus adjuvant radiotherapy, and in one of the instances of definitive radiotherapy – Lack of radiotherapy use was associated with 4.7 times the risk of local failure compared with treatment regimens that involved radiotherapy – In patients receiving radiation to the tumor bed, tumors of a maximum dimension greater than 10 cm were 4.3 times more likely to fail locally than those with smaller tumors

Datrice [39]	2012	Retrospective case series	19 treated for local recurrence and 38 had distant metastases	Surgery (and/or radiofrequency ablation in 3 patients)	– Overall results reported for treatment of local and distant disease – The median overall survival for patients with a DFI less than 12 months was 1.7 years (range: 2.8 months to >12 years), compared to 6.6 years (range: 3.6 months to >12 years) for a DFI greater than 12 months The median DFS of patients rendered with no evidence of disease (NED) after first metastectomy was 6 months. The median PFS of the population not rendered NED was 2.4 months
Dy [40]	2013	Retrospective case series	67 treated with surgical resection and 26 had non-operative therapy or no intervention (Includes local and distant recurrence)	Surgery or no surgery (medical therapy or no intervention)	– A comparison of survival for these three groups (surgery, non-surgical therapy and no intervention) at 1,2 and 5 years of patients was 82%, 67%, and 30% in the surgery group, 26%, 13%, and 0% in the non-surgical therapy group, and 30%, 10% and 0% in those patients treated with supportive care alone
Erdogen [41]	2013	Retrospective case series	101 had surgical resection of recurrence and 53 treated medically	Surgery followed by chemotherapy or chemotherapy only	– Patients who underwent either incomplete (R2-resection or tumor debulking) or no surgery had a similar progression-free survival, whereas overall survival was worst in patients who were not operated at all

DFI disease free interval, *DFS* disease free survival, *NED* no evidence of disease, *PFS* progression free survival

Search Strategy

A focused review of available literature was conducted. Original articles were identified using a PubMed search strategy. The following search terms were used in combinations: recurrent adrenocortical carcinoma, surgery, chemotherapy, radiation, radiofrequency ablation, mitotane and treatment.

Surgical Management

The management of patients with ACC requires a multi-disciplinary approach. The main goal of treatment in patients with limited disease is complete surgical resection with negative margins (R0). Surgery should involve an *en bloc* resection of the tumor with involved adjacent structures. It is crucial to take caution in preserving the integrity of the tumor capsule to prevent tumor spillage, which may lead to future tumor recurrence [4, 5]. Studies have shown a correlation between the ability to achieve clear margins and prognosis [18, 28, 40]. In addition to careful pathological assessment, evaluation of hormone levels post-operatively can be used to assess the completeness of surgical resection. In patients who present with metastatic disease or advanced tumors, then tumor debulking may be of benefit, specifically when control of excess hormone secretion is required. However, data on this is scare and a survival data is controversial [3, 40].

Despite having an adequate resection, up to 85% of patients with ACC will develop a local or distant recurrence (Fig. 31.1) [16, 17, 42]. Traditionally, surgical resection was thought to be contraindicated in patients with recurrent and metastatic disease. More recently, our understanding of the biology of ACC has improved and criteria such as DFI and resectability of the tumor recurrence has evolved as predictors of a possible improved outcome with re-operation.

An earlier study by Jensen et al., compared treatment with chemotherapy and surgical resection followed by chemotherapy in recurrent ACC [21]. Survival following

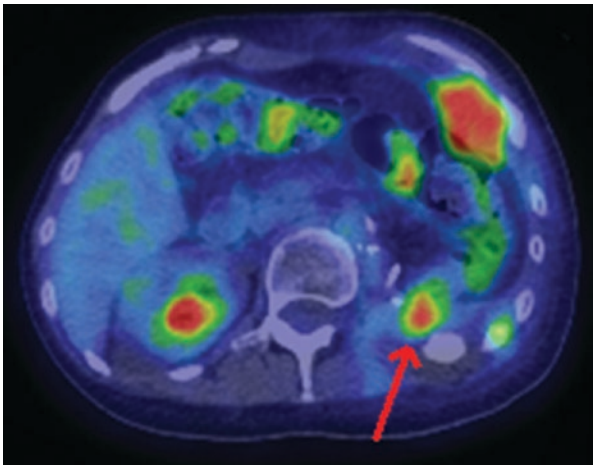

Fig. 31.1 PET-CT image showing a retroperitoneal ACC recurrence

first recurrence was significantly longer in patients treated with chemotherapy plus aggressive surgical resection of recurrent disease than in patients treated with chemotherapy alone (27 vs 11 months, $p < 0.05$). Five patients in the study (33%) survived greater than 5 years from the time of first recurrence. In addition, the authors noted that an initial time to recurrence of greater than 12 months was associated with a significantly improved overall survival. More recently, Erdogen et al., published a larger series showing similar findings [41]. The study represented the collective experience from the German Adrenocortical Carcinoma Registry and found that a time to first recurrence greater than 12 months as well as a complete R0 resection of the recurrent tumor was associated with improved patient survival and outcome. In addition, a recurrence that occurred early within the first 6 months indicated a poor prognosis with a progression-free survival (PFS) of 3 months and an overall survival of 13 months, compared with patients who developed a recurrence after more than 24 months where the PFS was 17 months and overall survival was 115 months.

When performed, surgical resection for ACC recurrence has been shown to be associated with low post-operative mortality. Schulick et al. published a retrospective series from Memorial Sloan Kettering Cancer Center which included 47 patients who underwent a second resection for locally recurrent of metastatic disease [28]. Of a total of 83 repeat resections in this cohort, the authors reported a 30-day mortality of 3.6%. In this study, stratification of patients by completeness of the repeat resection revealed a higher median survival of 74 months in patients undergoing a complete resection compared with 16 months when the resection was incomplete. Thus, emphasizing the prognostic value of achieving a complete resection in patients with recurrent ACC as described by other authors. Similar results were seen in a study by Cricitti et al., where a complete resection was associated with a longer-disease free survival and overall survival than in those patients who have recurrent disease that is not amenable to surgical resection (DFS 41.5 months versus 15 months and OS at 5 years of 50% versus 8% respectively) [18].

Our experience at Mayo Clinic was recently published and included 67 patients who underwent reoperation for recurrence and 26 patients who had non-operative therapy or no intervention [40]. A comparison of survival for these three groups (surgery, non-surgical therapy and no intervention) at 1, 2 and 5 years of patients was 82%, 67%, and 30% in the surgery group, 26%, 13%, and 0% in the non-surgical therapy group, and 30%, 10% and 0% in those patients treated with supportive care alone ($p < 0.0001$). In addition, the study showed that patients who did not achieve an R0 resection for recurrent disease had a reduced overall survival compared with those achieving a complete resection. Furthermore, debulking surgery was found to be associated with an improved medial survival of 3.5 years compared with patients who did not undergo surgery ($p = 0.002$). In contrast to the studies discussed earlier showing an improved survival in patients who had an initial DFI of more than 12 months, a time period of greater than 6 months was identified in this study to be independently associated with improved survival among patients proceeding with surgical resection of recurrent tumor [40]. Hence, these results in addition to other reports, support a role for surgical intervention in recurrent ACC.

The use of laparoscopic surgery for ACC is a subject of ongoing controversy. Open adrenalectomy is generally the preferred procedure for patients with proven ACC or where there is a high suspicion for this diagnosis. It also is the procedure of

choice in cases where the tumor is larger than 10–12 cm, there is evidence of invasion of adjacent structures, and lymphadenopathy [43, 44]. Studies to date have shown an increased local recurrence rate and intra-peritoneal dissemination of disease in cases of ACC resected by a laparoscopic approach [45]. Therefore, data extrapolated from these experiences do not support a laparoscopic approach in the recurrent setting.

Recommendation

A number of case reports and retrospective case series have been published showing a benefit for re-operation for recurrent ACC. In these studies, a complete resection was associated with an improved overall survival compared with an incomplete resection. A complete surgical resection, therefore, is recommended for patients who develop a recurrence of ACC more than 6–12 months following their initial therapeutic resection (evidence quality low, weak recommendation).

Non-surgical Management

Chemotherapy

To date, mitotane (ortho,para'-DDD or 1,1-dichloro-2-[*o*-chlorophenyl]-2-[*p*-chlorophenyl] ethane) has been shown to be the only adrenal specific agent for the treatment of ACC. Mitotane acts through several different mechanisms which include decreasing cortico-steroid biosynthesis and by inducing structural damage to the mitochondria in the zona reticularis and zona fasciculata, thereby leading to necrosis of both normal and tumor tissue [46, 47]. The actions of mitotane appear to be dose dependent. A correlation between plasma serum levels and survival have been shown with serum levels of more than 14 μg/mL [24]. As a result of improved understanding of the variability of response in patients with ACC, as well as the increasing half-life with prolonged administration of mitotane, various dosing regimens have been proposed [48, 49]. Side effects of mitotane are also dose dependent and are reversed by stopping therapy. The most common of these include gastrointestinal symptoms such as nausea, vomiting, diarrhea and anorexia [4, 42, 46]. Others include neuropsychiatric symptoms, hepatotoxicity, hematologic abnormalities, renal abnormalities and skin rashes [4, 46]. In addition, glucocorticoid replacement is warranted in patients treated with mitotane due to the suppressive effects on health adrenal tissue. The reported efficacy of mitotane in the treatment of patients with ACC is variable and unclear. It has been shown to be effective in inducing tumor response in 33% of patients treated [50]. Terzolo et al., reviewed the outcomes of patients with ACC who had undergone radical surgery and treated with mitotane compared with patients who were not treated with mitotane [42]. The study revealed that PFS was significantly prolonged in the mitotane group compared with the two control groups (42 months vs 10 and 25 months respectively). Multivariate analysis indicated that mitotane treatment had a significant advantage for PFS.

In addition to mitotane, chemotherapeutic agents have been shown to be of benefit in patients with ACC, especially those patients that do not responds to mitotane, experience severe side effects or patients advanced disease. Various combinations have been used and reported in retrospective series. These include cisplatin-based therapy in combination with etoposide, 5-fluorouracil and doxorubicin or streptozocin. The First International Randomized Trial in Locally Advanced and Metastatic Adrenocortical Carcinoma Treatment (FIRM-ACT) study is the only phase III randomized controlled trial in the treatment of ACC to be reported to date. This study compared two of the most successful regimen in the treatment of patients with advanced ACC (etoposide, doxorubicin and cisplatin (EDP) with mitotane and streptozocin with mitotane) and aimed to establish a treatment standard for advanced disease [51–53]. An objective tumor response was noted in 23.2% of patients in the EDP-mitotane group compared with 9.2% of patients in the streptozocin-mitotane group. The median DFI was 5.0 months in the EDP-mitotane group compared with 2.1 months in the streptozocin group [53]. The 12-month survival and median overall survival between the EDP-mitotane group and streptozocin-mitotane group was 26.1% and 14.8 months vs 7.2% and 12.0 months respectively. The study concluded that EDP-mitotane as first-line treatment reduced the risk of death by 21% as compared with streptozocin-mitotane [53]. Despite this small benefit, this trial is important in setting a standard for current practice (EDP-mitotane as first line combination treatment of advanced ACC) as well as providing a platform for further research in this area. The European Society of Medical Oncology (ESMO) guidelines recommend combination chemotherapy and mitotane for patients with inoperable ACC with high tumor volume and rapid disease, whilst mitotane alone can be used initially for patients with low tumor volume, slow progression or those patients who are unfit for surgery [54].

In the setting of tumor recurrence, the role of mitotane or chemotherapy-mitotane combinations, as well as consensus on the best treatment is yet to be fully elucidated. Reports of chemotherapy in recurrent ACC have not been consistent and have shown no increase in survival rates, long term disease control, as well as disease remission [4, 24, 31, 46, 55]. In addition, studies comparing medical treatment and surgery have consistently shown a survival benefit in patients treated with surgery (with or without further medical therapy) compared with no surgery [16, 21, 34]. Therefore, it is accepted that an evaluation of patients at the time of recurrence is important to establish the resectability of recurrent disease and patient fitness for surgery. Factors discussed in the previous section including DFS and tumor biology should be considered. Following surgical resection, patients may receive mitotane with or without chemotherapy and/or radiation.

In patients with excess hormone secretion, additional pharmacologic agents are available for use and have a role in controlling the production of steroids. This is particularly important in patients who may be unsuitable for further surgery or who have disease that in no amenable to a complete R0 resection. Such agents include metyrapone and ketoconazole. Metyrapone inhibits cortisol production, while ketoconazole is an imidazole antifungal agent that has a role in suppressing corticosteroid and androgen production and has an important role in benign adrenal disease. These agents, unfortunately, do not inhibit tumor growth. Other agents include etomidate and mifepristone.

Recommendation

The use of chemotherapy and other medical therapy in recurrent ACC is unclear and evidence to support its use is limited to retrospective case series and reports. These therapies should be considered in the following reoperation for recurrent ACC and for the treatment of patients who have disease that is not amenable to surgical resection (evidence quality low, weak recommendation).

Radiotherapy

The role of radiation treatment in ACC is yet to be fully elucidated. Radiotherapy has been traditionally reserved for the palliative treatment of patients with ACC. The main challenges in its utilization include the lack of clear treatment benefit as well as radiation effects on adjacent organs such as the kidney, liver and small bowel. A recommendation from a review of data from the German ACC Registry includes consideration of radiotherapy within 3 months of surgery to the tumor bed in patients at high risk of local resection, such as those with an incomplete resection (microscopically involved or indeterminate resection margins), stage III disease, tumors greater than 8 cm, or a Ki 67% of greater than 10%. A total dose of >40 Gy with single fractions of 1.8–2 Gy are suggested (including a boost volume to reach from 50 to 60 Gy) [56]. In addition radiotherapy is recommended for use for symptomatic metastases to bone, brain or vena cava obstruction [56].

A search of the literature regarding the use of radiotherapy in recurrent adrenocortical carcinoma is limited to retrospective case series. A retrospective series of patients with primary and recurrent ACC compared treatment with surgery alone, surgery plus adjuvant radiotherapy and definitive radiotherapy for unresectable disease [38]. This study showed that the lack of radiotherapy use was associated with 4.7 times the risk of local failure compared with treatment regimens that involved radiotherapy (95% CI, 1.2–19.0; $p = 0.030$). In patients receiving radiation to the tumor bed, tumors of a maximum dimension greater than 10 cm were 4.3 times more likely to fail locally than those with smaller tumors (95% CI, 1.5–13.0; $p = 0.004$). The heterogenous nature (primary vs recurrent, various treatment modalities) of the patients included is a limitation of this study.

Recommendation

The use of radiotherapy in recurrent ACC is unclear and evidence to support its use is limited to retrospective case series and reports. Radiotherapy should be considered in the following reoperation for recurrent ACC and for the treatment of patients who have disease that is not amenable to surgical resection (evidence quality low, weak recommendation).

Tumor Ablation

Radiofrequency ablation (RFA) delivers minimally invasive local treatment utilizing high frequency alternating current. It works by transforming radiofrequency energy into heat, which is deposited into the tumor. It has been shown to be safe and effective treatment for a variety of tumors. In patients with ACC, it may constitute part of the treatment of patients of patients who are deemed as poor candidates for surgical resection and also as part of multimodality treatment. In the primary setting, evidence to date has shown that RFA is well tolerated with 53% of patients demonstrating a reduction in the size of their tumor (more notable response in tumors <5 cm, 67% complete response) or loss of enhancement on imaging [57]. Side effects reported include bleeding, infection, and injury to adjacent organs [58, 59]. Datrice et al. reported on the use of RFA in a cohort of patients with recurrent and metastatic ACC [39]. The authors reported on the safety and feasibility of this procedure when performed at a specialized institution and when combined with surgery to treat lesions that might otherwise be considered unresectable. It is unclear however from this report as to how many patients had RFA specifically for recurrence rather than treatment of metastasis.

Cryoablation is another form of ablative treatment (Fig. 31.2). This causes tumor necrosis as a result of rapid cell freezing. To our knowledge there is no data available of the use of cryoablation in the treatment of recurrent ACC. Its use, however, has been demonstrated in the treatment of adrenal metastasis from other tumors [60]. Xiao et al. reported on the use of cryoablation for benign adrenal tumors and adrenal metastasis [61]. This study revealed a complete response of 92.3% and a partial response of 7.7% with its use for primary adrenal lesions. In the setting of metastasis a complete response was seen in 30% and a partial response in 70%. A third method of ablation that can be used for adrenal gland disease is chemical ablation. This is performed using image-guided instillation of a chemical agent, most commonly ethanol or acetic acid. Li et al. reported a case of a patient with recurrent and metastatic ACC in which survival of 58 months was achieved with aggressive multiple trans-arterial embolization [62]. Addressing the role of these treatments in patients with ACC recurrence is challenging and further studies and reports are needed.

Recommendation

Evidence on the use of RFA in recurrent ACC is very limited. Further investigation is needed to address the long-term efficacy of this technique and its role in improving disease free and overall survival. As such, radiofrequency ablation may be considered alone or in combination with surgery in patients with recurrent ACC (evidence quality low, weak recommendation). There is no evidence to suggest that this treatment is superior to surgery alone or other treatment modalities.

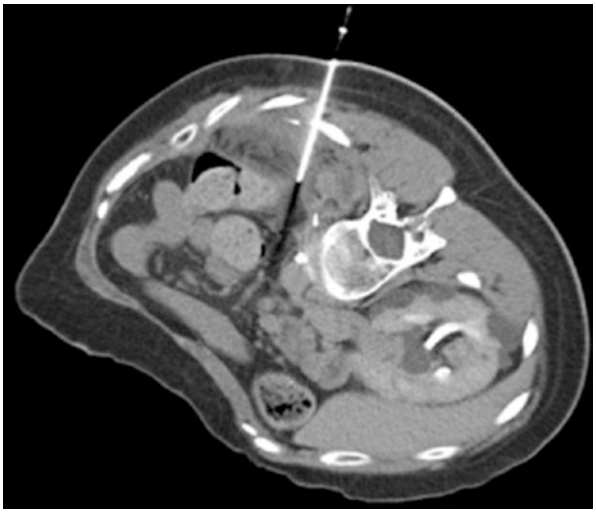

Fig. 31.2 CT-guided cryoprobe for ablation

Novel Therapies

A number of novel therapies are currently being investigated for the treatment of advanced ACC. These include the use of inhibitors of vascular endothelial growth factor (VEGF), epidermal growth factor receptor (EGFR), insulin-like growth factor receptor 1 (IGFR1) and mammalian target of rapamycin (mTOR). Other targets of interest include micro RNA therapies, targeting the Wnt/B-catenin pathway, interleukin-13 receptor alpha 2, and dimethylating agents. There is no evidence as yet to support their use in recurrent adrenocortical carcinoma and further research is needed.

Recommendation

There is no evidence for the use of novel targeted therapies in the treatment of recurrent ACC.

Conclusions

The management of patients with recurrent ACC poses a great challenge for the treating physician. Despite achieving a complete resection of the primary tumor and receiving adjuvant therapy, up to 85% of patients with ACC experience disease relapse. Appropriate patient referral to a specialized unit and a multidisciplinary approach to patient treatment are crucial. Surgical resection is recommended for patients with recurrent ACC who are suitable for further intervention and who develop a recurrence after 6–12 months of initial treatment (Fig. 31.3).

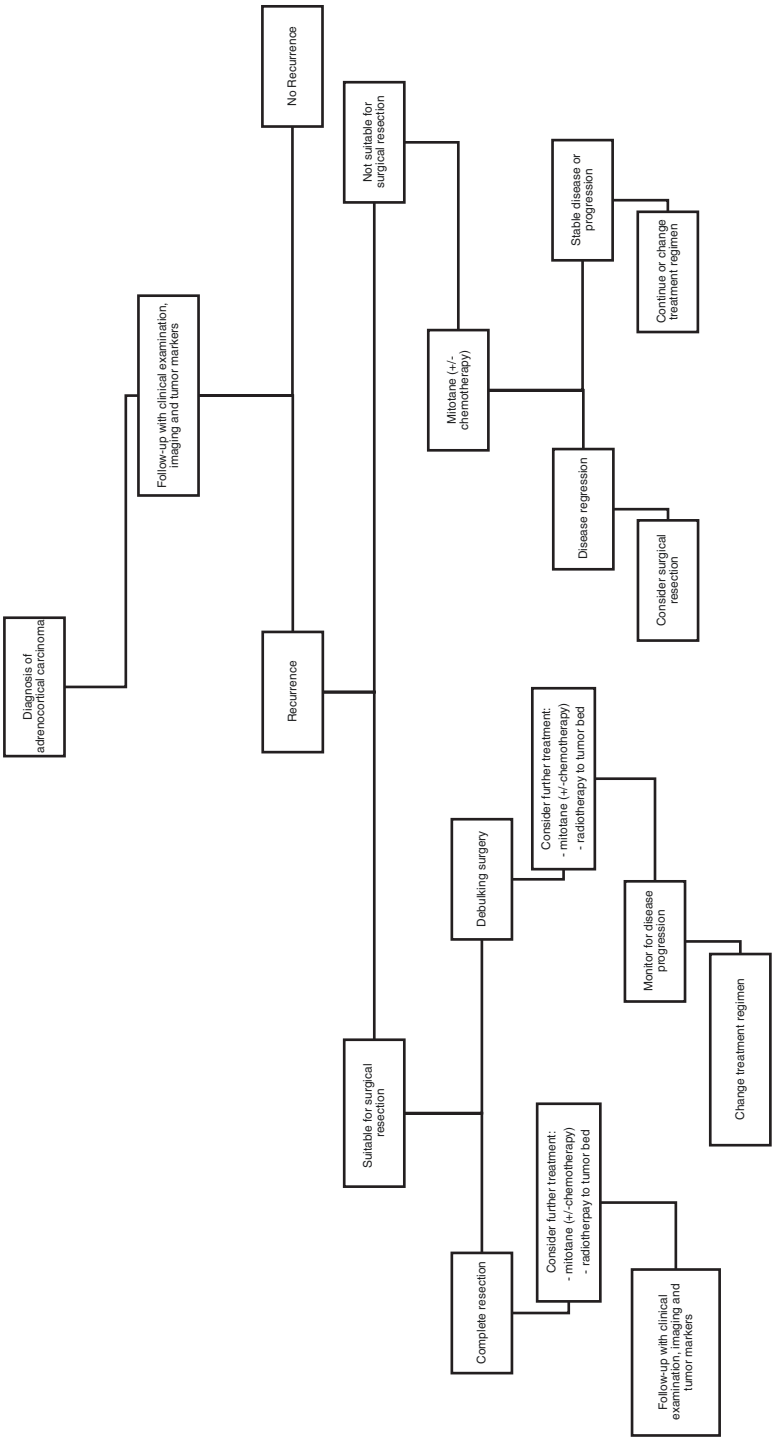

Fig. 31.3 Suggested algorithm for the treatment of patients with ACC

Recommendations Summary

Surgery

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Chemotherapy

The use of chemotherapy and other medical therapy in recurrent ACC is unclear and evidence to support its use is limited to retrospective case series and reports. These therapies should be considered in the following reoperation for recurrent ACC and for the treatment of patients who have disease that is not amenable to surgical resection (evidence quality low, weak recommendation).

Radiotherapy

The use of radiotherapy in recurrent ACC is unclear and evidence to support its use is limited to retrospective case series and reports. Radiotherapy should be considered in the following reoperation for recurrent ACC and for the treatment of patients who have disease that is not amenable to surgical resection (evidence quality low, weak recommendation).

Tumor Ablation

Evidence on the use of RFA in recurrent ACC is very limited. Further investigation is needed to address the long-term efficacy of this technique and its role in improving disease free and overall survival. As such, radiofrequency ablation may be considered alone or in combination with surgery in patients with recurrent ACC (evidence quality low, weak recommendation). There is no evidence to suggest that this treatment is superior to surgery alone or other treatment modalities.

Targeted Therapies

There is no evidence for the use of novel targeted therapies in the treatment of recurrent ACC.

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