Diagnosis and Management of Adrenocortical Carcinomas

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23.1 Introduction

Adrenal tumors are becoming increasingly common with the improvement in imaging techniques. Prevalence of incidental adrenal lesions detected by computed tomography (CT) or magnetic resonance imaging (MRI) exceeds 5 % with an estimated incidence of 7.3 % from autopsy series [1–3]. Although the majority of those lesions are benign adrenocortical adenomas, some of the lesions are malignant, known as adrenocortical carcinoma (ACC). ACC is a rare and highly aggressive tumor and is usually resistant to most of the conventional chemotherapeutics [4]. Overall 5-year survival is less than 40 % [5, 6]. Significant progress has been made in delineating the pathogenesis of ACC over the past 20 years. Surgery is the preferred treatment for localized ACC with the aim to achieve complete resection with clear margins. Unfortunately current treatment options other than surgery have limited efficacy in the adjuvant and advanced setting. Given the low incidence of the disease, a number of clinical trials in patients with ACC are limited and mostly retrospective; therefore treatment recommendations are generally based on retrospective data or expert opinions. In order to understand molecular mechanisms underlying the disease and develop more effective treatment for ACC, clinical and translational studies with international collaboration are needed.

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23.2 Epidemiology

The incidence of ACC is approximately 1–2 cases per million, and ACC accounts for 0.02–0.2 % of all cancer deaths. ACC can occur at any age. The disease has a bimodal incidence peak, with a larger peak in the 4–5th decade of life and another peak in the first decade of life. The incidence is slightly higher in females [6, 7].

In the largest published series of ACC ($n = 3{,}982$), the median age at diagnosis was 55 years, median tumor size was 13 cm, and distant metastases were found on presentation in 21.6 % of patients [6, 8]. ACCs may be nonfunctional and may present with symptoms due to mass-forming effects of the tumor, such as abdominal discomfort, pain, or indigestion, or can be functional with hormone-secreting features in up to 34–62 % of the patients. Presentation and clinical symptoms are based on the type of produced hormone. Cortisol secretion and resulting Cushing's syndrome is the most common presentation followed by either virilization or a combination of both [7–10]. Feminizing syndrome due to the secretion of estradiol, prolactin, and testosterone and hyperaldosteronism are also seen. In the later phases of the disease with the growing mass in the abdomen, approximately one-third of the patients experience nonspecific abdominal discomfort. Advances in the imaging techniques may have increased the frequency of asymptomatic presentations which may also translate into the improved survival rates. Kasperlik-Zaluska et al. reported that 28.5 % of their 63 patients with ACCs presented as incidentalomas [11]. The mean duration from the onset of symptoms to diagnosis of ACC varies from 6 to 16 months and appears to be independent of whether it is functional or clinically silent [12, 13].

23.3 Pathogenesis

The etiopathogenesis of ACC is rather complex; there is no identified causative environmental agent described yet. Although ACCs are mostly sporadic, certain inherited cancer syndromes may present with ACC. Detailed description of these hereditary cancer syndromes and involved genes will be very important in the future for describing carcinogenic pathways and development of new targeted therapies. Hereditary tumor syndromes associated with ACC are Li–Fraumeni syndrome, Beckwith–Wiedemann syndrome, Carney complex, multiple endocrine neoplasia (MEN1), congenital adrenal hyperplasia, and familial adenomatous polyposis (FAP) [10].

There are some genes involved in the pathogenesis of ACC and one of them is TP53; TP53 is a tumor suppressor gene; it causes cell cycle arrest or cell death in response to DNA-damaging agents. TP53 mutations in exons 5–8 may be seen in ACCs and patients having these mutations have shortened survival. The prevalence of TP53 gene mutation in adult patients with ACC was found to be 3.9 % [14]. Genetic counseling with germline testing for TP53 is recommended to all patients with ACC, particularly if age <40 [15].

Another important gene implicated in the pathogenesis of ACC is insulin-like growth factor-2 (IGF2) gene. Rearrangements, loss of heterozygosity (LOH), and abnormal imprinting of the 11p15.5 locus are associated with elevated IGF2 mRNA expression in ACC [16, 17]. IGF2 overexpression could be used as a diagnostic tool for discriminating benign from malignant adrenal masses because IGFR 2 overexpression is a consistent finding in ACCs [18–20]. Higher IGF2 levels are associated with a malignant phenotype, and overexpression of IGF2 is associated with an increased risk of ACC recurrence [21]. Demethylation of IGF2 is also found more frequently in ACCs and correlates with IGF2 mRNA expression [17, 18]. Furthermore, LOH of the 11p15 locus has been demonstrated more frequently in ACC (67 %) compared to adrenal adenomas (13 %). It has been postulated that this leads to overexpression of IGF2 because the maternal allele is lost with duplication of the paternal allele leading to a double dose of the expressed allele [17].

Activating somatic mutation of the *CTNNB1* (beta-catenin) gene has also been identified in ACCs. Wnt/beta-catenin pathway activation was linked to decreased disease-free and overall survival in patients with resected adrenal carcinoma [22]. Other genes potentially involved in the pathogenesis of ACC are *ZNRF3*, *CDKN2A*, *RB1*, *MEN1*, CYP21B, PRKAR1A, and GNAS genes [23].

A number of studies have assessed the use of molecular markers in discriminating ACCs from adrenal adenomas. Immunohistochemistry with Ki-67/MIB1 has been found to be useful in differentiating ACCs from adrenal adenomas [24–26] with a reported sensitivity of 87.5 % and specificity of 95.5 % [25]. Combining IGF2 with Ki-67/MIB1 IHC improved sensitivity and specificity for differentiating ACCs from adrenal adenomas to 100 and 95.5 %, respectively [25]. IHC with p53 has not been found to be particularly helpful because even though it is highly specific for ACCs, its sensitivity is low, ranging from 5.4 to 73 % [24–26]. Protein expression of matrix metalloproteinase type 2 (MMP2, also known as gelatinase A) has been found to be high in ACCs but low in adrenocortical adenomas. MMP2 protein expression in ACCs was focal in two-thirds of cases and diffuse in the remainder. More diffuse expression of MMP2 in ACCs was associated with shorter overall and disease-free survival [27]. Interestingly, while MMP2 mRNA was found more frequently in ACCs compared to adrenal adenomas, mRNA was actually found in surrounding stromal tissue and not the neoplastic cell itself [28]. Serum levels of MMP2 have not been found to be useful in predicting either ACCs or adrenal adenomas [29].

None of the mentioned markers have been validated in prospective studies or tested in clinical routine.

23.4 Clinical Presentation and Diagnosis

Approximately 60–70 % of adult patients with ACC present with clinical findings of hormone excess, mostly with Cushing's syndrome. Weight gain, weakness, virilization, feminization, or hyperaldosteronism may occur depending on the hormone

secreted. Diagnosis is based on clinical, laboratory, and radiologic findings. Signs and symptoms of Cushing's syndrome, hyperandrogenism, pheochromocytoma, and hyperaldosteronism should be assessed. Laboratory evaluation should include corticotropin (ACTH), serum cortisol, 24-h free cortisol in urine, total testosterone, dehydroepiandrosterone sulfate, and estradiol. Complete blood count and serum chemistries should also be obtained [10]. The European Network for the Study of Adrenal Tumors recommends plasma aldosterone and renin measurement if hypertension or hypokalemia is present and plasma metanephrine or urinary metanephrine and catecholamine measurement in all patients to exclude pheochromocytoma [30]. Excessive amounts of adrenal steroid precursors are detected in urine in recent studies; these markers may aid in the diagnosis and follow-up to detect the presence of tumor recurrence in patients with ACC [31].

Computed tomography (CT) is widely used in the diagnosis and differentiation of benign from malignant lesions. The size of the tumor is important as increased size of the adrenal mass usually is a sign of malignancy (>5 cm tumors are usually malignant). An adrenal tumor diameter of 5 cm identifies ACC with a sensitivity of 93 % and a specificity of 64 % [32]. Second, the radiologic appearance of the suspected mass is decisive; benign adenomas usually have higher lipid content, and this results in a low attenuation on CT scans (i.e., <10 Hounsfield unit). Another feature of benign adenomas is rapid contrast enhancement and rapid washout. Irregular shape and margins, presence of hemorrhage, and heterogeneity are features suggesting malignancy [33–35].

Magnetic resonance imaging (MRI) and FDG-PET scans are helpful in evaluating adrenal carcinoma. MRI may show high lipid content of the adrenal mass as well as hemorrhage and heterogeneity of the tumor. A recent meta-analysis showed that FDG-PET had 97 % sensitivity and 91 % specificity in discriminating benign from malignant adrenal masses. Integrated PET/CT scans have even higher sensitivity and specificity. Therefore PET/CT is an important diagnostic tool for ACC, particularly for evaluation of indeterminate masses [36–38].

23.5 Pathology

The only definitive criterion for malignant adrenal tumors is the presence of local invasion or distant metastases. Fine-needle aspiration biopsy cannot discriminate between adrenal adenoma and ACC but may be useful in distinguishing adrenal metastases. On macroscopic examination, ACCs are often large, with a tan-yellow cut surface, and areas of hemorrhage and necrosis may be seen. The tumors are usually encapsulated or lobulated and can be solid or cystic [39]. On microscopic examination, the tumor usually displays sheets of atypical, eosinophilic cells with some resemblance to the cells of the normal adrenal cortex. Polygonal cells are arranged in sheets, nests, trabeculae, or ribbons and may contain anaplastic features. Other signs of malignancy are increased mitotic activity and vascular and capsular invasion. Immunohistochemistry may help to differentiate ACCs from adrenal adenomas. ACCs usually show immunostaining with Ki-67 (>10 %) and overexpression of insulin-like growth factor 2. The presence of invasion and

increased mitotic activity helps differentiate small cancers from adrenocortical adenomas [39, 40].

Differential diagnostic scores have been developed for pathological diagnosis; currently the Weiss and modified Weiss scores are the most widely accepted scoring systems and are based on histological findings. The updated Weiss score consists of five criteria including mitotic rate >5 mitoses/50 high-power fields, cytoplasm (clear cells comprising 25 % or less of the tumor), abnormal mitoses, necrosis, and capsular invasion. Each criterion is scored 0 when absent or 2 for the first two criteria and 1 for the last three when present; a total score ≥3 is highly suggestive of ACC [41, 42].

There are several relatively rare variants of ACC. These histologic variants are oncocytic adrenal cortical carcinoma, myxoid adrenal cortical carcinoma, carcinosarcoma, adenosquamous adrenocortical carcinoma, and clear cell adrenal cortical carcinoma [39].

23.6 Staging

There are several staging systems in use. Macfarlane et al. proposed a staging system in 1958 [43]. This staging system has been later modified by Sullivan et al. in 1978 [44] and later by Lee et al. in 1995 [45] (Table 23.1). Based upon the definitions of this staging system, the American Joint Committee on Cancer (AJCC)/UICC staging scheme was developed [46] (Tables 23.2, 23.3, 23.4, and 23.5). According to this scheme, the stage of ACC is determined by the size of the primary tumor, the extent of local invasion, and whether it has spread to regional lymph nodes or distant sites. Stage I–II disease is confined to the adrenal gland with a tumor size of less than or greater than 5 cm, respectively. Stage III disease is defined as invasion into adjacent organs or regional lymph nodes, while stage IV disease denotes distant metastatic disease [43, 44].

In addition to the abovementioned AJCC staging, the European Network for the Study of Adrenal Tumors (ENSAT) staging system is widely used internationally [47]. The ENSAT staging system is essentially the same as the AJCC system, but this staging proposals tend to limit stage IV patients with distant metastasis. Presence of local invasion, venous tumor thrombosis, or local lymphadenopathy is

Table 23.1 Staging of ACCs

Stage	Macfarlane [43]	Lee et al. [45]
I	T1 (<5 cm) N0M0	T1 (<5 cm) N0M0
II	T2 (>5 cm) N0M0	T2 (>5 cm) N0M0
III	T3 (local invasion without involvement of the adjacent organs) or mobile positive lymph nodes	T3/T4 (local invasion as shown by histological evidence of adjacent organ invasion, direct tumor extension to IVC, or tumor thrombosis within IVC or renal vein), and/or N1 (positive regional lymph nodes), M0
IV	T4 (invasion of the adjacent organs) or fixed positive lymph nodes or M1 (distant metastases)	T1–4, N0–1, M1 (distant metastases)

Table 23.2 Definitions of TNM

Primary tumor (T)[a]	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤5 cm in greatest dimension, no extra-adrenal invasion
T2	Tumor >5 cm, no extra-adrenal invasion
T3	Tumor of any size with local invasion, but not invading adjacent organs[b]
T4	Tumor of any size with invasion of adjacent organs[b]

[a]Adopted from [90]
[b]Adjacent organs include the kidney, diaphragm, great vessels, pancreas, spleen, and liver

Table 23.3 Definitions of TNM

Regional lymph nodes (N)[a]	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastases in regional lymph node(s)

[a]Adopted from [90]

Table 23.4 Definitions of TNM

Distant metastasis (M)[a]	
M0	No distant metastasis
M1	Distant metastasis

[a]Adopted from [90]

Table 23.5 Definitions of TNM

Anatomic stage/prognostic groups[a]			
Stage	T	N	M
I	T1	N0	M0
II	T2	N0	M0
III	T1	N1	M0
	T2	N1	M0
	T3	N0	M0
IV	T3	N1	M0
	T4	N0	M0
	T4	N1	M0
	Any T		

[a]Adopted from [90]

defined as stage III. Most contemporary studies use this staging system because of superior prognostic stratification compared to AJCC scheme. According to the ENSAT scheme, 5-year disease-specific survival rates are 82 % for stage I disease, 61 % for stage II, 50 % for stage III, and 13 % for stage IV [48].

Proper staging should include CT of the abdomen and chest. Magnetic resonance imaging may increase specificity of CT evaluation. In-phase and out-of-phase T1-weighted imaging may be the most effective noninvasive method to differentiate benign from malignant adrenal masses. Extracapsular tumor invasion, extension into the vena cava, or metastases may be detected more accurately with MRI. Patency of surrounding vessels can often be demonstrated with gadolinium-enhanced sequences or flip-angle techniques [33, 35, 49].

23.7 Treatment

23.7.1 Surgical Resection

Complete surgical resection is the mainstay of treatment for ACC. Open surgical technique for adrenalectomy is recommended. Complete, en bloc, margin-negative resection should be the surgical goal [50, 51]. Lymph node dissection is recommended [52]. Resection of adjacent organs including the spleen, kidney, liver, or pancreas might be required if local invasion is present. Tumor extension into the inferior vena cava is not a contraindication to surgery, and resection can be performed by cardiopulmonary bypass. The role of laparoscopy is controversial; a number of previous studies showed that laparoscopic surgery for ACC increased the risk of local recurrence, peritoneal dissemination, and metastases [53–57], while others reported comparable results with open surgery particularly if the adrenal tumor is small [58]. Open surgery is currently the preferred approach by NCCN guidelines. Completeness of surgical resection is the most important factor that influences outcome [32, 59]. If resection is incomplete, repeated surgery for achieving clear margins should be considered.

Patients who undergo complete repeat resection of local recurrence or distant metastasis also have improved survival. One study showed that patients who had a complete second resection of local or distant recurrence had a median survival of 74 months (5-year survival, 57 %), whereas those with incomplete second resection had a median survival of 16 months (5-year survival, 0 %) [60]. Therefore surgery is still an important treatment in advanced disease when complete resection of recurrence and all metastases is feasible. Selected patients with uncontrollable symptomatic hormone excess might be candidates for debulking surgery.

The benefit of neoadjuvant systemic therapy prior to surgery for locally advanced disease is not known, and this is not considered a standard approach.

23.8 Systemic Therapy

23.8.1 Mitotane

Adrenocortical carcinoma is a rare tumor; thus there are no randomized trials of adjuvant therapy. Up to 80 % of the patients experience disease recurrence after radical resection; this forms the rationale behind adjuvant therapy. The only treatment which showed benefit in terms of disease-free and overall survival in retrospective reports is mitotane. Mitotane is a derivative of the insecticide dichlorodiphenyltrichloroethane (DDT or rothane). Mitotane is metabolized to an active metabolite which leads to necrosis of the zona fasciculata and reticularis of the adrenal cortex and inhibition of adrenocortical hormone production (blocking adrenal 11-beta-hydroxylation and cholesterol side-chain cleavage) [61]. The largest series of adjuvant mitotane use after surgery compared to surgery alone in 177 patients with ACC from 8 centers in Italy and 47 centers in Germany was published recently. All patients had radical resection with a follow-up of up to 10 years.

Forty-seven of the 177 patients received adjuvant mitotane after surgery, while the rest of the patients had surgery alone. Median recurrence-free survival was 42 months in the mitotane group, 10 months in the Italian control group ($p<0.001$), and 25 months in the German control group ($p=0.005$). Median overall survival was 110 months in the mitotane group, as compared with 52 months in the Italian control group ($p=0.01$) and 67 months in the German control group ($p=0.1$). Mitotane treatment had a significant advantage for recurrence-free survival in multivariate analysis [62]. The median duration of treatment was 29 months. Twenty-seven patients received 1–3 g/day and 20 patients received 3–5 g/day. Serum levels of mitotane were not assessed. Grade 3 gastrointestinal (nausea or vomiting or elevated serum GGT) or neurologic events (confusion, ataxia, vertigo) were observed in 15 and 20 % of the patients, and all occurred in patients who received the higher-dose mitotane regimen.

Adjuvant mitotane is indicated in patients with high risk of recurrence; however the definition of high risk is not uniform. This controversial topic was discussed in 2008 by an international panel of specialists for the treatment of patients with ACC. On these grounds, the panel unanimously stated that patients with potential residual disease (R1 or Rx resection) and/or Ki67 more than 10 % should be offered adjuvant mitotane, whereas adjuvant therapy was not considered mandatory in patients fulfilling all of the following criteria: stage I or II disease (based on the new European Network for the Study of Adrenal Tumors), histologically proven R0 resection, and Ki67 expressed in ≤10 % of neoplastic cells. The panel did not express a unanimous position with respect to whether or not patients with stage III ACC with R0 disease after surgery should receive adjuvant therapy in clinical routine [63]. Fassnacht et al. propose tumor size >8 cm and microscopic evidence of invasion of blood vessels or the tumor capsule as additional risk factors which require consideration of adjuvant therapy [4]. NCCN guidelines suggest that mitotane be “considered” (category 3 recommendation, with major disagreement that the intervention is appropriate) for all patients with resected low-grade or high-grade localized ACC regardless of stage or tumor size [52]. Intraoperative tumor spillage or fracture is also suggested by some authors as indication for adjuvant mitotane [64]. A large international randomized trial in 200 patients with low- to intermediate-risk resected disease [stage I to III, microscopically complete (R0) resection, Ki67 < 10 %] is currently ongoing (the ADIUVO trial, NCT00777244).

Response rates to single-agent mitotane in metastasized ACC are between 13 and 31 %. Responses are mostly partial and generally short-lived [65]. However these were early studies, mitotane doses were suboptimal, and response evaluations were not up to date. Median survival was less than 1 year. The main benefit of mitotane in patients with advanced disease is reduction in hypercortisolism symptoms. Mitotane is almost always administered in combination with cytotoxic chemotherapy in metastatic disease given the higher response rates.

Side effects including anorexia, nausea, vomiting, and diarrhea are common and can limit adjuvant mitotane use as a long-term treatment. Also monitoring for the blood level of mitotane is essential for effective treatment. Mitotane treatment starts 1 g twice daily orally and the dose is escalated up to 10 g/day. Patients

metabolize mitotane to different degrees. Optimum dose of the drug can be safely and accurately delivered by monitoring the blood levels. Therefore monitoring of plasma levels of mitotane is required, and a target serum level between 14 and 20 mg/L should be achieved for obtaining optimal response and decreased toxic side effects [66].

Use of mitotane routinely induces atrophy and/or steroidogenic inhibition of the normal adrenal glands, thereby necessitating replacement therapy for cortisol deficiency; the zona glomerulosa is more resistant to the adrenolytic effect of mitotane, and aldosterone deficiency may occur after several months of therapy. Monitoring of blood sodium, potassium, creatinine, and 24-h urinary free cortisol levels is mandatory to assess adrenal insufficiency. Higher doses than the routine maintenance can be needed to avoid adrenal insufficiency. If signs or symptoms of mineralocorticoid deficiency (i.e., postural hypotension, hyperkalemia, etc.) develop, fludrocortisone should be added. Patients should also be monitored for hypogonadism and hypothyroidism. The most common side effects are fatigue, nausea, vomiting, and anorexia, but skin rash, diarrhea, lethargy, sedation, confusion, dizziness, ataxia, gynecomastia, arthralgias, leukopenia, prolonged bleeding time, hematuria, and reversible growth arrest in children also occur. Mitotane has significant drug interactions and can reduce efficacy of some calcium channel antagonists, opioids, benzodiazepines, macrolide-type antibiotics, and many other drugs [67].

There is no evidence for the role of cytotoxic chemotherapy in the adjuvant treatment of ACC. However, Fassnacht et al. from the German consortium suggest 3 cycles of 90 mg/m^2 cisplatin in addition to mitotane in patients with Ki67 >30 % and a large tumor thrombus in the vena cava [68].

23.9 Chemotherapy

Unfortunately recurrences are seen very often in ACC after complete surgical resection with reported rates of 21–91 %. Recurrences are generally treated with chemotherapy–mitotane combination. Response rates of ACC to various chemotherapy agents are reported to be between 10 and 40 %. Chemotherapeutic agents should be used in combination rather than monotherapy as ACCs usually express multidrug resistance gene MDR-1 and develop resistance to chemotherapeutic agents over time.

Regarding the data in the literature, combination of mitotane with etoposide, doxorubicin, and cisplatin (m-EDP) and combination of mitotane with streptozotocin [69, 70] are the two reasonable options for the management of patients with advanced ACC [71]. These two promising combinations were compared in the FIRM-ACT trial (which is still the only published randomized trial in ACC), results of which was published in 2013. A total of 304 patients were enrolled. Response rates were 23 % in the EDP–mitotane group versus 9 % in the streptozocin–mitotane group ($p < 0.001$). The first group had a 5-month progression-free survival compared to 2 months for the streptozotocin–mitotane group

($p < 0.001$), and overall survival was similar (14.8 vs 12 months, $p = 0.07$) [72]. Thus, evidence-based first-line treatment of choice is m-EDP in advanced ACC. However, the following comments were made by the investigators of this trial; as median PFS was 5 months and overall survival was 14.8 months, the outcome was actually poor. M-EDP regimen had similar activity in the second-line treatment as it was in the first line in previous studies. Therefore, patients with presumably less aggressive disease (slow tumor growth, long disease-free interval after initial surgery) might receive mitotane monotherapy in the first line followed by combination chemotherapy upon progression. Second, this patient group might also be good candidates for up-front experimental therapies as efficacy of several drugs is diminished once mitotane is used due to increased drug metabolism [68].

Patients receiving mitotane with or without chemotherapy should be assessed at 2-month intervals for tumor progression. Patients who show tumor regression or stable disease should be considered for surgical resection or continuation of therapy. Patients with progressive disease should consider other chemotherapy regimens or be enrolled in a clinical trial. There are currently no established second- or third-line chemotherapy regimens for systemic disease. However, there are phase II trials of gemcitabine plus capecitabine, and this combination has shown response rates as high as 46 %. Treated patients had stable disease for more than 4 months. This combination might represent a promising second-/third-line regimen [73].

Patients should be considered for clinical trials if they have progressive disease with conventional treatment.

23.10 Radiotherapy

Radiotherapy is not routinely used in the treatment of ACC. Formerly ACC was considered radioresistant. However, recent retrospective data showed efficacy of RT both in adjuvant and advanced setting, although no prospective randomized trials exist. Older radiotherapy techniques had higher toxicity because of the proximity of the adrenal bed to radiosensitive organs such as the kidney, liver, spinal cord, and small bowel [74]. Conformal radiotherapy techniques resulted in better efficacy and less toxicity; nevertheless optimal dose delivery may not always be possible in every patient depending on anatomic extension of the tumor.

Adjuvant radiotherapy to tumor bed after surgical excision is a controversial issue in ACC. Fassnacht et al. reported outcomes of 14 patients from the German ACC registry who received adjuvant radiotherapy to the tumor bed with a matched control group of 14 patients who did not. Local recurrence was significantly lower in the radiotherapy group, 14 % compared to 79 % in the control group. Disease-free and overall survival, however, were not significantly different [75]. Sabolch et al. reported 4.7 times higher risk of local recurrence in patients with ACC who did not receive adjuvant RT, again with no difference in DFS or OS [76] compared to those who did. On the other hand, a recent report from MD Anderson Cancer Center showed no benefit of adjuvant radiotherapy compared with surgery alone

[77]; however radiotherapy indications were not uniform, and RT was applied in various community centers in this study.

Guidelines proposed by the German ACC consortium recommend adjuvant radiotherapy within 3 months of surgery for patients with microscopically involved or indeterminate resection margins and stage III disease regardless of resection status. In addition, radiotherapy should be considered for tumors greater than 8 cm, with a Ki-67 Index >10 % or invasion of adjacent vasculature [48].

In patients with locally advanced disease not amenable to surgical resection, definitive radiotherapy represents an applicable option [76]. Radiotherapy has been shown to effectively palliate symptomatic bone, brain, and inferior vena cava disease [48, 76, 78].

In conclusion, adjuvant RT in high-risk patients seems to reduce local recurrence rate without any improvement in DFS or OS. Definitive radiotherapy is an option in inoperable cases. Palliative radiotherapy may be used for symptomatic tumoral lesions.

23.11 Radiofrequency Ablation

Percutaneous image-guided radiofrequency ablation (RFA) is a minimally invasive and reasonable method for unresectable localized disease. Previous studies have shown that RFA can produce local control of primary ACC particularly for tumors less than 50 mm in size and is anatomically suitable. Among 8 patients with 15 ACC primary or recurrences, RFA resulted in decrease in tumor size or loss of enhancement on imaging in 53 % of patients. Smaller tumors had better response (<50 mm), with up to 67 % demonstrating complete ablation [79]. RFA, alone or in combination with surgical resection, may allow for better disease control in local and isolated systemic recurrences.

RFA is not an effective method of treatment in tumors near blood vessels as the vessels act as a "coolant" while RF ablation. Bleeding, infection, and injury to adjacent organs can occur. With advancing technology and growing experience, RFA has the potential to have a role in treatment options of recurrent and/or unresectable ACC in selected patients [78, 80].

23.12 Targeted Therapies

The results of studies with targeted therapies including antiangiogenic drugs, multityrosine kinase inhibitors, and epidermal growth factor receptor inhibitors are largely disappointing. Epidermal growth factor receptor (EGFR) is highly expressed in ACC; however the combination of erlotinib and gemcitabine in salvage treatment showed limited activity with low response rates [81]. Vascular endothelial growth factor (VEGF) is upregulated in ACC tumor tissue, but bevacizumab plus capecitabine also failed to show any benefit [82]. Although there are case reports of sustained clinical response with antiangiogenic drugs sunitinib or sorafenib, clinical

trials yielded disappointing results [83, 84]. Inefficacy of tyrosine kinase inhibitors in ACC may be secondary to significant interaction with mitotane, given the very long half-life of mitotane. Therefore, clinical trials using these drugs in first-line treatment (before mitotane) should be designed to overcome drug interaction.

Insulin-like growth factor 1 receptor (IGF-1R) is overexpressed commonly in ACC. A study of the oral tyrosine kinase inhibitor (OSI-906) which targets IGF-1R has shown promising results in phase I, with stabilization of disease seen in five out of 16 patients [85]. An international phase III trial of OSI-906 in patients with ACC has been recently completed and results are awaited (NCT00924989). mTOR is a downstream signaling node for a number of receptor tyrosine kinases including IGF-1R [86]; Fraenkel et al. studied an mTOR inhibitor, everolimus, as a single agent in salvage treatment of ACC, but there was no response. Inhibition of mTOR alone possibly leads to compensatory activation of other pathways, and this may limit the use of everolimus as a single agent for the treatment of ACC [87]. In a recent phase I trial, combination of everolimus with an IGF-1R antibody cixutumumab resulted in disease stabilization in 42 % of the patients for a minimum of 6 months [88]. This type of combinations warrants further clinical research.

Steroidogenic factor 1 is a nuclear receptor expressed virtually by all ACCs, and in vitro studies using inverse agonists of this receptor showed activity against ACC cell lines [89]. Heat shock protein inhibitors and proteosome inhibitors are other agents with promising in vitro study results [68].

Conclusion

In recent years, major progress has been made in understanding the pathogenesis and treatment of ACC. Molecular profiling studies in patients with ACC showed that ACC is a very heterogeneous disease. Exon-sequencing studies identified recurrent alterations in known driver genes and in genes not previously reported in ACC [23]. Chemotherapy does not seem to work but still needs further trials mototan treatment adjuvantly and in metastatic disease shows promising results. However, overall prognosis is still poor. International collaboration is needed to design translational research and prospective clinical trials. New insights into the pathogenesis of ACC and identification of potential "driver" pathways will highlight the opportunity for more personalized treatment strategies in the future.

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