Management of patients with adrenal cancer: recommendations of an international consensus conference

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Abstract

Adrenocortical carcinomas are rare, highly malignant tumors that account for only 0.2% of deaths due to cancer. Given the limited number of patients seen in most medical centers with this diagnosis, series usually reported are small and clinical trials not randomized or blinded. In an attempt to answer important questions concerning the management of patients with adrenal cancer, a consensus conference was organized and held at the University of Michigan in Ann Arbor, MI, 11–13 September 2003, with the participation of an international group of physicians who had reported on the largest series of patients with this disease and who had recognized basic and clinical research expertise in adrenal cortical cancer. Totally 43 questions were addressed by the presenters and recommendations discussed in plenary and breakout sessions. Evidence for the recommendations of this conference was at the 2–4+ level and based on available literature and participants' experience.

In addition to setting up guidelines in specific areas of the diagnosis and treatment of adrenal cancer, the conference recommended and initiated the planning of an international prospective trial for treatment of patients with adrenal cancer in stages III and IV. In terms of new therapies, first trials of dendritic cell therapy in human subjects with adrenal cancer have been started, but it is too early to comment on efficacy. Different strategies of immunotherapy, including DNA vaccination are currently being tried in animal models. There are no clinical gene therapy trials for human adrenal cortical cancer. The adrenals are a preferred target for adenovirus and the results of gene therapy in preclinical studies are promising. In addition, there is evidence that histone deacetylase inhibitors can further enhance the rate of adenoviral infectivity in human adrenal cancer cells. Testing of retroviral vectors, non-viral vectors, small interfering RNA technology, and combined approaches could be performed in various laboratories. Anti-angiogenic substances have only been applied in preclinical studies. The use of these and other agents in the treatment of adrenal cancer should be hypothesis-driven and based on a thorough analysis of tumor biology.

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Introduction

Adrenocortical carcinomas (ACCs) are rare, highly malignant tumors that account for only 0.2% of deaths due to cancer. Their incidence has been estimated at 2 per million people per year. Approximately 50% of these tumors are functioning and produce hormonal and metabolic syndromes leading to their discovery. The other 50% are silent and discovered only when they

attain a large size and produce localized abdominal symptoms or metastases. Occasionally children have been found to have ACC but most cases occur between ages 30 and 50 (Brennan 1987). An exception to this age distribution occurs in southern Brazil, where the annual incidence of ACC in children is unusually high, ranging from 3.4 to 4.2/million children, compared with a worldwide incidence of 0.3/million children younger than 15 (Figueiredo *et al.* 1999). The etiology

of adrenal cancer is unknown but molecular cytogenetic cloning studies in the past 5 years have described chromosomal abnormalities possibly associated with tumorigenesis (Lynch *et al.* 1985, Grayson *et al.* 1994, Lin *et al.* 1994, Reincke *et al.* 1994, Miyamoto *et al.* 1996, McNicol *et al.* 1997, Bornstein *et al.* 1999). While genetic defects may predispose to adrenal cortical tumor formation, environmental factors have been implicated in southern Brazil because the distribution of the tumors follows a regional rather than familial pattern.

There are multiple publications on the diagnosis and management of patients with ACC. However, there is no validation or evidence-based consensus on the diagnosis, prognosis and management of patients with this disease. Given the limited number of patients seen in most medical centers with this diagnosis, the series usually reported are small and clinical trials not randomized or blinded. In an attempt to answer important questions concerning the management of patients with adrenal cancer, a consensus conference was organized and held at the University of Michigan in Ann Arbor, MI, 11–13 September, 2003, with the participation of an international group of physicians who had reported on the largest series of patients with this disease and who had recognized basic and clinical research expertise in ACC. This report summarizes the main recommendations made during this conference.

Method

A list of questions was prepared and mailed to all invited participants for evaluation. Questions were modified or reformulated and additional questions added. The final questions were grouped into ten major categories as follows: (i) diagnosis; (ii) prognosis; (iii) surgical treatment; (iv) adjuvant therapy; (v) radiation therapy; (vi) emergent therapies; (vii) follow-up during treatment; (viii) adrenal cancer in children; (ix) metastatic disease; and (x) data collection.

Data collection

A literature review was carried out and relevant articles that reported on series of patients (not single case reports) were listed. These articles addressed the topics covered by the questions. Articles were assembled on a CD and mailed to all participants in anticipation of the conference. All participants were assigned a topic for discussion and were expected to specifically answer each question pertinent to the topic. Two or three participants were asked to address the same topic and questions. Presentations were limited to 20 min and

time was allowed for general discussion. Each day included breakout sessions at which participants were asked to formulate a consensus on the questions asked. This consensus became the conference preliminary recommendations. Final recommendations were agreed upon at a final plenary session.

Participants and program

The names of participants, their country of origin and topic covered are summarized in Table 1. The moderators and discussants for each section are listed with each category of questions.

Consensus recommendations

We summarize below the topics discussed by the conference and its recommendations. The recommendations are based on the assumption that upon suspicion of ACC, patients are referred to a medical center with appropriate expertise with this disease. The objective is to achieve definitive diagnosis including endocrinological and oncological staging and definitive initial surgery (open adrenalectomy) with curative intent. Evidence for the recommendations of this conference was based on available literature of non-randomized or observational studies and expert opinion of participants (evidence level 2–4+). References providing the background for discussion and recommendations are listed for each set of topics and when available, references are indicated for a particular one. Each session in which a specific set of topics was discussed had two moderators and two or three discussants.

Diagnosis

Moderators: Melvyn Korobkin, Milton Gross

Lead Discussants: Franco Mantero, Martin Reincke, Oscar Bruno

Determination if a unilateral adrenal mass is cancer in a patient without known primary tumor (Arteaga *et al.* 1984, Copeland 1984, Farge *et al.* 1987, Grondal & Curstedt 1991, Schteingart 1992, 2000)

The suspicion of ACC is raised by a combination of clinical, biochemical and radiological criteria and finally verified by histopathology. Approximately 50% of ACCs are functional, and Cushing's syndrome with virilization is the most frequent presentation.

The mean tumor size of ACC is 10 cm; 95% of ACC are larger than 5 cm. The prevalence of ACC in surgical series of adrenal incidentalomas is 2% in tumors

Table 1 Participants in the International Consensus Conference

Name	Specialty	Affiliation	City/Country
Ahlman, Hakan, MD.	Surgery	Goteborg University	Goteborg, Sweden
Aron, David, MD, MS	Epidemiology	Education Office	Cleveland, OH, USA
Barson, Luisa, MD	Histology, microbiology	University of Padova	Padua, Italy
Ben Josef, Edgar, MD	Radiology	University of Michigan	Ann Arbor, MI, USA
Beuschlein, Felix, MD	Endocrinology	Albert Ludwigs University	Freiburg, Germany
Bornstein, Stefan, MD	Endocrinology	University of Dusseldorf	Dusseldorf, Germany
Bertagna, Xavier, MD	Endocrinology	Hop Cochin	Paris, France
Bruno, Oscar, MD	Endocrinology	University of Buenos Aires	Buenos Aires, Argentina
Campbell, Karen, MS	Molecular biology	Cushing Support & Research Foundation	Pleasanton, CA, USA
Chrousos, George, MD	Endocrinology	NICHD, NIH	Bethesda, MD, USA
Doherty, Gerard, MD	Endocrine surgery	University of Michigan	Ann Arbor, MI, USA
Fassnacht, Martin, MD	Internal medicine	University of Wuerzburg	Wuerzburg, Germany
Fojo, Antonio, MD	Oncology	NCI, NIH	Bethesda, MD, USA
Gauger, Paul, MD	Endocrine surgery	University of Michigan	Ann Arbor, MI, USA
Giordano, Thomas, MD, PhD.	Pathology	University of Michigan	Ann Arbor, MI, USA
Grekin, Roger, MD	Endocrinology	University of Michigan	Ann Arbor, MI, USA
Gross, Milton, MD	Nuclear medicine	University of Michigan	Ann Arbor, MI, USA
Hammer, Gary, MD, PhD	Endocrinology	University of Michigan	Ann Arbor, MI, USA
Kandeel, Fuad, MD, PhD	Endocrinology	City of Hope National Medical Center	Duarte, CA, USA
Kasperlik-Zaluska, Anna, MD	Endocrinology	Bielanski Hospital	Warsaw, Poland
Kirschner, Lawrence, MD, PhD	Endocrinology	Ohio State University	Columbus, OH, USA
Korobkin, Melvyn, MD	Radiology	University of Michigan	Ann Arbor, MI, USA
Koch, Christian, MD	Endocrinology	NICHD, NIH	Bethesda, MD, USA
Kudelka, Andrzej, MD	Gynecology/medical oncology	University of Texas, MD Anderson	Houston, TX, USA
Lacroix, Andre, MD	Endocrinology	CHUM University of Montreal	Montreal, Canada
Latronico Ana, MD	Pediatric endocrinology	University of Sao Paulo	Ribeirao Preto, Brazil
Mantero, Franco, MD	Endocrinology	University of Padova	Padua, Italy
Montie, James, MD	Urology	University of Michigan	Ann Arbor, MI, USA
Norton, Jeffrey, MD	Surgical oncology	Stanford Cancer Center	Stanford, CA, USA
Reincke, Martin, MD	Endocrinology	University of Freiburg	Freiburg, Germany
Ribeiro, Raul, MD, PhD	Pediatric endocrinology	St Jude Children's Hospital	Memphis, TN, USA
Scheingart, David, MD	Endocrinology	University of Michigan	Ann Arbor, MI, USA
Shulkin, Barry, MD	Nuclear medicine	University of Michigan	Ann Arbor, MI, USA
Skogseid, Britt, MD	Endocrinology	University of Uppsala	Uppsala, Sweden
Starkman, Monica, MD	Psychiatry	University of Michigan	Ann Arbor, MI, USA
Stratakis, Constantine, MD, PhD	Genetics/endocrinology	NICHD, NIH	Bethesda, MD, USA
Terzolo, Massimo, MD	Internal medicine	University of Turin	Orbassano, Italy
Thompson, Norman, MD	Endocrine surgery	University of Michigan	Ann Arbor, MI, USA
Vassilopoulou-Sellin, Rena, MD	Endocrine oncology	University of Texas, MD Anderson Cancer Center	Houston, TX, USA
Worden, Francis, MD	Oncology	University of Michigan	Ann Arbor, MI, USA
Wolf, Stuart, MD	Urology	University of Michigan	Ann Arbor, MI, USA

<4 cm, 6% in tumors 4–6 cm, and 25% in tumors with a diameter >6 cm.

Imaging criteria indicating a high probability of adrenal adenoma have been defined for computed tomography (CT), magnetic resonance imaging (MRI), NP-59 scintigraphy and fluorodeoxyglucose (FDG) positron emission tomography (FDG-PET) (Hamper *et al.* 1987, Gross *et al.* 1988, Smith *et al.* 1989, Leshinen Kallio 1994, Korobkin *et al.* 1995, Juhlin *et al.* 1998, Yasuda *et al.* 2000, Yun *et al.* 2001).

The number of patients with ACC in imaging studies has been limited. Direct comparison of different imaging techniques for ACC is not available. Current criteria suggestive of a benign adenoma include attenuation values (expressed as Hounsfield Units) <10 HU on unenhanced CT, <30 HU on enhanced scans. Tumors with >10 HU include lipid-poor adenomas, pheochromocytomas, metastasis and ACC. Most of the data indicate that a 15 min delayed CT wash-out greater than 60% is suggestive of adenoma.

There is no evidence suggesting that MRI is superior to CT. MRI criteria for ACC are heterogeneous signal intensity on T1 and T2, peripheral nodular enhancement and central hypoperfusion on contrast MRI. MRI should be performed in large tumors prior to surgery to assess vascular invasion. Sensitivity, specificity, positive predictive value and negative predictive value for CT and MRI are around 90%.

Data for FDG-PET and adrenal scintigraphy are promising. Neither technique is widely available. Owing to the limited experience and high costs, FDG-PET is currently not routinely recommended.

**Indication for fine needle biopsy (FNB)
(Gaboardi *et al.* 1991)**

FNB is currently not indicated for the diagnosis of primary ACC because of poor differentiation from adenoma and the possibility that capsular breach could cause spillage of tumor cells into the surrounding tissues along the path of the needle.

FNB is indicated only in patients with a history of other cancers (particularly lung, breast, kidney), no signs of other metastases, and a heterogeneous mass with a high unenhanced attenuation value (>20 HU) after exclusion of pheochromocytoma.

Positive predictive value of histological and molecular markers (Weiss 1984, Cibas *et al.* 1990, Medeiros & Weiss 1991, Fetsch *et al.* 1999)

Histopathological assessment should follow current guidelines. ACC should be suspected in tumors with a Weiss score > 2.

Histological algorithms, such as those of Weiss, Hough and van Sloten, have high negative and positive predictive values for the diagnosis of ACC. According to these criteria, a Weiss score (0–9) was determined for each patient, according to the presence or absence of the following nine histological features: (i) high mitotic rate; (ii) atypical mitoses; (iii) high nuclear grade; (iv) low percentage of clear cells; (v) necrosis; (vi) diffuse architecture of tumor; (vii) capsular invasion; (viii) sinusoidal invasion; and (ix) venous invasion. The three most commonly found are a mitotic rate greater than 5 per 50 High Power Field (HPF), atypical mitotic figures and venous invasion. The mitotic rate is an important criterion not only for distinguishing malignant from benign tumors but also for predicting clinical virulence of ACCs. Patients with carcinomas with a high mitotic rate (more than 20

mitoses per 40 HPF) have a shorter disease-free survival period as compared with those with low mitotic rates (less than 20 mitoses per 40 HPF).

Immunohistochemical markers, such as Ki67, are additionally helpful to confirm malignancy and, like D11, melan A and chromogranin A to define or exclude the adrenocortical origin of the tumor. Molecular markers are promising new tools for the diagnosis of ACC and may predict prognosis. To date, the data are preliminary, and cannot be recommended for routine use.

Value of the four-stage MacFarlane classification modified by Sullivan (MacFarlane 1958, Sullivan 1978)

The MacFarlane classification provides a useful staging system which allows pre-operative stratification of the patients and predicts prognosis. Table 2 shows the MacFarlane classification as currently framed.

However, the prognosis of ACC patients with stage I and II disease is not different. This has suggested the need for a different staging classification. The modification proposed by Icard (1992) and Lee (1995) suggests restricting stage IV disease to patients with distant metastases. In addition, stage III could be subcategorized as local or regional.

The MacFarlane/Sullivan classification should be revised to include more precise prognostic implications.

Table 2 The MacFarlane classification as currently framed

Stage	Size	Lymph nodes	Local invasion	Metastases	TNM
I	<5 cm	–	–	–	T ₁ N ₀ M ₀
II	>5 cm	–	–	–	T ₂ N ₀ M ₀
III	Any size	+	+	–	T _{1,2} N ₁ M ₀
IV	Any size	+	+	+	T _{1,2} N ₁ M ₁

Prognosis (Bradley 1975, King & Lack 1979, Hogan 1980, Didolkar *et al.* 1981, Thompson 1983, Bodie *et al.* 1989, Venkatesh *et al.* 1989, Luton *et al.* 1990, Kasperlik-Zaluska 1994, 1995, Wajchenberg *et al.* 2000, Schteingart & Homan 2001)

Moderators: Gerard Doherty, Thomas Giordano
Lead Discussants: Xavier Bertagna, Luisa Barzon, Andrejz Kudelka

Recommended criteria for determining prognosis (Weiss *et al.* 1988)

Size of tumor (largest diameter on CT or MRI) gives an estimate of tumor burden. A large tumor burden (>12 cm) is associated with poor prognosis. Localized disease at diagnosis and complete tumor resection at any stage offers the best prognostic advantage, since no effective medical therapy is available for ACC.

Histological and molecular markers of cell proliferation may predict tumor behavior.

Clinically and/or histologically oriented parameters (gender, age, tumor secretory status) are clearly second-choice predictors that are often also described. It is possible that older age and cortisol or aldosterone hypersecretion contribute to unfavorable prognosis, whereas androgen hypersecretion may be associated with a more favorable outcome. Non-functioning tumors have been associated with longer survival in some series.

Relative value of histology, molecular markers, stage of the disease for determining prognosis (Weiss 1984, Cibas *et al.* 1990, Medeiros & Weiss 1991, Fetsch *et al.* 1999)

Precise tumor pathological examination by expert pathologists provides some highly reliable prognostic factors; among them a Weiss score >3 or mitotic index >6/10 HPF (intratumoral hemorrhage or necrosis and lymph–vascular invasion are independent prognostic factors).

A number of molecular markers have been studied that are associated with malignancy. Among them, IGF-II overexpression, Uniparental Paternal Disomy (UPD) for 11p15, Loss of Heterozygosity (LOH) for 17p13 and Topoisomerase (TOP)2A overexpression, are particularly promising as independent markers for malignancy. However, for most of the markers, their prognostic value has not been validated in prospective studies. In one study, LOH at 17p13 was shown to be an independent predictor of tumor recurrence after ‘curative’ surgery of stage I/II tumors.

Staging is the most important and better-validated prognostic factor. It requires thorough assessment at surgery to identify stage (I, II, III), as well as the modern imaging studies that can be performed pre-operatively (CT, MRI, PET scan) to identify or rule out distant metastases (stage IV).

Way of predicting patients who will have aggressive disease from those in whom the disease will follow an indolent course (Bradley 1975, Hogan 1980)

Tumor staging and pathological features are the best predictors of disease outcome.

Molecular markers are associated with aggressive tumor phenotype, but further studies are needed to assess their prognostic value and utility to predict responsiveness to therapy.

How does prognosis affect choice of therapy: chemotherapy, surgery, radiation (Bradley 1975, King & Lack 1979, Hogan 1980, Thompson 1983, Bodie *et al.* 1989, Luton *et al.* 1990, Dickstein *et al.* 1999)

Patients with presumed stage I/II tumors will always be offered surgery. Following tumor removal at first operation, a definite staging should be assessed, as well as detailed pathological assessment of the tumor (Weiss score, mitotic index).

In the case of residual tumor, further local–radio-frequency ablation (RFA), irradiation or systemic (chemotherapy) should be considered.

In the case of ‘complete’ resection, the recurrence risk should be assessed (Weiss score, mitotic index); follow-up is mandatory and adjuvant therapy (mitotane, irradiation) can be considered but its value still needs to be validated.

Surgical resection should be considered for relapses in highly selected patients with excellent performance status and symptomatic (i.e. from hormone hypersecretion), loco-regional recurrence or isolated distant metastases if complete resection can be achieved.

Surgical resection is rarely indicated if there is a probability of only incomplete resection or in the presence of unresectable, distant metastatic disease.

Adjuvant mitotane may not improve disease-free and overall survival in ACC, but there are reports indicating that early administration of mitotane after surgery may improve overall survival. Definitive studies are lacking.

Mitotane may lead to tumor regression in some cases of stage III/IV disease. New chemotherapy protocols based on tumor biology are needed. Radiation can be palliative for bone metastases.

Assessment of prognosis and selection of further therapy when first and second-line therapy fail

Complete tumor resectability should always be assessed. Resectability of recurrent tumor masses is the feature associated with better prognosis after primary therapy fails.

The patient’s age does not influence prognosis, even though longer survival in younger patients has been reported.

Further medical therapy should be based on tumor biology. No reliable molecular markers are yet available, but progress should come from new techniques aimed at assessing the 'molecular signature' of a given tumor. It could improve our ability to predict: (i) survival; (ii) risk of recurrence after 'complete surgical removal'; and (iii) the eventual response to chemotherapy.

Surgical treatment (Thompson 1983, Bodie et al. 1989, Jensen et al. 1991, Icard et al. 1992, 2001, Pomier & Brennan 1992, Schteingart 1992, Bellantone et al. 1997, Peix et al. 1998, Munver et al. 2003)

Moderators: Norman Thompson, James Montie
Lead Discussants: Hakan Ahlman, Jeff Norton

Place for laparoscopic surgery in the resection of primary malignant lesions

There is no role for laparoscopic removal of a known or likely ACC but there is controversy on the role of laparoscopic removal of indeterminate incidentalomas that could admittedly be small ACCs.

While the benefits of laparoscopic adrenalectomy are clear, and will be provided to many patients, the negative influence of laparoscopic surgery for ACC is not yet fully appreciated and will potentially affect few patients.

Selection of patients with an indeterminate incidentally discovered adrenal mass for laparoscopic or open adrenalectomy

Consideration should be given to the recommendations of the NIH State of the Science Conference on the Adrenal Incidentaloma:

- Remove by an anterior approach any lesion >6 cm or with clear imaging characteristics of malignancy (indistinct borders/unclear relationship to surrounding organs/obliteration of fat planes), unenhanced density >10 HU (relative), 15 min delayed enhancement washout <60%, absence of signal intensity loss on out-of-phase MRI or non-visualization on NP-59 (if available).
- Consider a laparoscopic approach for resection of 4–6 cm lesions if there are no suspicious imaging characteristics.
- Convert from the laparoscopic to the open approach if there is any evidence of malignancy at exploration, including local invasion or metastasis.

Extent of surgical approach

One should plan a feasible operation to provide for gross total removal without capsular breach. For patients in stages II and III, concomitant resection of kidney, liver, spleen, pancreas, stomach, colon and wall of the vena cava should be considered if indicated because of direct tumor extension to those structures, if it is feasible and safe.

The threshold for en bloc resection of the kidney should be low for any patient in whom there is a concern about involvement of the renal capsule or renal vein.

Indication of surgery for resection of metastatic disease (stage IV)

If complete resection of primary and metastases is feasible at initial operation, it should be done (even if done in two stages). If it is anticipated that >90% of the tumor burden can be removed, an operation should be considered. However, there are no convincing data to indicate what percent of tumor burden needs to be removed in order to make surgery worthwhile.

If debulking would amount to limited tumor removal, it should not be done, unless it will clearly palliate a severe hormonal syndrome or facilitate successful RFA.

Indicators of tumor biology (e.g. long disease-free interval, slow progression) should be used to individualize decisions. Histological indicators of tumor malignancy (low grade vs high grade) could be considered in making individual decisions but definitive data are lacking.

Adjuvant therapy (Martz & Straw 1977, Bates et al. 1991, VanSeters & Moolenaar 1991, Pomier & Brennan 1992, Schteingart et al. 1993, Vassilopoulou-Sellin et al. 1993, Wooten & King 1993, Haak et al. 1994, Kasperlik-Zaluska 1994, Cai et al. 1995, Pinerio-Sanchez et al. 1995, Terzolo et al. 2000, Munver et al. 2003)

Moderators: David Schteingart and Frank Worden
Lead Discussants: Rena Vassilopoulou Sellin, Anna Kasperlik-Zaluska

Treatment of patients in stages I and II: surgery alone or surgery plus adjuvant chemotherapy (Kasperlik-Zaluska 1994, Percarpio & Knowlton 1976)

The benefit of adjuvant therapy has not been established. However, published reports suggest benefit

of low-dose mitotane therapy following surgery for primary tumor. Prospective, randomized clinical trials are recommended (see below). Malignancy grade should not determine use of adjuvant treatment because treatment may be effective in low grade or high grade malignancy.

Types of drugs to use; mitotane vs other drugs

There is no well-controlled head-to-head comparison studies of mitotane and other drugs used as adjuvant therapy. There is a need to perform prospective, randomized trials with mitotane first and to select additional agents for study afterwards.

Prediction of response to mitotane from *in vitro* assays (Martz & Straw 1977, Schteingart *et al.* 1993, Cai *et al.* 1995, Pineiro-Sanchez *et al.* 1995)

There is the potential use of tests such as a tritium release assay to determine the ability of tumor tissue to metabolize mitotane. The ability to metabolize mitotane and covalently bind the metabolite may determine the adrenalytic effect of the drug. However, there are no definitive clinical studies to determine if this test can predict response. Prospective studies of this type could help answer this question.

Utility of mitotane levels in following patients on adjuvant therapy (VanSeters & Moolenaar 1991, Haak *et al.* 1994, Terzolo *et al.* 2000)

Mitotane levels should be obtained during treatment and dose should aim for levels of 14–20 µg/dl if tolerated (see guidelines for mitotane use below).

Since mitotane needs to be metabolized for adrenalytic activity, measurement of urinary metabolites could be used in assessing the therapeutic dose. However, there are no studies to confirm the utility of such measurements.

Guidelines for mitotane use (Haak *et al.* 1994)

The usually tolerated dose is 3.0–4.0 g/day. However, use serum levels and patient tolerance to determine optimal dose. Aim for 2 years but treat longer if patient is doing well.

A recommended protocol for mitotane use is as follows:

- Begin with 2 g/day and advance to achieve serum levels of 14–20 µg/dl (4–6 g/day). The target blood level may be unattainable because of side effects, in which case one should adjust the dose to tolerance.

- Monitor patients clinically and by measuring adrenocorticotropin (ACTH)/Urinary free cortisol (UFC)/electrolytes.
- Adjust the dose of cortisol replacement to assure adequate adrenal replacement. Patients may need a higher dose of cortisol if they present with gastrointestinal side effects.
- Monitor and correct as needed thyroid function, serum testosterone and lipids.
- Provide vigorous anti-emetics/other support.

A role for non-mitotane-based adjuvant regimens?

There are no data to support a specific protocol. Consideration should be given to a co-operative, multicenter clinical trial:

- Prospective, randomized, two- (or three-) arm trial depending on size calculations.
- Surgery alone vs surgery + mitotane (vs surgery + mitotane + streptozotocin).
- Active therapy for 2 years, then follow-up for 2–3 years.
- Primary outcome: time to first recurrence.
- Assume 50% recurrence in 2 years; calculate trial size for 50% improvement with adjuvant therapy.

Radiation therapy (Percarpio & Knowlton 1976, Magee *et al.* 1987, Haak *et al.* 1994, Wood *et al.* 2003)

Moderator: Melvyn Korobkin, Barry Shulkin
Lead Discussants: Edgar Ben Josef, Antonio Fojo

Indications for local radiation therapy: (i) after initial tumor resection and (ii) after local tumor recurrence post-surgery

There are very few data in the medical literature documenting efficacy of radiation therapy in ACC. Limited available data and anecdotal reports suggest that radiation therapy is probably as effective in ACC as in the majority of other solid tumors. As with other solid tumors, radiation therapy is recommended in the treatment of bone, brain and other metastases. Radiation therapy is also recommended in the treatment of symptomatic local recurrences.

While in other solid tumors radiation therapy is routinely recommended to provide local control, the use of radiotherapy for asymptomatic, unresectable local recurrences is controversial. The risk/benefit ratio should be individually assessed.

Radiation treatment of the adrenal bed can be administered to a patient with an incomplete local resection or after a local recurrence. The latter should not replace surgery, especially in a patient without evidence of other sites of disease, but rather, could be used post-operatively as an adjunct to surgery.

Efficacy of Radio Frequency Ablation (RFA) of local recurrence or hepatic metastases (Haak et al. 1994, Wood et al. 2003)

RFA offers an alternative to surgery in some patients with metastatic adrenocortical cancer but its utility and value remain to be proven.

RFA can be considered in the treatment of lesions less than 5–6 cm in size that are not near indispensable tissues or large blood vessels.

Metastatic disease (Hogan 1980, Nader et al. 1983, Johnson & Greco 1986, Brennan 1987, Bodie et al. 1989, Luton et al. 1990, Pomier & Brennan 1992, Schteingart 1992, Schlumberger et al. 1995, Beruti et al. 1998, Khan et al. 2000, Williamson et al. 2000)

Moderators: Frank Worden, Barry Shulkin
Lead Discussants: Martin Fassnacht, Britt Skogseid, Massimo Terzolo

Role of FNB and PET in evaluating metastatic lesions

In general, FNB is not needed. Because of its wide availability and physical characteristics, FDG is currently the best PET tracer to evaluate ACC. Sensitivity and specificity still need to be evaluated in a larger cohort of patients with adrenal tumors.

Adrenocortical-specific tracers (metomidate) are under investigation for clinical practice.

Regimens that should be offered as first-line therapy

The evidence regarding efficacy of first-line therapy is very limited (level C). Possible protocols are:

- Etoposide + doxorubicin + cisplatin + mitotane
- Streptozotocin + mitotane
- Mitotane alone or platin + etoposide + mitotane

All protocols with mitotane should also include replacement with cortisol and fludrocortisone (if aldosterone deficiency is evident).

Regimens that should be offered as second-line therapy

Regimens that should be offered as second-line therapy are: (i) treatment not used as first-line; and (ii) those not validated by controlled studies (limited studies or anecdotal responses): streptozotocin + mitotane, taxotere + gemcitabine, taxol + doxorubicin.

Emerging therapies

Influence of tumor biology on therapy

Moderators: Thomas Giordano, Gary Hammer
Lead Discussants: Constantine Stratakis, Lawrence Kirschner

Role of gene array data in determining clinical behavior of adrenal cancer

There is a potential role for gene array data to be used in predicting behavior, prognosis, choice of and response to therapy. This is based on recent preliminary data that identified certain signaling pathways are highly correlated with histology of the tumor (e.g. IGF-II). This should be pursued by: (i) development of quality resources through multinstitutional programs but centralized through main referral centers database coordination; (ii) ensuring the quality of the collected tissue and its processing; and (iii) development of molecular criteria that will group tumors into diagnostic groups and the software that will take these into account.

Role of secreted factors (ACTH, corticotropin-releasing hormone, IGF-II, inhibin, etc) in the development and growth of adrenal carcinoma

IGF-II is the leading growth factor associated with malignancy in adrenocortical tissue, but its causal association with other prognostic factors (metastasis, response to treatment) is not known but probable.

The differential effects of ACTH vs additional proopiomelanocortin (POMC)-derived peptides (e.g. N-terminal fragment of POMC) on adrenocortical tissue is an area of active research.

There are no good data for other secreted factors and their respective signaling pathways and their effect on prognosis and management, although currently they are under intense investigation.

Recent microarray and secreted factor data have not been applied in treatment decisions. However, microarray data looking at particular signaling pathways hold great potential for target identification and in the future, determining response to treatment. This technology will eventually lead to the development of

specifically designed therapies tailored to each tumor's (or tumor group) molecular signature.

New therapies

Moderators: Frank Worden, Gary Hammer

Lead Discussants: Stefan Bornstein, Tito Fojo, Felix Beuschlein

New chemotherapeutic drugs: available protocols and response

There are no controlled clinical trials with new chemotherapeutic agents for adrenocortical cancer. Studies involve small case series, single-patient trials and anecdotal unpublished communications. Compounds that have been used include established chemotherapeutic agents for treatment of other solid tumors, as well as more recent compounds, used in single cases. These agents include streptozotocin, gemcitabine, navelbine, docetaxel and taxol. The best evidence is for streptozotocin. However, available evidence does not allow for any conclusions on the efficacy of these agents in ACC.

Prospects for immunotherapy and gene therapy

Tumor immunotherapy with dendritic cells is currently used in a variety of human cancers. This therapy holds promise, but it is still experimental. First trials in humans with adrenal cancer applying dendritic cell therapy have been started, but it is too early to comment on efficacy. Different strategies of immunotherapy, including DNA vaccination are currently being tried in animal models.

There are no clinical gene therapy trials for human adrenal cortical cancer. There are studies using different approaches of cytotoxic adenoviral gene therapy in human adrenocortical cancer cells *in vitro* and in human adrenal cancer xenografts in mice. The adrenals are a preferred target for the adenovirus and the results in preclinical studies are promising. In addition, there is evidence that Histone deacetylase (HDAC) inhibitors can further enhance the rate of adenoviral infection in human adrenal cancer cells.

Testing of retroviral vectors, non-viral vectors, Small interfering RNA (siRNA) technology and combined approaches could be performed in various laboratories.

Role of anti-angiogenic drugs, small molecules and antibody strategies

There is currently a multicenter trial employing gefitinib (Iressa), which inhibits the intracellular phosphorylation of numerous tyrosine kinases associated

with the epidermal growth factor receptor. There have been single trials with thalidomide. Anti-angiogenic substances have only been applied in preclinical studies.

Systematic testing of small molecule therapies (e.g. tyrosine kinase inhibitors) on adrenal cortical cancer cell lines may be attempted in collaboration with pharmaceutical companies. The use of these and other agents in adrenocortical cancer should be hypothesis-driven and based on a thorough analysis of adrenocortical tumor biology.

Follow-up of patients during treatment (Schteingart *et al.* 1966, Contreras *et al.* 1985, La Rocca *et al.* 1990)

Moderators: David Schteingart, Melvyn Korobkin

Lead Discussants: Andre Lacroix, Fuad Kandeel, Christian Koch

Follow-up of patients after initial surgery

Immediate post-operative care

Required for hormone-secreting tumors. Hypothalamic–pituitary–adrenal axis function should be evaluated to assure adequate glucocorticoid replacement status.

The tumor hormone profile should be re-evaluated to assess the completeness of surgical resection. Treatment should be adjusted for related co-morbid conditions such as diabetes mellitus, hypertension, hypercoagulable state, etc. Appropriate therapies should be instituted in order to restore physiological ranges of adrenal hormones in patients with incomplete tumor resection.

Long-term care of patients with hormone-secreting tumors

In patients with complete tumor resection, evaluation of endocrine markers for disease recurrence should be performed every 3 months including cortisol (urinary free cortisol, evening salivary cortisol, or an overnight 1 mg dexamethasone suppression test), androgens (dehydroepiandrosterone sulfate, androstenedione, testosterone), 17-hydroxyprogesterone and/or 11-deoxycortisol, based on pre-operative hormonal profile.

In patients with incomplete tumor resection, adjustment and/or institution of appropriate therapies are needed to maintain adrenal hormones within the physiological range and to adjust for changes in hormone secretion profiles.

Frequency of imaging

An enhanced CT scan of chest and abdomen is recommended every 3 months for 1 year post-operatively, followed by repeat scans every 3–6 months for 5 years and at least annually thereafter if there is no evidence of tumor recurrence.

Bone scans and brain MRI should be based on symptoms.

PET is a promising tool that is currently under clinical investigation and should not yet be considered a standard of care in patient follow-up.

Sensitivity of hormonal/humoral markers vs imaging findings

No data are currently available to answer this question. All patients should be followed with anatomical imaging studies regardless of tumor hormone status.

Adrenal cancer in children (Teinturier *et al.* 1996, Ribeiro *et al.* 2001)

Moderators: Frank Worden, Paul Gauger

Lead Discussants: Ana Latronico, Raul Ribeiro

Difference in the course of adrenal cancer in children and adults

Tumors in children are more hormonally functional and there is a relatively low frequency of non-functioning tumors (incidentally discovered).

Virilization is the most frequent clinical manifestation (70%), followed by mixed endocrine syndrome and Cushing's syndrome. Hyperaldosteronism and feminization occur rarely.

ACC in children may be associated with genetic cancer syndromes. Brazilian children with ACC tumors present the p53 mutation Arg337His in high frequency (78–97%). Evidence of LOH was demonstrated in 90% of the children, including the p53 locus, as well as the entire chromosome 17.

The established criteria for distinguishing benign from malignant adrenocortical tumors in the adult population have not been helpful in predicting the biological behavior in the pediatric population. Patients with histologically malignant appearing tumors do well, often better than their adult counterparts.

Features associated with worse patient outcome are metastatic and recurrent disease and extension into periadrenal soft tissue and/or surrounding organs and invasion into the vena cava. Features associated with high probability of malignant behavior are:

- Histology
 - >400 g (higher weight is predictive of patient outcome)
 - >10.5 cm: Confluent necrosis with severe nuclear atypia and frequent and atypical mitoses
- Age: Younger children (<5 years) have a significantly better prognosis than older children and adolescents whose tumors present similar behavior to adults

Molecular defects do not predict the biological behavior of the tumor.

Recommended course of therapy

- Surgical
 - Adrenalectomy
 - Adrenalectomy + nephrectomy
 - Adrenalectomy + partial hepatectomy
 - Adrenalectomy + splenectomy
 - Resection of intracaval thrombus
- Medical
 - Mitotane
 - Alternative chemotherapy regimens
- Radiation therapy

Recommended follow-up

Hormonal monitoring every 2 months in the first year, followed by monitoring every 4 months in the second year and every 6 months from then on.

Imaging studies are indicated only in the presence of hormonal abnormalities.

Local recurrence and isolated metastases should be resected.

Data collection

Moderators: Paul Gauger, David Schteingart

Lead Discussants: David Aron, Thomas Giordano

Goals for developing an adrenal cancer registry and an inter-institutional database

Development of an adrenal cancer registry and an inter-institutional database could meet multiple goals:

- They could facilitate the improvement of quality of care for patients with adrenal cancer by providing the data that underlie the evaluation and improvement of treatment regimens as well as the development and implementation of guidelines and protocols.

- A registry can provide the data to answer epidemiological questions, e.g. the frequency of, causes of, and survival from adrenal cancer.

Existing registries

There are currently several adrenal cancer registries in Europe and the United States, many of which are multi-institutional. These include NISGAT (National Italian Study Group on Adrenal Tumors), COMETE (CORTico-MEdullo surrénale Tumeurs Endocrines), in France, and GANIMED (German Adrenal Network Improving Medical Research and Education), the University of Michigan, and others.

Barriers to developing a database

Barriers to merging data include different elements, different data definitions, and regulatory issues, among many others. However, some have already established a collaborative network: the European Network for the Study of Adrenal Tumors, which includes the three networks above and representatives from the UK, Greece and other countries.

However, there is precedent for collaboration for research and improvement in oncology. The Pediatric Oncology Group conducted sequential outcomes analysis of >7000 with rare forms of cancer (diagnoses from 1976 to 1989) from clinical trials, with constant eligibility and high participation rates. Collaboration gave statistical power and working from a unified database, significant improvement in outcome occurred in most of the diseases studied. Adrenal cancer is rare, but the group of clinicians dealing with such patients is broader than in pediatric oncology.

Ideally, there should be financial resources to convene an expert panel to design a registry and to ensure uniform data collection. However, certain steps can be taken now. For example, data dictionaries could be shared to assess the degree of commonality. Along with the creation of a Website outlining a minimum data set, this step could encourage movement towards standardization.

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