

The Cushing's Syndrome Newsletter is a half-yearly publication reporting on a number of recent important events and provides up-to-date information on Cushing's Syndrome and Adrenal Cortical Carcinoma, published by John-Libbey-Eurotext. © 2008.



Introduction

The 2nd annual *International Adrenal Cancer Symposium*, hosted by Gary Hammer and the adrenal cancer program of the University of Michigan (USA), was held on March 14-15, 2008. The symposium was attended by many clinical and basic scientists in the field of adrenal cancer.

Surgical Decision Making

J. Lee from the Anderson Cancer Centre, S. Libutti from NIH and G. Doherty, University of Michigan (USA), discussed the role of surgery in adrenocortical carcinoma (ACC). Surgery is the only curative therapeutic option of ACC and of great prognostic value. Open laparotomies when combined with the skillness of the surgeon are two critical points making the quality of this therapeutic option, as reported by J. Lee. Indeed, completeness of surgery has been shown to be a pivotal prognostic parameter and was emphasised by several groups. It was stressed that

differences in quality and completeness of surgery may be primarily responsible for differences in ACC recurrence rates. It is important therefore that the primary surgery is performed in a specialist referral centre. Due to the risk of peri-operative rupture of tumor

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and spillage of tumor cells, it is still strongly advised to perform an open procedure in cases of large tumors, for malignancy suspected lesions. Indeed, it is suggested that open adrenalectomy should remain the standard of care. If surgery is considered appropriate to treat small unsuspected adrenal lesions, then consideration of laparoscopic techniques may be suggested. ● ● ●

In Short

- **Surgical Decision Making: the role of surgery in adrenocortical carcinoma (ACC).**
- **What is the role of nuclear imaging in ACC diagnosis? 24% of suspect lesions on CT were not seen on PET; 22% of lesion on PET were not seen on CT.**
- **Molecular carcinogenesis and murine models of ACC... By utilizing this animal model, further analysis might delineate novel genetic mechanisms of adrenal carcinogenesis.**
- **How to improve treatment response? One way to improve efficacy of drugs is to better characterize predictors of response.**

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● ● ● Surgical Decision Making

The intermediate sized tumors (max 6 cm) may be operated by laparoscopy in experienced hands. Conversion to open procedure is necessary when the tumor invades adjacent organs and tissues. Multi-organ resection may be required in patients with ACC. More than one-third of ACC first surgery involved additional procedures including adjacent organs resection. Lymph node dissection is still considered an optional strategy by the same team taking into considerations the low number of positive lymph nodes (10%) at initial surgery together with the scarcity of lymph node recurrences.

Surgery in ACC may also apply in case of recurrence or in the metastatic setting as reviewed by S. Libutti from NIH (USA). In these two clinical conditions the ability to achieve a complete remission remains crucial in the final therapeutic decision. Additionally, in metastatic ACC patients, response or at least stabilisation under chemotherapy may help to select patients for surgery as suggested by the same author.

Neo-adjuvant chemotherapy, and even embolization or radiotherapy to shrink tumor pre-operatively may be of benefit for disease control.

abdominal lesions. [¹¹C]Metomidate, specifically binding to adrenal CYP11B enzymes, as PET transducer has a high sensitivity (0.89) and specificity (0.96) in proving adrenal lesions in a German series. O. Lindhe, Uppsala University (Sweden), showed excellent visualization of metastasized ACC with Metomidate PET. [¹²³I]Iodometomidate as a SPECT tracer for scintigraphy, proves specifically to accumulate in adrenocortical tissues, benign and malignant. [¹²³I]Iodometomidate may prove to be useful in the future not only in diagnosing and staging of ACC, but also in delivering targeted therapy.



Molecular profiling of Adrenocortical Carcinoma

As presented by J. Bertherat, Cochin Institute Paris (France), and T. Giordano, University of Michigan, (USA), gene expression profiling of adrenocortical tumor specimen can be utilized to readily distinguish between benign and malignant tumor entities using a cluster of genes related to IGF dependent action and steroidogenic properties, respectively. Interestingly, within the group of ACC patients, subgroups could be identified with a more malignant and a more benign clinical course that was associated with a distinct gene profile. Collectively, these results provide insights into the biology and pathology of adrenocortical tumors and might provide clues for new therapeutic strategies.

In the context of the German ACC registry concomitant collection of paraffin embedded tissue has enabled the colleagues of B. Allolio, University of Würzburg (Germany), to establish a significant number of tissue microarrays from clinically well annotated patients. Based on these tissue arrays expression of the EGF receptor was quantified and correlated with clinical outcome data within the patient cohort. These experiments, however, did not reveal a significant correlation with overall survival. In contrast, expression studies of ERCC1

What is the role of nuclear imaging in ACC diagnosis?

S. Hahner, University of Würzburg (Germany), discussed the role of nuclear imaging in ACC diagnosis. [¹⁸F]FDG PET has proved to be of great value as additional imaging modality in combination with CT/MRI. 24% of suspect lesions on CT were not seen on PET; 22% of lesion on PET were not seen on CT. Sensitivity of FDG PET is low for the diagnosis of small lesions < 1cm, particularly lung metastases. FDG PET is of value for early detection of local relapse and other

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which has been reported to predict resistance to platinum based chemotherapies was applied in this ACC cohort. Interestingly, expression was significantly associated with survival in patients with platinum compounds in a univariate and multivariate analysis.

In an attempt to identify mechanisms of treatment response (TGen initiative) M. Demeurere from the Arizona Cancer Center (USA) reported on new screening approaches utilizing chip based comparative genomic hybridization (CGH) which allows detection of genetic gains and losses in individual ACC specimen. To further increase the sensitivity of the method, the group chose to apply a sorting strategy with enrichment of aneuploid tumor cells which resulted in detection of more tumor specific CGH profiles. Furthermore, a siRNA screening approach was applied to identify gene products that are required for adrenolytic therapy. Overall, these experiments might have the potential to systematically approach a more targeted therapy which could be adapted to an individual patient's tumor.



How to improve treatment response?

One way to improve efficacy of drugs is to better characterize predictors of response. Cisplatin is considered the most active cytotoxic chemotherapy in ACC and ERCC1 has been reported to predict the resistance to platinum compounds. B. Allolio, University of Würzburg (Germany), reported promising preliminary results showing a 14% to 29% shift of objective responses to platinum in ERCC1 positive or negative patients, respectively.



Molecular carcinogenesis and murine models of ACC

According to recent research from L. Barzon, University of Padova (Italy), although virus infections seem not to have a major role in adrenocortical tumorigenesis, they could serve as cofactors in modulating proliferative and functional properties of adrenal tumors. Moreover, viral vectors will provide important tools for delivering of genetic material in experimental settings and for potential future gene therapy applications. Recent evidence from a mouse model with a mutation in a telomerase complex member (Tpp1/Acd) demonstrates an increase in senescence-associated markers in adrenocortical cells. Conversely, the vast majority of human adrenocortical samples could be assigned to telomere maintenance mechanisms either through telomerase activity or paradoxically telomere lengthening. Taken together, these data, presented by T. Else, University of Michigan (USA), provide evidence that telomere dysfunction has an important impact in adrenal tumorigenesis and function.

As presented by I. Huhtaniemi, Imperial College London (UK), linkage analysis from backcrosses of inbred mouse strains with high and low incidence of gonadotropin dependent adrenal tumorigenesis revealed a major significant locus for the tumorigenesis on chromosome 8 and another on chromosome 18. Although the underlining genes have not been identified so far, analysis of candidate genes in the loci demonstrated that the tumor suppressor gene Sfrp1 is differentially expressed in the neoplastic areas. By utilizing this animal model, further analysis might delineate novel genetic mechanisms of adrenal carcinogenesis.

« **Telomere dysfunction has important impact in adrenal tumorigenesis and function** »



ACC international Networks

As a first step towards an appropriate therapeutic management of ACC, several national networks are engaged in the process of defining a better prognostic stratification of patients with ACC. M. Fassnacht from the University of Würzburg (Germany) demonstrated the power of large clinical registries in identifying and validating prognostic factors for rare diseases like ACC. M. Fassnacht reported the preliminary results of *the German Adrenal Cancer Registry* with 450 ACC patients and in collaboration with the ENS@T network. A better discriminating staging system was proposed by classifying patients as stage III in case of local, venous or lymph node tumor spread; stage I-II being defined by intra adrenal ACC and stage IV by ACC with presence of distant metastases.

The prognostic role of mitotic index, whatever the stage, was recalled by the same group but also M. Papotti, University of Turin Medical School (Italy), reporting the results from the group in Turin. Finally additional prognostic parameters were discussed including, loss of p53 function and clusters of genes proposed by J. Bertherat and T. Giordano, respectively.

C. Rodriguez-Galindo from the St. Jude Children's Research Hospital, Memphis (USA) described the cooperation in the Children Oncology Group and several Brazilian institutes. An *International Pediatric Adrenocortical Tumor Registry* (IPACTR) as well as a prospective protocol is developed by this network. This study aims to investigate the effect of surgery and chemotherapy, and will provide further insight in the biology of ACC in children.

M. Skogseid, Uppsala University Hospital (Sweden) presented an update on the recruitment rate in the First International Randomized trial in locally advanced and Metastatic Adrenocortical Carcinoma Trial (FIRM-ACT). In this first randomized, multicentre study, 185 patients were included so far from 9 countries. A total of 300 patients is needed and is expected to be reached in 2009. From this collaboration various other cooperative initiatives arise such as adjuvant therapy trials and new, so far third line, therapy trials. New phase 1-2 trials are ongoing which target angiogenesis but also IGF1 receptor inhibitions.

The FIRM-ACT collaborative was started as a result from and soon after the first *International Adrenal Cancer Meeting* in 2003. This study brings clear evidence that even in very rare disease, academic international efforts support the setting up of randomized trials.

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