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Adrenocortical carcinoma: A population-based study on incidence and survival in the Netherlands since 1993

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Abstract ***Background:*** The reported annual incidence of adrenocortical carcinoma (ACC) is 0.5–2.0 cases per million individuals. Updated population-based studies on incidence are lacking. The aim of this nationwide survey was to describe the incidence and survival rates of ACC in the Netherlands. Secondary objectives were to evaluate changes in both survival rates and the number of patients undergoing surgery.

Methods: All ACC patients registered in the Netherlands Cancer Registry (NCR) between 1993 and 2010 were included. Data on demographics, stage of disease, primary treatment modality and survival were evaluated.

Results: Included were 359 patients, 196 of whom were female (55%). Median age at diagnosis was 56 years (range 1–91). The 5-year age-standardised incidence rate decreased from 1.3 to 1.0 per one million person-years. Median survival for patients with stage I–II, stage III and stage IV disease was 159 months (95% confidence interval (CI) 93–225 months), 26 months (95% CI: 4–48 months) and 5 months (95% CI: 2–7 months), respectively ($P < 0.001$). Improvement in survival was not observed, as reflected by the lack of association between survival and time of diagnosis. The percentage of patients receiving treatment within 6 months after diagnosis increased significantly from 76% in 1993–1998 to 88% in 2005–2010 ($P = 0.047$), mainly due to an increase in surgery for stage III–IV patients.

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Conclusion: These nationwide data provide an up-to-date survey of the epidemiology of ACC in the Netherlands. A trend towards a decreasing overall incidence rate was observed. Survival rates did not change during this period despite an increased number of surgical procedures.

1. Introduction

Adrenocortical carcinoma (ACC) is an aggressive neoplasm with a reported annual incidence of 0.5–2.0 cases per million persons.[1–3] Data on the incidence of ACC are scarce, being based mainly on the United States National Cancer Institute (NCI) survey from the 1970s and a study of US Surveillance, Epidemiology and End Results (SEER) database published in 2006.[2,3] The only European study on ACC incidence thus far has been a Norwegian study published in 1992.[4] These latter two studies show an ACC incidence rate of 0.7 per million and 1.5 per million, respectively.[2,4]

ACC can be part of rare hereditary syndromes (e.g. Beckwith–Wiedemann syndrome, Li–Fraumeni syndrome), but most ACCs occur as sporadic tumours, of which the molecular pathogenesis is poorly understood.[5] Most patients present in the sixth or seventh decade of life and a female predominance has been reported.

Patients present with symptoms related either to a mass effect of the tumour or hormonal overproduction. Serendipitous discovery of ACC occurs in up to 16% of cases.[7] In recent reports, overall survival remains low with a stage-dependent 5-year survival of 84% for stage I and 15% for stage IV.[1,2]

Radical resection of the primary tumour is the only curative option for patients with local or locally advanced disease.[1,5] Surgical treatment should also be considered in selected patients with distant metastases or recurrent disease, since this could yield a survival benefit.[8,9] Treatment with the adrenolytic drug mitotane is the mainstay of therapy for metastasised disease.[10] It is also used increasingly as adjuvant therapy: retrospective evidence suggests a significant increase in recurrence-free survival of 17–32 months.[11–13] A prospective trial to confirm these results (Efficacy of Adjuvant Mitotane Treatment-trial or ADIUVO-trial) is currently recruiting. In advanced stages cytotoxic chemotherapy can be added to the treatment with mitotane. A regimen of etoposide, doxorubicin and cisplatin (EDP) is the most effective first-line therapy, as was recently demonstrated in a large multicentre trial.[14] However, the objective response rate of EDP was only 23% and the median duration of progression-free survival was 5 months. New developments in treatment focus on targeted therapies, but major breakthroughs have not yet been reported.

The aim of this study was to present recent data on population-based incidence and survival of patients with ACC in the Netherlands. In addition, we examined whether treatment or survival of patients with ACC changed during the study period.

2. Patients and methods

2.1. Patients

Data were obtained from the Netherlands Cancer Registry (NCR), a nation-wide, population-based registry containing clinical data on cancer patients diagnosed since 1989. Completeness of case ascertainment is estimated to be at least 95%.[15] Registration and coding is conducted according to the guidelines of the World Health Organisation and the International Association of Cancer Registries.[16] The NCR contains data on all patients with histopathologically proven disease, as well as most patients with cancer diagnosed otherwise. In the Netherlands, hospital pathology departments all participate in a nationwide network (PALGA), thereby supplying NCR with data on patients and their corresponding diagnoses. The NCR also obtains data from the offices of hospital medical records, which provide lists of the diagnoses of both outpatients and hospitalised cancer patients. Trained registrars from the NCR extract patient and tumour characteristics from the medical records. Topography and histology are coded according to the International Classification of Diseases for Oncology, third edition (ICD-O-3).[17] All tumours with ICD-O-3 topography code C74.0 (adrenal cortex) and classification 'malignant' were selected. The following data were used: age at time of diagnosis, diagnostic modality, sex, tumour laterality, stage of disease, treatment modality employed within the first 6 months after diagnosis (surgery, chemotherapy, radiation therapy, other) and overall survival. Notably, the use of mitotane is not registered in the NCR. Vital statistics in the NCR are updated on a yearly basis through a link with the Municipal Personal Records Database, which contains personal files for everyone who lives or has lived in the Netherlands. Malignant adrenocortical tumours have been registered in the NCR since 1st January 1993. In order to have at least 1 year of follow-up, the cut-off date for inclusion was 31st December 2010 and the end of the observation period was 31st December 2011.

In order to facilitate comparison of our data with other studies, disease staging was converted to the system proposed by the European Network for the Study of Adrenal Tumours (ENS@T-staging, Table 1).[18,19]