ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Adrenocortical carcinoma's incidence and mortality in Central Serbia

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SUMMARY
Introduction/Objective Adrenocortical carcinomas (ACCs) are very rare tumors with grave prognosis despite multimodal treatment.
The aim of our study was to determine the incidence and mortality of ACCs in Central Serbia.
Methods The study period was from 1999 to 2012. We used data from the Cancer Registry of Central Serbia. Incidence and mortality rates were sex- and age-standardized according to Segi's world population.
Results In the defined period of the study, 128 patients with a diagnosis of ACC were registered and the female-to-male ratio was 1.3:1. The median age of affected individuals was 42.3 years. There were two main age peaks – one in childhood (0–9 years), and the other in the fifth and sixth decade of life. In this period, the average standardized incidence rate of ACC amounted to two per million people with slightly increasing trend. The largest number of male patients with ACC (22; 39.2%) was registered in the age group of 0–9 years, while the largest number of patients in females was shown to be in the age group of 40–49 years (29; 40.3%). During the study period, there were 35 deaths registered in patients with ACC (mean age of 61.2 years). The average mortality rate of ACC was 0.3 per million people. The male-to-female ratio was 1.5:1. Most fatal outcomes were registered in the age groups of 50–59 and 60–69 years, so 91.4% of all deaths took place in the age groups 50+.
Conclusion ACC is an extremely rare tumor that occurs more often in women than in men. However, fatal outcomes occur more frequently in males.
Keywords: adrenocortical carcinoma; incidence; mortality

INTRODUCTION

Adrenocortical carcinomas (ACCs) are very rare tumors with grave prognosis, despite multimodal treatment, wherein surgery occupies central place. These tumors are detected due to their compressive effects, hormonal hyperfunction, or as incidentalomas [1]. Despite the fact that computed tomography (CT) is used widely and that tumors of the adrenal gland (incidentalomas) are revealed more often, ACCs are still classified as rare tumors. When CT scans of the abdomen are performed for some other reason, tumors of the adrenal gland are detected in 3–4% of the cases [2, 3, 4]. Fortunately, these tumors are benign adenomas of the adrenal cortex in the vast majority of cases. In autopsy studies, tumor alterations of the adrenal glands are described in about 2% of the cases [5–8].

ACC occurs in both sexes and in all ages, but in age distribution two clear peaks are identified, so we can say that there is a bifocal occurrence. The first peak occurs in children approximately five years old, and the second peak occurs at the age of 50 [8–13].

Data of ACC incidence and mortality are as rare as the tumor itself. The incidence is one to two per million, and the mortality rate is less than one per million [1, 2, 7, 8]. According to the Rarecare and RarecareNet studies, carcinomas of adrenal cortex belong to a rare cancer group in Europe, with a crude incidence rate of 0.22 per 100,000 people per year [14]. According to Cancer Incidence in Five Continents (CI5), age-standardized adrenal gland cancer's incidence ranges from 0.1 to 1.5 per 100,000 people. Data in this registry for carcinoma of adrenal gland include both ACC and malign pheochromocytoma together [15].

The aim of our study was to determine whether there is a change in the incidence and mortality of ACC in Central Serbia, and to compare these data with the data from other parts of Europe and of the world.

METHODS

The time period observed in this study ranged from January 1, 1999 to December 31, 2012.

We used material from the Statistical Office of the Republic of Serbia (population census data) and from the Institute for Public Health of Serbia "Dr Milan Jovanovic – Batut" (Cancer Registry of Central Serbia). This Cancer Registry has been collecting data since 1996, when it had been reorganized in accordance with the

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recommendations of the International Agency for Research on Cancer – IACR, and the European Network of Cancer Registries – ENCR. Information sources concerning new cancer cases represented data from oncology clinics, hospitals, histopathology laboratories, and death reports. Within the Cancer Registry, the source for mortality data were unpublished data of the Statistical Office of the Republic of Serbia. Registration and coding of tumors was performed according to the guidelines of the World Health Organization and IACR [16]. The percentage of the Cancer Registry data completeness was estimated to be over 80% and no significant changes were observed over time. According to the International Classification of Diseases, Tenth Revision (ICD-10) and the Third Edition of International Classification of Diseases for Oncology, ACCs are coded as C74.0, which means malignant neoplasm of cortex of adrenal gland (C indicates neoplasm, 74 is code for adrenal gland, .0 is for cortex of adrenal gland) [17]. In this way we excluded benign tumors of adrenal cortex, benign and malign pheochromocytoma, and metastatic tumors of the adrenal gland.

Central Serbia had a population of 5,255,053 inhabitants (according to the 2011 population census). Information on all cancer patients in Central Serbia in relation to sex and age were included.

As a denominator for the calculation of crude rates, population data from the census years (2002, 2011) were used, while for the remaining years population estimates were used. For the calculation of standardized rates we used the method of direct standardization according to the Segi's world population. Time trends for incidence and mortality of ACC were assessed using the annual percent change, estimated through Poisson regression models (age period cohort models – APC), taking into account the number of cases in each year and the population as an offset variable.

RESULTS

Incidence

In the period 1999–2012 in Central Serbia there were 128 patients with ACC. Out of total number, 56 patients were male and 72 were female. The female-to-male ratio was 1.3:1 (Table 1). The median age of the affected individuals was 42.3 years.

There were two main age peaks. The largest number of patients was in the age group of 40–49 years, 42 patients (32.8%). The second peak was in childhood, at the age group of 0–9 years, where there were 32 patients (25%), as shown in Figure 1.

The largest number of male patients with ACC was registered in the age group of 0–9 years, a total of 22 (39.2% of all male patients), while in females – in the age group of 40–49 years, a total of 29 patients (40.3% of all female patients).

In the period 1999–2012, the average standardized incidence rate of ACC in Central Serbia was two per one

Table 1. Number of new cancer cases and deaths and distribution by sex and age groups of adrenocortical carcinomas (ACCs) in Central Serbia, based on the Cancer Registry, for period from 1999 to 2012

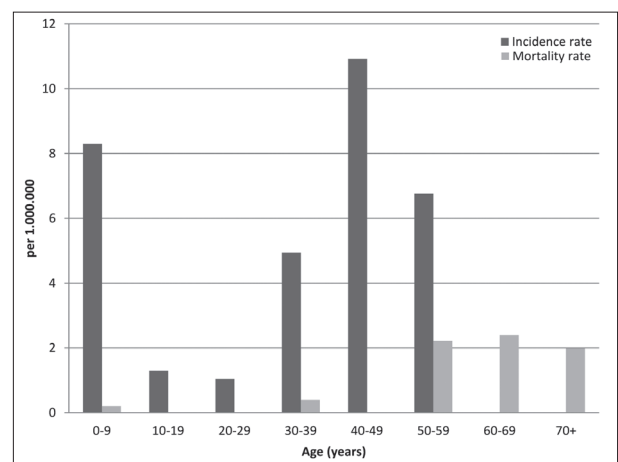| Age (years)	New cancer cases of ACC			Deaths from ACC		
	Male (%)	Female (%)	Both (%)	Male (%)	Female (%)	Both (%)
0–9	22 (39.2)	10 (13.9)	32 (25)	1 (4.8)	0	1 (2.9)
10–19	1 (1.8)	4 (5.6)	5 (3.9)	0	0	0
20–29	1 (1.8)	3 (4.2)	4 (3.2)	0	0	0
30–39	9 (16.1)	10 (13.9)	19 (14.8)	1 (4.8)	1 (7.1)	2 (5.7)
40–49	13 (23.2)	29 (40.3)	42 (32.8)	0	0	0
50–59	10 (17.8)	16 (22.2)	26 (20.3)	7 (33.3)	4 (28.6)	11 (31.4)
60–69	0	0	0	7 (33.3)	4 (28.6)	11 (31.4)
≥ 70	0	0	0	5 (23.8)	5 (35.7)	10 (28.6)
Total	56 (100)	72 (100)	128 (100)	21 (100)	14 (100)	35 (100)

Figure 1. Average annual age-specific incidence and mortality rate of adrenocortical carcinomas (ACCs) per 1,000,000 people in 1999–2012, both sexes, Central Serbia

million people. In the observed period, a slight increase in the incidence is registered, shown by the Poisson regression model (APC = 2.6; confidence interval 95% 1.8–3.8; p = 0.01). The highest standardized incidence rate of ACC in Central Serbia was registered in 2009 (3.4 per million), while the lowest was in 2005 (1.2 per million), as shown in Figure 2.

Mortality

In Central Serbia, in the period of 1999–2012, a total of 35 deaths were registered in patients with ACC, aged 5–82 years. Out of the total number of patients, 21 (60.0%) were male and 14 (40.0%) were female. The male-to-female ratio was 1.5:1. Most fatal outcomes were registered in the age groups 50–59 and 60–69 years, and there were 11 in both groups (31.4% of all deaths per group). There is a notable continuous increase in the number of deaths at the age above 50, and 91.4% of all deaths took place in the
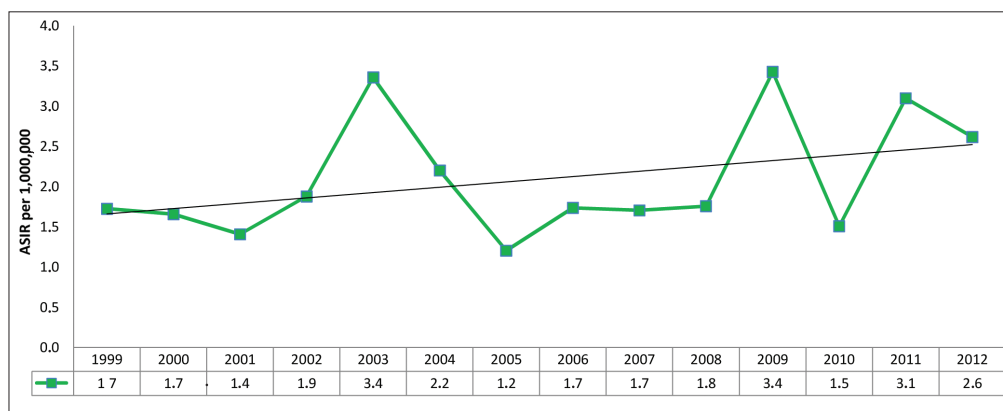
Figure 2. Age-standardized incidence rate (ASIR, World) of ACC per 1,000,000 in 1999–2012, both sexes, Central Serbia
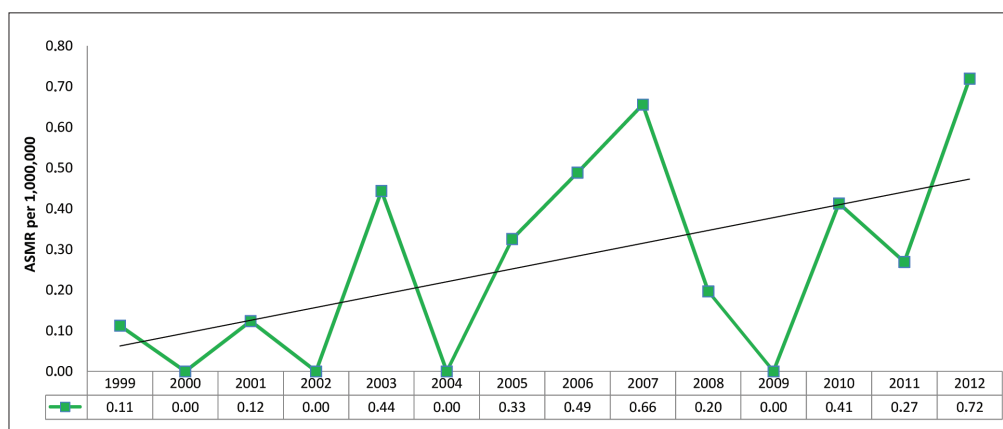
	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
	1 7	1.7	1.4	1.9	3.4	2.2	1.2	1.7	1.7	1.8	3.4	1.5	3.1	2.6

Figure 3. Age-standardized mortality rate (ASMR, World) of ACC per 1,000,000 in 1999–2012, both sexes, Central Serbia

	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
	0.11	0.00	0.12	0.00	0.44	0.00	0.33	0.49	0.66	0.20	0.00	0.41	0.27	0.72

age groups 50+ (Table 1, Figure 1). The average age of the deceased was 61.2 years.

At the age younger than five years there were no registered deaths from this malignancy in the study period. Additionally, there were only three deaths in patients younger than 50. The average mortality rate of ACC in Central Serbia amounts to 0.3 per one million people. In the reporting period an increased trend of mortality was registered, which was shown by the Poisson regression model (APC = 0.7; confidence interval 95% 0.3–1.4; p = 0.01). The highest mortality rate of ACC in Central Serbia was registered in 2012 (0.7 per million), while in 2000 and 2009 there were no recorded cases with fatal outcome (Figure 3).

DISCUSSION

The results of our study show that the standardized incidence rate for ACC is two per one million, while the mortality rate is 0.3 per one million inhabitants, showing a slight increase of morbidity and mortality trends. In literature, there is not much data on ACC incidence. Fortunately, even though there is an increase in the number of diagnosed tumors and a larger number of operations of the adrenal gland, an increased incidence was not found. The annual ACC incidence in the available literature ranges from 0.5 up to two cases per million [1, 2, 3, 8, 16, 18]. ACC is annually diagnosed in 100 to 200 patients in the

United States [6]. This data is consistent with data from our study (two new cases per one million). It is assumed that a larger number of timely operations of the adrenal gland is the reason why the ACC incidence is even slightly decreasing in the Netherlands in the last 20 years from 1.3 to one per million per year [1]. Our study showed a slight increase trend in the incidence rate and the mortality rate of ACC, indicating that the level of health care should be improved, i.e. benign alterations in the adrenal gland should be detected and treated earlier, before they transform into ACC.

In our study, the median age was 42.3 years. Other studies found that median age was from 46.7 to 51.2 years [1, 2, 13, 16, 19]. The largest study of this kind (n = 4,275), conducted by Kutikov et al. [3], from the United States National Cancer Database, showed the average age at the time of the diagnosis of ACC to be 54.5 years. Taking all this into account, we can say that patients with ACC in our study were diagnosed earlier than patients in the mentioned study.

Generally, ACC may occur in both sexes and at all ages, but in the age distribution two clear peaks are observed, so we can say that there is a bifocal occurrence. The first peak occurs in childhood, around the age of five years, and the second peak occurs around 50 years of age [8, 10, 12]. Results of our study are similar, with two peaks of incidence – one in early childhood (0–9 years), and the other in the fifth and sixth decade of life. Our data also

indicate that ACC in childhood are slightly more common in boys, while in the older population these tumors are more frequent in women [8]. The age-specific standardized incidence of ACC in people younger than 20 years is 0.2 per million, with an average age of 4.1 years [10].

In our study, the female-to-male ratio was 1.3:1. This is in accordance with the ratios found by Kerkhofs et al. [1] in their Netherlands study (1.2:1), Soreide et al. [20] in a Norway study (1.17:1), and Bilimoria et al. [8] in a US study (1.4:1). More frequent ACC occurrence in females can be explained by one of the main characteristics of all endocrine system tumors –they affect women more often than men due to their differences of sex hormones [7–10, 20, 21]. Although our study had a smaller number of patients, the results were still in concordance with the findings of other studies. This can be explained by the fact that study populations were probably similar.

Data on mortality is even more scarce, but it is estimated that it is less than one per one million inhabitants. That was also demonstrated in our study (0.3 deaths per one million) [8, 22]. A probable reason for such rare mortality data lies in the fact that methodologically well designed epidemiological studies investigating this pathology are difficult to conduct since ACCs are rare tumors. In overall cancer mortality, the adrenal cortex carcinomas account for 0.2% of deaths; in overall cancer morbidity this tumor is responsible for 0.02% of fatal outcomes [8, 10]. This actually means that one out of 5,000 cancer deaths represents a death from ACC.

ACC represents the most aggressive endocrine system tumor, after anaplastic carcinoma of the thyroid gland [5, 18]. The low mortality rate (0.3 deaths per million in our study) is explained by its fortunately low incidence rate. Although ACC occurs more often in women, death outcome is more frequent in men.

Results of our study show that, contrary to the two age peaks of incidence, there is only one peak of mortality, in the seventh decade of life. The peak of incidence in the elderly occurs 10–15 years earlier than the mortality peak. Surprisingly, no new ACC cases above the age of 59 were registered. Other studies have also shown that ACC is more aggressive in advanced age, with a much shorter five-year survival [8, 23, 24].

Carcinoma of the adrenal cortex represents 0.02% of all pediatric malignancies [25]. Low mortality in childhood indicates that there are differences between ACC biology in children and in the elderly. For example, symptoms of hormonal hyperproduction are more likely to occur in pediatric patients than in adults [23, 24, 25]. Additionally, it has even been suggested that ACC in patients under four years of age actually represents a separate type of tumor, since it originates from fetal adrenal tissue [24]. The incidence of ACC in the pediatric stage is the highest in southern Brazil – 15 times higher than in the rest of the world due to frequent gene mutations (*p.R337H*) of the

TP53 gene [12]. Even in these pediatric cases where ACC occurrence is associated with the gene mutation, survival is not related with poor prognosis, as it is the case for adults with the *TP53* gene mutation (*p.R337H*) [12].

Although surgery represents the main treatment strategy, application of adjuvant mitotane therapy is of great importance. This approach is used in both pediatric and adult patients and its implementation represents and independent positive prognostic factor [26]. In adult patients, besides mitotane, cisplatin and etoposide are applied in adjuvant treatment, along with radiotherapy in the advanced stage of the disease [7, 18, 19, 20].

In most countries, including Serbia, ACC is mostly diagnosed and surgically managed in highly specialized centers. For this reason, reporting data on ACC is highly reliable. This represents one of the strengths of our study. This study reports the incidence and mortality rates of ACC, and, to our knowledge, it is the first study of this kind that reports such data regarding Southeast Europe.

Limitation of our study lies in the fact that it is based on a cancer registry, which can contain flaws, no matter how precise it is maintained. Certainly, the most important possible flaw is underreporting, which can have an impact on the results, since the study is analyzing a rare tumor (i.e. this may lead to lower incidence and mortality rates). Also, our study provides data based on results from one country, so we believe that large-scale studies, which would include multiple countries in this part of Europe, would provide more complete information about ACC.

CONCLUSION

This is the first study from the Balkan region that presents incidence and mortality rates and time trends of ACC in comparison to data from certain countries of Europe and the USA, which have been only scarcely represented in literature to date. ACC is an extremely rare tumor with an average incidence of two per one million per year. In Serbia, it occurs more often in women than in men (1.3:1 ratio). There are two peaks in the ACC occurrence. The first peak is in the range of 0–9 years of life, and the second one at the age of 50. There is a slight increase in the number of patients in the observed period in Central Serbia. The incidence of ACC in our study is one of the highest in Europe. The average mortality rate of ACC in Central Serbia is 0.3 per million people, with male-to-female ratio being 1.5:1.

ACKNOWLEDGEMENT

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Инциденција и морталитет од адренокортикалног карцинома у централној Србији

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САЖЕТАК

Увод/Циљ Адренокортикални карциноми (АКК) веома су ретки тумори, са лошом прогнозом, упркос мултимодалном приступу у лечењу.

Циљ овог рада је био да се одреде инциденција и морталитет од АКК у централној Србији.

Методе Студија је обрађивала период од 1999. до 2012. Коришћени су подаци из Регистра за рак за Централну Србију. Стопе инциденције и морталитета су стандардизоване према полу и узрасту уз помоћ Сегијеве светске популације.

Резултати У испитиваном периоду регистровано је 128 пацијената са АКК, и однос жена према мушкарцима је био 1,3 : 1. Медијана година оболелих је била 42,3. Постојала су два главна узрасна врха инциденције, један у детињству (0–9 година) и један у петој и шестој деценији. У овом испитиваном периоду просечна стандардизована стопа инциденције

АКК је била два на милион становника, са благим трендом пораста. Највећи број пацијената мушког пола са АКК (22; 39,2%) регистрован је у старосној групи 0–9 година, док је највећи број пацијената женског пола био у старосној групи 40–49 година (29; 40,3%). Током испитиваног периода регистровано је 35 смртних случајева од АКК (аритметичка средина 61,2 година). Просечна стопа морталитета од АКК је била 0,3 на милион становника. Однос мушког и женског пола је био 1,5 : 1. Највећи број смртних случајева је регистрован у старосним групама 50–59 и 60–69 година, 91,4% свих смртних случајева је у старосној доби преко 50 година.

Закључак АКК је веома редак тумор који се чешће јавља код жена него код мушкараца. С друге стране, смртни исход је чешћи код мушкараца.

Кључне речи: адренокортикални карцином; инциденција; морталитет