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Results of the treatment of adrenocortical cancer patients at the Maria Sklodowska-Curie National Research Institute of Oncology – Krakow Branch

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Introduction. Adrenocortical carcinoma (ACC) has an incidence of 1–2 cases per million and the 5-year overall survival (OS) is 16–47%. Surgery is the treatment of choice. Post-operative radiotherapy has been shown to prolong overall survival and the purpose of this work was to show our own, first time in Poland, results of adjuvant radiotherapy in treating this disease.

Material and methods. Between 2012 and 2021, 12 patients with ACC were treated. The analyzed group included 9 women and 3 men at a mean age of 44 years (range: 33 to 76 years). A significant increase of tumor size was found in 30% of the subjects. In the analyzed group, 12 patients were qualified to adjuvant radiotherapy, but it was feasible only in 7 patients. The other 5 patients did not undergo radiotherapy. Two patients were disqualified due to metastatic disease and in 3 patients radiotherapy could not be performed due to excessive tumor size and too high a risk of complications within the critical organs.

Results. 3 out of 7 patients who received adjuvant radiotherapy are still alive and 4 of them died. Mean overall survival time was 32 months. The 12-month overall survival rate was 80%. In the group of 5 patients who have not received radiotherapy, 2 patients are still alive. The mean overall survival time is 13.5 months and the 12-month overall survival rate is 60%.

Conclusions. Due to rapid disease progression and poor prognosis associated with ACC, patients with tumors located in the adrenal gland require urgent surgical treatment at a reference center. Adjuvant radiotherapy improves treatment results significantly, but is not feasible in some patients due to cancer progression or the tumor location. In patients with ACC, it is important to diagnose the disease and to start adequate treatment as early as possible.

Key words: adrenocortical cancer, surgery, radiotherapy, mitotane

Introduction

Adrenocortical carcinoma (ACC) is a very rare and aggressive malignancy, with an incidence of 1–2 cases per million [1–11, 14–16]. In 2018, 56 cases of ACC were noted among men and 70 cases – among women in Poland. In the Małopolska region there were 2 and 3 cases, respectively. In Poland, in 2018,

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this cancer was the cause of death in 33 men and 36 women. In the Małopolska region there were 2 and 6 deaths, respectively [2]. ACC occurs most often between 40 and 50 years of age. It may induce mixed Cushing's syndrome and hyperandrogenism/virilization or may show no hormonal activity. Any focal lesion in the adrenal area found in the ultrasound examination requires confirmation by a CT or MRI scan. Wide access to imaging studies results in more and more frequent detection of adrenal lesions, in about 4% of the middle-aged population and in 10% of the elderly [5]. Surgery, performed after appropriate hospital-based preparation, is the treatment of choice for ACC. Videoscopy/laparoscopy adrenalectomy is the primary reference method of surgery. This procedure is only possible in reference centers experienced in the treatment of this difficult problem [4–6]. Only definitive surgery gives the patient a chance of cure. The risk of recurrence after such definitive surgery is 30% whereas in the case of a non-definitive operation this risk is as high as 65% [9]. Liver metastases are found in 42% of patients [9–11]. The risk of metastatic disease increases with advancing local tumor stage and two years after surgery it is 27%, 46%, and 63% for stages I, II, and III, respectively [11]. Adjuvant treatment with mitotane and radiotherapy prolongs the time to disease progression. It has been demonstrated that post-operative radiotherapy in patients with ACC has an effect on the time to local recurrence and overall survival and reduces the risk of death of patients with positive surgical margins by 40% [17]. Post-operative radiotherapy reduces the risk of recurrence by 50% [18].

Material and methods

In reaction to the reports published in 2012, suggesting that adjuvant post-operative radiotherapy in patients with ACC prolongs the time to progression and is likely to prolong the overall survival, at the National Research Institute of Oncology in Krakow, in cooperation with the Clinic of Endocrinology of the Medical College of the Jagiellonian University in Krakow, we started treatment with radiotherapy in this group of patients.

Until recently, adjuvant treatment of ACC has been conducted only by endocrine medicine specialists. In association with study results that showed prolongation of the time to local recurrence and overall survival in the ACC patients with postoperative radiotherapy, the purpose of this work was to show our own, first time in Poland, results of adjuvant radiotherapy of this rare and very aggressive cancer.

Between 2012 and 2021, 12 patients with this disease were treated. The analyzed group included 9 women and 3 men at a mean age of 44 years (range: 33 to 76 years). Patients reported the following symptoms prior to the diagnosis of ACC:

- high-amplitude blood pressure fluctuations (90%),
- hormonal disorders (40%),
- body weight increase (40%),
- depressive disorders (20%),
- weakness (80%),
- diabetes (20%).

Based on imaging studies, such as ultrasound, CT, and MRI, a rapid increase in tumor size was observed, up to 8 cm per year, in 40% of the patients. In the analyzed group, a significant increase of tumor size was found in 30% of the subjects. The size of the operated tumor ranged from 4 to 23.5 cm – the mean diameter was 9 cm (tab. I).

All patients underwent non-definitive (R1) surgery in the first instance, which was the main indication for adjuvant radiotherapy. All patients received adjuvant treatment with mitotane. 12 patients were qualified to adjuvant radiotherapy, but it was feasible only in 7 patients due to technical limitations. Radiotherapy was performed with a photon beam of energy adjusted to the depth of the tumor bed, using the conformal IMRT or VMAT technique in a period of 6 to 12 weeks after surgery. The patients received a total dose of 45 Gy to 50.4 Gy and the fraction dose was 1.8 Gy with mean overall radiotherapy time of 37 days [12]. The irradiated volume included the tumor bed and the regional lymph nodes (fig. 1). All patients completed the treatment in accordance with the treatment plan. Radiotherapy was well tolerated, and the most common complaints reported during the treatment included fatigue and intermittent diarrhea of minor severity.

5 patients were not treated with radiotherapy. In two cases, metastatic disease was the cause of disqualification from radiotherapy – one patient had liver and lung metastases

Table I. Characteristics of the analyzed group of ACC patients

Patients	Treatment with use of radiotherapy	Treatment without radiotherapy
gender:		
female	5	4
male	2	1
mean age: 44 years	range: 33–76	range: 33–60
disease stage:		
I	1 (14%)	0
II	4 (57%)	2 (40%)
III	2 (29%)	2 (40%)
IV	0	1 (20%)
mean tumor size: 9 cm	range: 4–8.5 cm	range: 8–23 cm
Ki-67 index:		
<20%	2	1
≥20%	2	1
not examined	3	3
location:		
right-sided	5	4
left-sided	2	1
non-definitive surgery	7 (100%)	5 (100%)
mitotane	7 (100%)	5 (100%)
cortisol production:		
yes	3	3
no	4	2

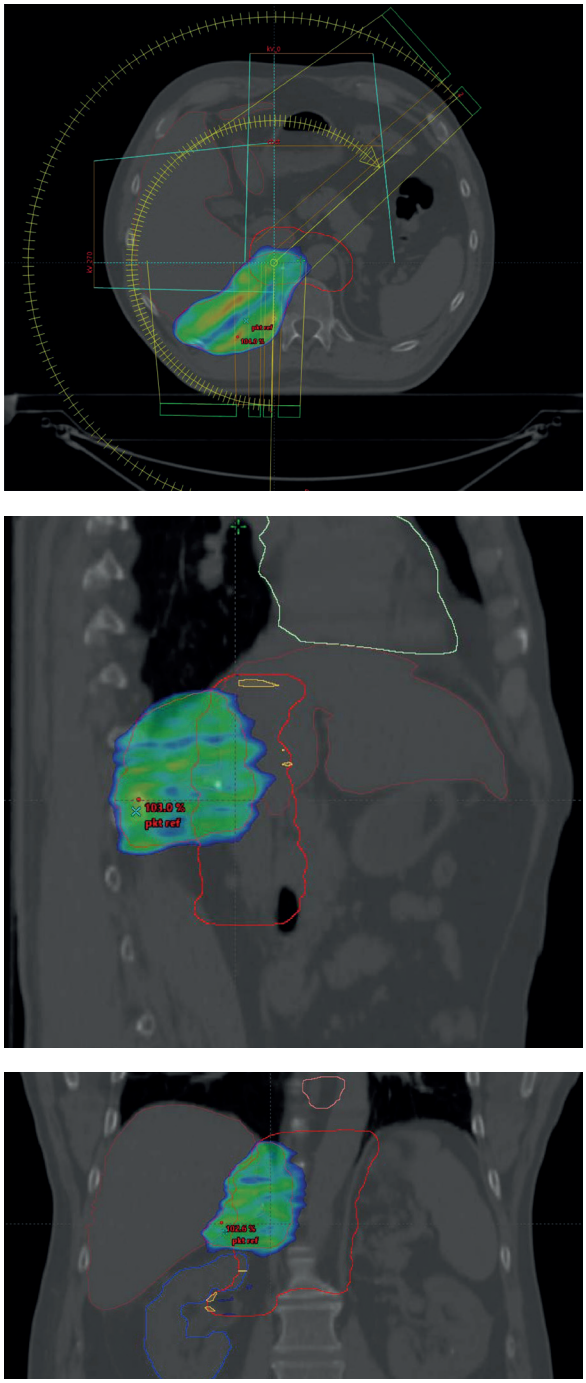

Figure 1. A 56-year-old man with adrenocortical carcinoma status post adrenalectomy and post tumor recurrence surgical resection. Postoperative radiation therapy during mitotane chemotherapy to decrease the risk of total recurrence. The planned target volume (PTV) of the elective lymph node group is in red. The PTV of the tumor bed with dose distribution is colored

and in the other one the disease had spread to the inguinal nodes and scrotum. In 3 patients, radiotherapy planning had started but due to the tumor size and/or right-sided tumor location, radiotherapy could not be performed due to an excessive risk of treatment-induced complications within the critical organs when balanced against any possible benefit [13].

Results

Out of 7 patients who received adjuvant radiotherapy 3 are still alive (43%) and 4 of them (57%) have died. The mean overall survival was 32 months. The 12-month overall survival rate was 80%. In one patient tumor-bed recurrence and generalized metastatic disease was found after 3 years of follow-up. In the group of 5 patients who did not receive radiotherapy, 3 (60%) have died and 2 (40%) are alive. The mean overall survival is 13.5 months. The 12-month overall survival rate is 60%. In 3 (60%) patients, liver and lung metastases were found.

Discussion

The results of treatment of patients with ACC are unsatisfactory, with 5-year overall survival varying from 16 to 47% [14], and for the advanced disease (stage 4) overall survival is less than one year. Local recurrence was found in 85% of patients who underwent definitive surgery (data for the year 2009). ACC used to be considered a radiation-insensitive tumor. Patient age less than 54 years, no endocrine activity, and localized disease are associated with a better prognosis of patients with ACC.

In 2009, Polat et al. [14] observed that 57% of patients treated for ACC responded to radiotherapy. Non-definitive surgery (the R1 feature) was the indication for adjuvant radiotherapy. Post-operative radiotherapy has been found to reduce the risk of local recurrence. The authors report that in some patients, the location of the tumor prevents radiotherapy because tolerance doses would be exceeded in such critical organs as the kidney and liver. These studies have contributed to the initiation of adjuvant radiotherapy in patients with ACC. Radiotherapy was well tolerated and in some patients only nausea and loss of appetite were noted.

In 2014, Sabolch et al. [15] have shown in a group of 360 patients with ACC that post-operative radiotherapy significantly reduced the risk of local recurrence. An improvement of treatment results was noted for all ACC stages, regardless of surgery radicality and mitotane treatment. However, no effect on the overall survival was noted.

Viani et al. [16] have shown in 2019 that adjuvant radiotherapy in patients with ACC significantly reduces the risk of local recurrence and the treatment is well tolerated. Gharzai et al. [17] reported in 2019 that post-operative radiotherapy in patients with ACC significantly improved the 3-year overall survival rate from 48.8% to 77.7%, and the 3-year local recurrence-free survival rate from 34.2% to 59.5%. The size of the tumor in the irradiated group ranged from 0.6 to 22.5 cm (mean: 10.4 cm) and in the non-irradiated group – from 4.1 to 23 cm (mean: 11.7 cm). In this study group, 46.2% of patients showed no disturbances of hormone levels and 56.4% – no cortisol production. Radiotherapy was well tolerated and only nausea and loss of appetite were noted.

In 2020, Zhu et al. [18] found that the use of adjuvant radiotherapy in patients with ACC has a statistically significant effect on prolongation of the overall survival and of the time

to progression and reduces the chances of local recurrence. These studies also have confirmed the role of adjuvant radiotherapy in the treatment of ACC. According to Cerquetti et al. [19], mitotane used in combination with radiotherapy acts as a radiosensitizer.

The mean age of patients in our group was 44 years, which is consistent with the literature data [8]. Similarly to other investigators, we have observed that patients undergoing radiotherapy live longer [17, 18]. In the analyzed group, 80% of patients treated with post-operative radiotherapy survived 12 months, compared to 60% of patients who did not receive this treatment. The mean overall survival in the irradiated group was 32 months, as compared to 13.5 months in the non-irradiated group.

We found a treatment failure in one patient in the treated group. The size of the tumor in the irradiated group was smaller, which enabled the use of this adjuvant modality. In 40% of patients, a rapid increase in the tumor mass was noted based on imaging studies (ultrasound, CT, MRI), up to 8 cm per year. In the study group, the high dynamics of tumor growth in some patients resulted in an inability to perform post-operative radiotherapy (too large an area requiring irradiation) and an inability to deliver a curative dose due to the high risk of complications in the critical organs. In 3 non-irradiated patients, a rapid metastatic spread of the disease was found. Symptoms reported by the patients, such as blood pressure jumps, large blood pressure amplitude fluctuations, hormonal disturbances, weight gain, depressive disorders, weakness, or diabetes should prompt physicians to perform urgent diagnostics, including imaging studies such as: ultrasound and abdominal CT and MRI scans. Only an early diagnosis of ACC gives the patient a chance for curative treatment. Abnormal adrenal function and disorders of the somatrotopic pituitary axis are related to mental disorders observed in patients. 20% of patients treated for ACC reported mood disturbances and these observations are in line with the Baranowska-Bik report [20].

Limitations

Adrenocortical carcinoma is a rare neoplasm, therefore the study group is small. The main purpose of this work is to present our experience in the treatment of this disease. For this reason, binding and firm conclusions regarding adjuvant radiotherapy should be drawn on the basis of larger groups that can be obtained by meta-analysis.

Conclusions

Due to the rapid disease progression and poor prognosis associated with ACC, patients with tumors located in the adrenal gland require urgent surgical treatment at a reference center. Adjuvant radiotherapy improves treatment results significantly, but it is not feasible in some patients due to cancer progression or tumor location. In patients with ACC, it is important to diagnose the disease and to start adequate treatment as early as possible.

Conflict of interest: none declared

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