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BRIEF REPORT

Efficacy of Adjuvant Radiotherapy of the Tumor Bed on Local Recurrence of Adrenocortical Carcinoma

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Context: Local tumor recurrence is common in adrenocortical carcinoma (ACC) and is the most frequent cause for reoperation. Although radiotherapy is often considered ineffective in the treatment of ACC, the limited number of available studies does not support this statement.

Objective: The objective of the study was investigation of adjuvant tumor bed irradiation in the treatment of ACC.

Design: We performed a retrospective analysis.

Patients: The German ACC Registry (n = 285) was screened for patients who had received tumor bed radiotherapy in an adjuvant setting (no macroscopic evidence for residual disease after surgery). Fourteen patients without distant metastases (World Health Organization stage I, one patient; stage II, seven; stage III, three; and stage IV, three) were matched with 14 patients for resection status, adjuvant mitotane treatment, stage, and tumor size. Median follow-up of patients still alive (n = 15) was 37 months.

Main Outcome Measure: Survival without local recurrence and disease-free survival was the main outcome measure.

Results: Local recurrence was observed in two of 14 patients in the radiotherapy group and in 11 of 14 control patients. The probability to be free of local recurrence 5 yr after surgery differed significantly [79% (95% confidence interval, 53–100) *vs.* 12% (0–30); $P < 0.01$]. However, disease-free and overall survival were not significantly different between the two groups. Acute adverse events related to radiotherapy were mostly mild. One patient developed a partial Budd-Chiari syndrome.

Conclusion: These data from the largest series of ACC patients treated with adjuvant tumor bed irradiation suggest that radiotherapy is effective in reducing the high rate of local recurrence in ACC. A randomized trial in high-risk patients is needed to further evaluate the efficacy of radiotherapy as an adjuvant treatment option in ACC. **(*J Clin Endocrinol Metab* 91: 4501–4504, 2006)**

ADRENOCORTICAL CARCINOMA (ACC) is a rare malignancy with a poor prognosis (1–3). Even after seemingly complete surgical resection, most patients develop recurrence within 5 yr (4, 5). Therefore, adjuvant treatment concepts after complete surgical resection are urgently needed. Adjuvant treatment with mitotane is often used, but evidence of its efficacy is still lacking (3, 6, 7). Local recurrence is particularly frequent in ACC, often leading to reoperation (8, 9).

Radiotherapy has often been considered ineffective for treatment of ACC (9–11). However, several reports with a limited number of patients have described tumor response rates up to 42% (4, 11–17). Although methods and response criteria in these studies do not fulfill modern standards, these reports indicate that ACC is not resistant to radiotherapy. Stewart *et al.* (18) were the first to use radiotherapy in an adjuvant setting (n = 4). Long-term results of this series showed that three of the four patients treated with radiotherapy of the tumor bed survived longer than 10 yr without recurrence (14). In addition, King and Lack (12) reported that all patients treated with adjuvant radiotherapy (n = 4) survived more than 5 yr. Based on these observations, we and other colleagues in Germany have in recent years offered postoperative radiotherapy of the tumor bed to patients with ACC and perceived high risk of recurrence. Here, we analyze the outcome of these patients with matched controls derived from the German ACC registry.

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Abbreviations: ACC, Adrenocortical carcinoma; CT, computed tomography; 3D, three-dimensional; R, resection.

Patients and Methods

Patients

We reviewed the German ACC registry (n = 285) for cases who had received tumor bed irradiation (1986–2004). The following inclusion criteria were defined in advance: 1) macroscopically complete tumor resection, 2) no evidence for distant metastases, 3) radiotherapy in an adjuvant setting (no evidence of tumor recurrence) within 6 months after first surgery, 4) a minimum of 12 months follow-up after surgery, and 5) availability of complete follow-up data (up to the death of the patient or follow-up information not older than 3 months at the time of analysis). Fourteen patients met these criteria. Every patient was matched with one control patient for resection (R) status, adjuvant mitotane treatment, tumor stage according the World Health Organization classification 2004 (19), and tumor size. Control patients were selected from a cohort of the German ACC Registry fulfilling the same inclusion criteria but not having received radiotherapy (n = 109). Matching was performed by an

independent person not involved in the analysis of the data by using clinical information from the time of the primary diagnosis.

Surgery

All tumors were localized at the time of primary diagnosis with no evidence for distant metastases. In all but two patients, conventional open surgery was performed. Surgical removal was macroscopically complete in all patients. In each group, no residual tumor (R0) was detectable in eight patients and microscopic residual tumor (R1) was detectable in two patients. However, in four patients either tumor spillage occurred or the report by the local pathologist contained no information indicating whether or not the resection was microscopically complete. These cases were given the resection status RX.

Radiotherapy

All irradiated patients were centrally reviewed, including full treatment charts and port films. Seven of the 14 patients were treated in our center. The target volumes included the former tumor bed, and in seven patients additionally the locoregional lymphatic drainage (with bilateral paraaortic lymph nodes) because regional lymph node involvement was either demonstrated by histopathology or was considered very likely (*e.g.* large tumor size, infiltration of the tumor capsule, lymphangiosis carcinomatosa). Radiotherapy started in most patients within 8 wk after surgery using a linear accelerator with photon energies from 6–18 MV. Twelve of 14 patients had computed tomography (CT)-based three-dimensional (3D) treatment planning. In two patients, conventional simulator planning was performed. Radiation treatment was given in 1.8 to 2.0 Gy fractions daily for 5 d/wk. The median dose was 50.4 Gy (range, 41.4–56 Gy; mean total dose, 49.2 ± 4.9 Gy). In eight of 14 patients, boost treatment was given after initial doses of 41.4 to 46.6 Gy to a larger treatment volume.

Documentation of adverse events

Medical records were reviewed for the following adverse events: gastrointestinal (nausea, vomiting, abdominal pain or cramps, diarrhea, constipation, enteritis, ileus), skin (dermatitis, hyperpigmentation, and atrophic skin), general symptoms like fatigue and anorexia, pulmonary (pneumonitis within 3 months after radiotherapy or pulmonary fibrosis), kidney function (increase of serum creatinine > 0.3 mg/dl or decrease of creatinine clearance > 20 ml/min), pain (abdominal pain or cramps), hematological (leucopenia, thrombopenia, anemia), and neurological (sensory or motoric neuropathy). All adverse events were scored according to the National Cancer Institute-Common Terminology Criteria-Adverse Events (NCI-CTC-AE) classification (20).

Statistical analysis

Analyses for survival were performed using the Kaplan-Meier method, and differences between the two groups were analyzed by Student's *t* test, Wilcoxon test, and log-rank test, respectively. *P* values < 0.05 were considered as statistically significant.

Results

Characteristics of the patients

A total of 28 patients were included in the radiotherapy group (n = 14) and the control group (n = 14), respectively. Exact matching for R status and adjuvant mitotane treatment was possible. In only eight patients in each group, the resection of the tumor was classified by the pathologist as R0 (no residual tumor), in two cases in each group residual tumor was detected microscopically (R1), and in four cases the resection status was not reported (RX, including two and three cases, respectively, with tumor spillage). Five patients in each group received adjuvant mitotane. The radiotherapy group did not differ significantly from the control group in tumor size (mean, 11.7 ± 3.8 cm *vs.* 11.0 ± 4.3 cm; $P = 0.3$), tumor weight (505 g *vs.* 399 g; $P = 0.13$), or age (42 ± 15 yr *vs.* 48 ± 15 yr; $P = 0.36$) (Table 1). The median Weiss score was 5 (4–8, n = 9) *vs.* 4 (3–6, n = 8; $P = 0.04$). The median follow-up of patients still alive (n = 15) was 37 months (range, 13–72 months).

Local recurrence and survival analysis

Local recurrence was observed in 11 of 14 patients in the control group, indicating the high risk of the selected cohort. In contrast, in the radiotherapy group only two of 14 patients developed a local recurrence. More than 70% of local recurrences occurred within 2 yr. The probability of being free of a local recurrence 5 yr after surgery differed significantly [radiotherapy group, 79% (95% confidence interval, 53–100%) *vs.* 12% (0–30%) in controls; $P < 0.01$) (Fig. 1). However, disease-free survival did not differ significantly between the two groups (Fig. 1). Nine patients in the radiotherapy group developed distant metastases (lung, n = 5; liver, n = 6; bone, n = 1) compared with 11 patients in the control group (lung, n = 8; liver, n = 5; bone, n = 1). After recurrence, treatment was similar in the radiotherapy group compared with controls (surgery, n = 6 *vs.* n = 7; mitotane, n = 9 *vs.* n = 8; cytotoxic chemotherapy, n = 6 *vs.* n = 4). Overall survival was also not significantly different ($P = 0.9$; data not shown). In each group, six patients died as a result of progressive disease.

Adverse events in radiotherapy group

Acute adverse events related to radiotherapy were mostly mild (Table 2). Three of the eight patients with gastrointes-

TABLE 1. Characteristics of patients

	Age (yr)	No. of patients with functional ACC	No. of patients with resection status			No. of patients receiving mitotane	No. of patients in tumor stage				Tumor size (cm)	
			R0	R1	RX		I	II	III	IV	Mean	Median
Radiotherapy group	43 ± 15	9[a]	8	2	4	5	1	7	3	3	11.7 ± 3.8	12.0 (4.5–19)
Control group	48 ± 15	9[b]	8	2	4	5	1	8	5		11.0 ± 4.3	10.3 (3–20)

None of the patients received any other adjuvant therapy. R0, No residual tumor; R1, microscopic residual tumor; RX, presence of residual tumor cannot be assessed (tumor spillage or the report by the local pathologist contained no information indicating whether or not the resection was microscopically complete).

[a] Glucocorticoid excess (n = 3), androgen excess (n = 2), glucocorticoids plus other hormones (n = 4), hormonally inactive (n = 2), not documented (n = 3).

[b] Glucocorticoid excess (n = 5), androgen excess (n = 2), glucocorticoids plus other hormones (n = 2), hormonally inactive (n = 1), not documented (n = 4).

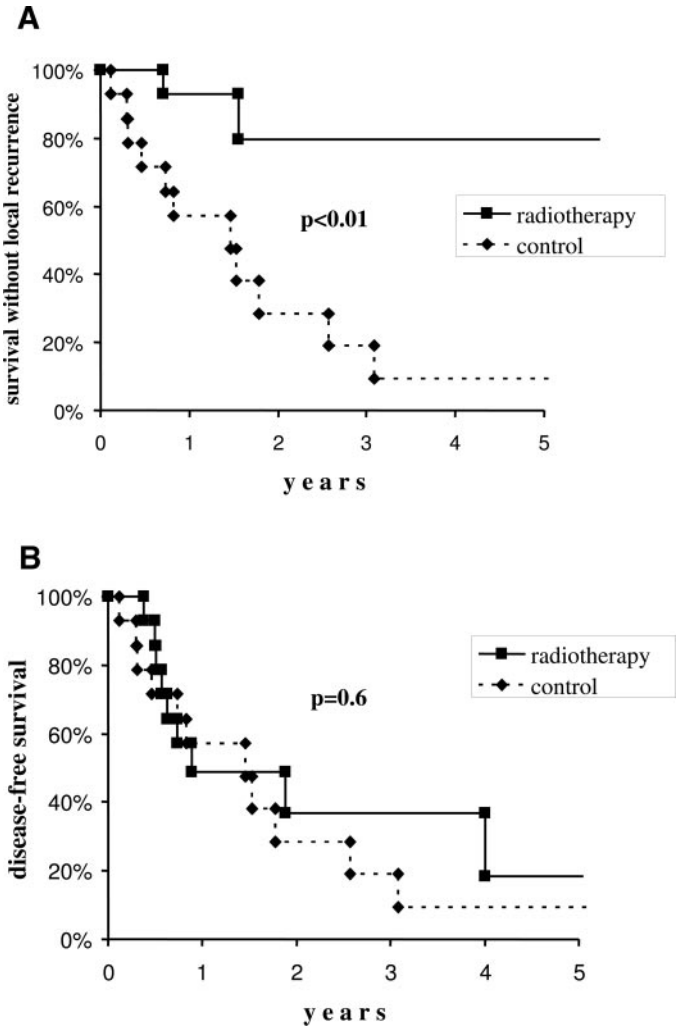

FIG. 1. Kaplan-Meier estimates of survival without local recurrence (A) and of disease-free survival (B). Two of 14 patients in the radiotherapy group developed a local recurrence, one patient died in an accident without evidence of disease, and 11 patients were censored. In contrast, in the control group 11 patients experienced local recurrence and three patients were censored. Nine of 14 patients in the radiotherapy group developed a recurrence, one patient died in an accident without evidence of disease, and four patients were censored. In the control group, in 11 patients recurrence was documented, and three patients were censored.

tinal symptoms were on mitotane, which may also have caused nausea. One patient developed a partial Budd-Chiari syndrome 3 months after radiotherapy but is presently free of hepatic symptoms or specific treatment 5 yr after treatment. In one patient, elevated blood pressure was observed 18 months after radiotherapy together with a decrease in kidney size and an increase of serum creatinine (CTC grade I).

Discussion

The results of our study indicate that adjuvant radiotherapy may significantly reduce the rate of local recurrence in patients with ACC. These findings are in agreement with two previous reports including a total of eight patients with ACC also suggesting a benefit of adjuvant radiotherapy. However, our study not only comprises the largest patient group to date but also for the first time for inclusion of a control group matched for tumor status and additional adjuvant therapy with mitotane.

TABLE 2. Adverse events

	Adverse event	Grade
Acute		
Gastrointestinal	Nausea (n = 8)	I-II
Skin	Dermatitis (n = 4)	I
	Hyperpigmentation (n = 1)	I
Others	Anorexia (n = 2)	I
	Fatigue (n = 3)	I-II
	Abdominal pain (n = 2)	I
Long-term	Impaired kidney function, increased serum creatinine (n = 1)	I
	Partial Budd-Chiari syndrome (n = 1)	

Adverse events were classified according the NCI CTC criteria v3.0 (20). All events that occurred within 3 months of radiotherapy were classified as acute.

Local tumor recurrence after seemingly curative surgery for ACC is common, and a recent analysis of data from the German ACC registry indicates that 60% of patients develop a local recurrence within 5 yr after complete tumor resection (Fassnacht, M., A. C. Koschker, and B. Allolio, unpublished data). However, this rather high recurrence rate in patients from the German ACC registry is even exceeded by the recurrence rate in our control group. The increased risk of recurrence in this patient cohort is most probably related to the fact that our study also included cases with advanced tumor stage or evidence for tumor spillage during surgery, respectively. In this context, the low rate of local recurrence in the group receiving radiotherapy is even more impressive.

The reduced rate of local tumor recurrence after radiotherapy contradicts the view that ACC is resistant to radiotherapy as it is stated in several publications (9, 10). This view is based on a limited number of studies that are often anecdotal or omit important technical aspects of radiotherapy. Furthermore, the results of these reports are conflicting. However, there are also reports indicating some efficacy of radiotherapy (4, 11–17). Moreover, the recent consensus conference on the management of ACC treatment judged radiotherapy in ACC as effective (6). Based on the limited available data, the authors stated that radiotherapy is recommended in the treatment of bone, brain, and other metastases as well as in symptomatic local recurrence. In the last few decades, the technique of radiotherapy has been significantly improved and CT-based 3D planning, use of multiple field technique with individual collimation, and high photon energy dosage are now established methods, whereas several of the older studies were performed without these techniques.

It is well known from radiotherapy in other tumor entities that major adverse events after abdominal radiotherapy are rare when using CT-based 3D planning with calculated target volumes and protection of critical organs like spinal cord, kidney, and liver. In our series, none of the patients developed any grade III or IV adverse events. Of note, three of eight patients who experienced gastrointestinal problems were concomitantly treated with mitotane, which may in-

duce similar symptoms. Therefore, the true rate of side effects might be even lower.

In our study, no significant reduction in disease-free and overall survival was found. This might indicate that disease-free survival and overall survival are more dependent on the development of distant metastases than on local recurrence. However, the sample size of our study population is small and follow-up is still short, limiting the statistical power to detect differences. Moreover, the detailed analysis of the matched pairs reveals that in the radiotherapy group more patients were diagnosed in a more advanced stage (three patients with stage IV *vs.* no patients in the control group). Thus, a larger trial with a longer follow-up is required to fully assess the efficacy of adjuvant radiotherapy.

Our study has important limitations. Firstly, the analysis was performed retrospectively. Moreover, matching of controls was hampered by the still limited number of patients included in the German ACC registry. Accordingly, complete matching for all different parameters was not possible in all cases. However, the small remaining differences between the groups would have favored a poorer outcome in the radiotherapy group.

In conclusion, adjuvant radiotherapy should be considered in patients at high risk of local recurrence, and a prospective randomized trial of this treatment option is now justified.

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References

1. **Wajchenberg B, Albergaria PM, Medonca B, Latronico A, Campos CP, Ferreira AV, Zerbini M, Liberman B, Carlos GG, Kirschner M** 2000 Adrenocortical carcinoma: clinical and laboratory observations. Cancer 88:711–736
2. **Dackiw AP, Lee JE, Gagel RF, Evans DB** 2001 Adrenal cortical carcinoma. World J Surg 25:914–926
3. **Allolio B, Fassnacht M** 2006 Adrenocortical carcinoma: clinical update. J Clin Endocrinol Metab 91:2027–2037
4. **Pommier RF, Brennan MF** 1992 An eleven-year experience with adrenocortical carcinoma. Surgery 112:963–970; discussion, 970–971
5. **Stojadinovic A, Ghossein RA, Hoos A, Nissan A, Marshall D, Dudas M, Cordon-Cardo C, Jaques DP, Brennan MF** 2002 Adrenocortical carcinoma: clinical, morphologic, and molecular characterization. J Clin Oncol 20:941–950
6. **Schteingart DE, Doherty GM, Gauger PG, Giordano TJ, Hammer GD, Korobkin M, Worden FP** 2005 Management of patients with adrenal cancer: recommendations of an international consensus conference. Endocr Relat Cancer 12:667–680
7. **Hahner S, Fassnacht M** 2005 Mitotane for adrenocortical carcinoma treatment. Curr Opin Investig Drugs 6:386–394
8. **Bellantone R, Ferrante A, Boscherini M, Lombardi CP, Crucitti P, Crucitti F, Favia G, Borrelli D, Boffi L, Capussotti L, Carbone G, Casaccia M, Cavallaro A, Del Gaudio A, Dettori G, Di Giovanni V, Mazziotti A, Marrano D, Masenti E, Miccoli P, Mosca F, Mussa A, Petronio R, Piat G, Marazano L** 1997 Role of reoperation in recurrence of adrenal cortical carcinoma: results from 188 cases collected in the Italian National Registry for Adrenal Cortical Carcinoma. Surgery 122:1212–1218
9. **Hutter Jr AM, Kayhoe DE** 1966 Adrenal cortical carcinoma. Clinical features of 138 patients. Am J Med 41:572–580
10. **Luton JP, Cerdas S, Billaud L, Thomas G, Guilhaume B, Bertagna X, Laudat MH, Louvel A, Chapuis Y, Blondeau P, Bonnin A, Bricaire H** 1990 Clinical features of adrenocortical carcinoma, prognostic factors, and the effect of mitotane therapy. N Engl J Med 322:1195–1201
11. **Percarpio B, Knowlton AH** 1976 Radiation therapy of adrenal cortical carcinoma. Acta Radiol Ther Phys Biol 15:288–292
12. **King DR, Lack EE** 1979 Adrenal cortical carcinoma: a clinical and pathologic study of 49 cases. Cancer 44:239–244
13. **Didolkar MS, Bescher RA, Elias EG, Moore RH** 1981 Natural history of adrenal cortical carcinoma: a clinicopathologic study of 42 patients. Cancer 47:2153–2161
14. **Magee BJ, Gattamaneni HR, Pearson D** 1987 Adrenal cortical carcinoma: survival after radiotherapy. Clin Radiol 38:587–588
15. **Nader S, Hickey R, Sellin R, Samaan N** 1983 Adrenal cortical carcinoma. A study of 77 cases. Cancer 52:707–711
16. **Venkatesh S, Hickey RC, Sellin RV, Fernandez JF, Samaan NA** 1989 Adrenal cortical carcinoma. Cancer 64:765–769
17. **Markoe AM, Serber W, Micaily B, Brady LW** 1991 Radiation therapy for adjunctive treatment of adrenal cortical carcinoma. Am J Clin Oncol 14:170–174
18. **Stewart DR, Jones PH, Jolleys A** 1974 Carcinoma of the adrenal gland in children. J Pediatr Surg 9:59–67
19. **DeLellis RA, Lloyd RV, Heitz PU, Eng C** 2004 World Health Organization classification of tumours. Pathology and genetics of tumours of endocrine organs. New York: WHO; 136
20. 2003 Common Terminology Criteria for Adverse Events v3.0 (CTCAE). http://ctep.cancer.gov/reporting/ctc.html

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