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The Role of Radiation Therapy in the Management of Adrenal Carcinoma and Adrenal Metastases

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The use of radiation therapy (RT) to treat adrenal tumors has historically been limited by the risk of normal tissue toxicity, given the proximity of the adrenals to radiosensitive structures, such as the kidney, stomach, intestine, and spinal cord. However, contemporary techniques have made RT safe and effective for use in the management of adrenal carcinoma and adrenal metastases. Data on recent advances in the use of RT to treat adrenocortical carcinoma and adrenal metastases are reviewed, in both surgical and non-surgical settings.
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KEY WORDS: adrenal; radiation

INTRODUCTION

Historically, external beam radiation therapy (RT) has not been a preferred treatment option for adrenal tumors. The proximity of the adrenals to radiosensitive structures, such as the kidney, stomach, intestine, and spinal cord, limited the use of RT due to the risk of normal tissue toxicity. With older RT techniques, large radiation fields were used, encompassing the adjacent organs and limiting the doses that could be safely prescribed. Several technological advances have addressed these challenges. First, computed tomography (CT)-based planning allows accurate localization of the target and of nearby organs, so three-dimensional treatment plans can be developed that minimize dose to sensitive structures. Intensity-modulated radiation therapy (IMRT), a further refinement of three-dimensional treatment planning, uses detailed beam shaping and non-uniform dose across each field to create unique conformal dose distributions with sharp gradients, thus increasing the ability to target defined volumes and limit normal tissue exposure. Additionally, image guidance, using diagnostic quality imaging and cone-beam CT scans on the linear accelerator, allows confirmation of accurate patient and target positioning at the time of treatment. Finally, four-dimensional CT scans, which can be performed at the time of the treatment planning, provide information about moment-to-moment movement of both the tumor and normal tissues within the treatment field with breathing. The degree of tumor motion can be measured and used to plan treatments that account for the respiratory motion of the target, allowing reduction of the dose to the normal surrounding tissues. Using these contemporary techniques, RT may be used to safely and effectively treat adrenal carcinoma and should be considered as part of multidisciplinary management. Below, we review the data regarding use of RT in the treatment of adrenocortical carcinoma (ACC) and adrenal metastases.

ADRENOCORTICAL CARCINOMA

ACC is a rare malignancy, with an annual worldwide incidence of 1–2 cases per million people [1]. It is characterized by a high risk of recurrence and a poor prognosis; the reported 5-year disease-free survival ranges from 13% to 82% [2]. Although the cornerstone of treatment is surgical resection, rates of local recurrence are high. Even after seemingly complete resections, local control ranges from 19% to 60% [3–6]. Furthermore, the extent of residual local disease after resection is significantly associated with outcome. According to a National Cancer Data Base analysis, the 5-year overall survival for patients with uninvolved margins was 46%, with microscopically involved margins was 21%, and with macroscopically involved margins was 10% ($P < 0.0001$) [7]. These findings suggest an important role for additional local therapy after surgery, particularly in the setting of positive margins. In addition, approximately one-quarter of patients present with unresectable disease and may benefit from a non-surgical modality to provide local control [7].

The role of RT in the management of ACC continues to be defined. RT had been considered ineffective in the treatment of ACC because several small, older series reported a poor response and concluded that ACC was a radioresistant tumor [8–13]. However, since the publication of these reports, radiotherapeutic techniques have undergone significant improvements.

Two studies making use of contemporary techniques show a promising role for RT in the management of ACC. First, in a recent publication, Sabolch et al. [14] reported their experience with ACC patients who underwent surgical resection, resection with adjuvant RT, or RT with definitive intent. Their series included 58 patients, representing 64 individual instances of treatment: 37 for primary disease and 27 for recurrent disease. Fifty instances of treatment were to the adrenal gland or fossa, and 14 were to metastatic sites. In addition to surgery and/or RT, 19 patients received mitotane, 9 received cytotoxic chemotherapy, and 21 received both. RT was used in 26 instances, 10 of which were in the adjuvant setting. Three-dimensional conformal RT techniques were used for the majority of patients, although several patients treated later during the study period received IMRT. For patients treated with postoperative RT, the median dose was 53.4 Gy (range: 45–57 Gy) to the tumor bed, with a standard fractionation schedule of 1.8–2.0 Gy/day. For patients receiving definitive RT, the gross tumor was treated to 39.2 Gy (range: 22.5–73.5 Gy), with various fractionation schedules.

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Local failure occurred in 16 of the 38 instances of surgery alone, in 2 of the 10 instances of surgery with adjuvant RT, and in 1 of the 16 instances of RT alone. Patients who did not receive RT were at 4.7 times the risk of local failure compared with those who did receive RT (95% CI: 1.2–19.0, $P = 0.030$) [14].

Additionally, Fassnacht et al. [6] screened the German ACC Registry for patients who had received adjuvant RT after a macroscopically complete resection and compared their outcomes to matched patients who had not received RT. Fourteen patients were identified who had received adjuvant RT to the adrenalectomy bed; of these, 7 were also treated to the bilateral para-aortic lymph nodes. The median dose was 50.4 Gy (range: 41.4–56 Gy), given in 1.8–2.0 Gy daily fractions. Twelve patients were treated with three-dimensional conformal RT; the remaining two patients were treated with two-dimensional planning. Local recurrence appeared in 2 of 14 patients in the RT group and in 11 of 14 patients in the control group [6]. These recurrences developed in the adrenalectomy bed and the adjacent ipsilateral and contralateral interaortocaval lymph nodes [15]. The probability of freedom from local recurrence at 5 years after surgery was 79% in the RT group versus 12% in the unirradiated group ($P < 0.01$) [6].

The findings of these two studies challenge the belief that ACC is radioresistant. Both studies show that RT significantly lowers the risk of local recurrence postoperatively. Additionally, Sabolch et al. found good local control in the setting of radiation monotherapy, suggesting that it should be considered for patients with surgically unresectable disease. Furthermore, in both studies, RT was well tolerated, consistent with the more extensive data regarding irradiation of adrenal metastases.

Although data regarding adjuvant or definitive RT in ACC are limited, RT has a well-established role in the palliative setting. Multiple series have reported use of RT to palliate symptoms from bone metastases or bulky abdominal tumors. In the majority of patients, symptomatic control has been achieved [13,16–18].

Experts have recognized the potential role of RT in the management of ACC. An international panel recommended use of RT for palliation of symptoms from metastases or large primary tumors. Given the limited data regarding definitive or adjuvant RT, they did not make a firm recommendation and stated that for each patient ''the risk/benefit ratio should be individually assessed'' [1]. Another group of experts recommended adjuvant RT in the setting of microscopically or macroscopically positive margins after maximal safe resection, locoregionally advanced disease, and/or positive lymph nodes without evidence of distant metastases. In patients with localized tumor and an R0 resection, adjuvant RT was recommended if the tumor measures greater than 8 cm in diameter, invades the vasculature, or has a high proliferative index. Regarding RT technique, the panel recommended irradiation of the surgical bed and draining lymphatics to $\geq$40 Gy and a boost to the surgical bed to $\geq$50 Gy with conventional fractionation. They additionally advised starting RT within 3 months of surgery and treating with concurrent mitotane [15].

Despite these expert recommendations, ACC patients in the United States rarely receive RT. Analyses of the Surveillance, Epidemiology, and End Results database and the National Cancer Data Base show that RT was used in the management of ACC patients in 9.5–11.7% of cases [7,19,20]. A possible reason for the rare use of RT is that studies have failed to demonstrate that it improves survival. One explanation why increased local control may not translate into a survival benefit is that patients die of distant disease, irrespective of local measures. However, it is possible that statistical significance could not be reached because of the small sample sizes, and a sufficiently powered study would reveal improved survival.

As progress is made in systemic therapy to address distant disease, the benefit derived from local control will likely increase. Furthermore, systemic therapy and RT may enhance one another's efficacy; recently published in vitro data suggest that ionizing radiation and mitotane, a steroidogenesis inhibitor and adrenolytic agent, synergistically inhibit adrenocortical cell growth [21,22].

In summary, ACC patients would likely benefit from a multidisciplinary approach that incorporates the use of RT with surgery and systemic therapy. While both adjuvant and definitive RT appear to improve local control, it remains to be demonstrated whether this effect translates into improved survival.

ADRENAL METASTASES

Given their rich blood supply, the adrenal glands are frequently involved by metastatic disease. In a review of 1,000 consecutive autopsies of patients with carcinoma, the adrenal glands were involved in 27% of the cases [23]. The majority of adrenal metastases are from melanoma and lung, breast, renal, and gastrointestinal tumors [23–25].

Historically, local therapy had been used only to palliate symptoms in patients with metastatic cancer. Recently, however, aggressive management of metastases in the setting of oligometastatic disease has been shown to improve survival. As one example, several studies have demonstrated that adrenalectomy improves survival in select patients with adrenal metastases from various primary tumors [26–31]. Tanvetyanon et al. [32] performed a meta-analysis of non-small cell lung cancer patients who underwent resection of isolated adrenal metastases and found a 5-year survival rate of 25%. They noted that no survival at 5 years would have been expected with palliative chemotherapy alone and concluded that adrenalectomy should be considered as a therapeutic option for patients with metachronous or synchronous metastases [32].

However, not all patients are candidates for surgical resection due to medical comorbidities, locally invasive tumor, or personal preference. For these patients, RT may be an alternative to surgery. It is performed on an outpatient basis without sedation and with minimal morbidity.

Recent Advances

For isolated metastatic disease to the adrenals, highly focal RT to the metastatic lesion, without including regional nodes, may be an appropriate strategy. Stereotactic body radiation therapy (SBRT) makes use of CT-based planning, IMRT, and image guidance to deliver high individual doses of radiation with extreme precision (Fig. 1). Large doses of radiation are administered on 5 or fewer days, rather than the low daily doses administered over the course of several weeks with conventional fractionation. This hypofractionated schedule provides a greater tumor ablative effect [33].

Many groups have published favorable results using hypofractionated RT to treat adrenal metastases (Table I). Various fractionation schedules have been used, and a number of series describe a mixed population of patients who have been treated with both hypofractionated and conventionally fractionated RT. Hypofractionation has yielded better local control. For example, Casamassima et al. [34] treated 48 patients with 1–3 fractions of SBRT and achieved 90% local control at 2 years. Researchers using a lower total dose or greater fractionation have reported more local failures (Table I).

All available data are from retrospective, single-arm series; however, a number of authors comment that the survival rates compare favorably to historic controls. Oshiro et al. note that their patients were not candidates for surgical resection and therefore may have been expected to have a poorer prognosis than adrenalectomy patients; however, the survival rates of their patients with metachronous metastases were similar to those of the adrenalectomy patients

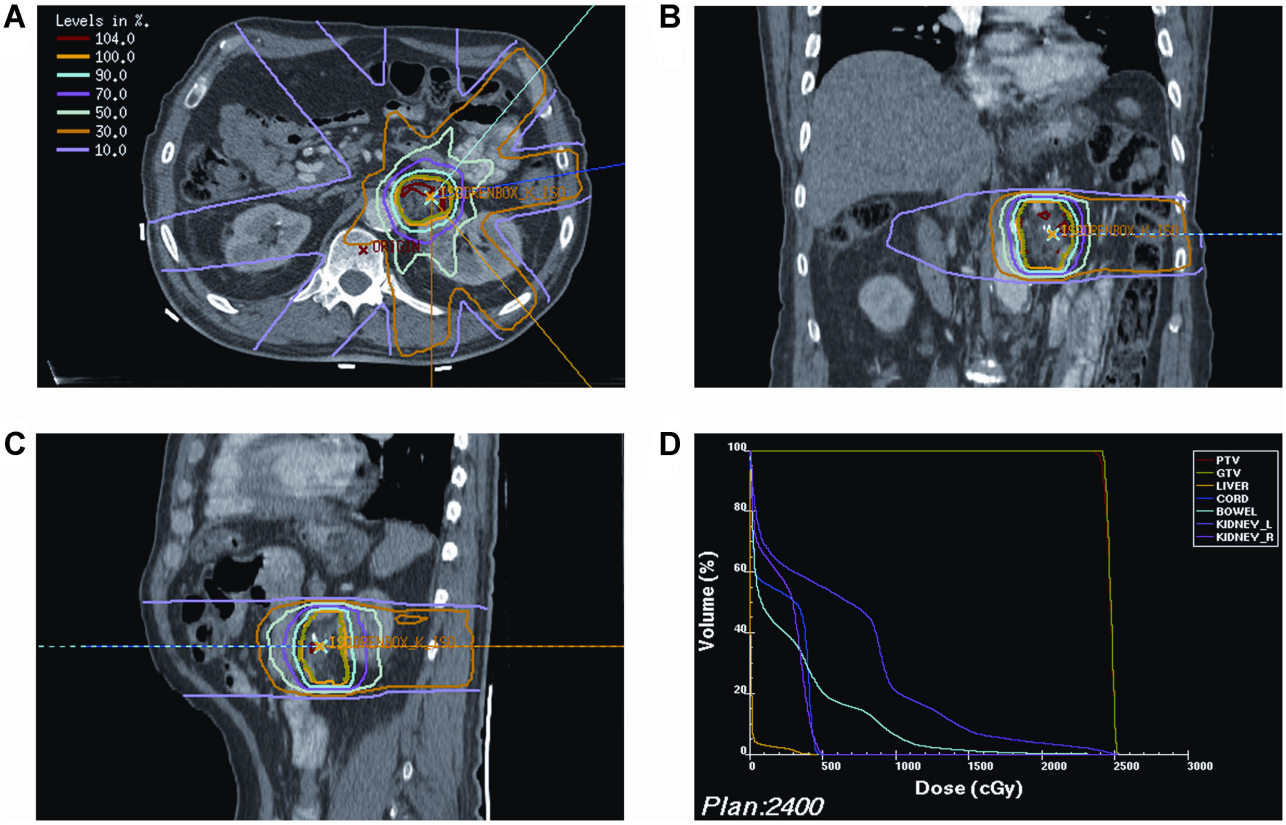

Fig. 1. Stereotactic body radiation therapy treatment plan for an adrenal metastasis. **A**: Axial slice. **B**: Coronal slice. **C**: Sagittal slice. **D**: Dose-volume histogram.

reported by Tanvetyanon et al. They suggest that RT may have a similar effect as adrenalectomy to improve survival in such patients [35]. Additionally, Holy et al. [36] report a median overall survival of 23 months among non-small cell lung cancer patients with isolated adrenal metastases treated with SBRT, a rate comparable to that of similar patients managed with adrenalectomy.

Complications from SBRT for adrenal metastases are rare. In the series listed in Table I, grade $\geq$3 toxicity was not observed.

Among patients with symptomatic adrenal metastases, a number of studies, including those listed in Table I, report excellent rates of palliation achieved with both hypofractionated and conventionally fractionated RT.

Thus, SBRT is a safe and effective local therapy for adrenal metastases. While it is useful for palliation, it may also be an alternative to adrenalectomy for oligometastatic patients who are not surgical candidates.

TABLE I. Reports of Stereotactic Body Radiation Therapy for Adrenal Metastases

Refs.	Number of patients/lesions	Primary tumor	Median dose/number of fractions	Treatment intent	Local control	Overall survival
Barney et al. [37]	6/6	Various	45 Gy/5	Definitive	98% at 6 months, 87% at 1 year[a]	90% at 6 months, 62% at 1 year[a]
Casamassima et al. [34]	48/48	Various	36 Gy/3	Definitive	90% at 1 and 2 years	39.7% at 1 year, 14.5% at 2 years
Chawla et al. [38]	30/35	Various	40 Gy/10	Definitive (14), Palliative (16)	91% at 6 months, 55% at 1 year, 27% at 2 years	44% at 1 year, 25% at 2 years
Holy et al. [36]	18/18	Lung	40 Gy/5	Definitive (13), Palliative (5)	Median progression-free survival 4.2 months	Median overall survival 21 months
Katoh et al. [39]	9/10	Various	48 Gy/8	Definitive	100% at 1 year	78% at 1 year
Oshiro et al. [35]	11/11 hypofractionation, 8/8 conventional fractionation	Lung	45 Gy/10	Definitive	79% at 10 months	56% at 1 year, 33% at 2 years, 22% at 3 years
Torok et al. [40]	7/9	Various	16 Gy/1	Definitive	63% at 1 year	Median overall survival 8 months

[a]Rates reported for population of 47 patients treated for 50 abdominopelvic tumors and not reported separately for adrenal patients.

CONCLUSIONS AND FUTURE DIRECTIONS

Recent studies reveal a promising role for RT in the definitive management of primary or metastatic adrenal carcinoma. The use of SBRT is emerging as a locally ablative therapy that has been effective for controlling metastatic lesions involving the adrenal glands and may also be another local therapy option for patients with unresectable ACC. Prospective, multi-institutional, randomized trials are needed to better define the role of RT as an alternative or adjunct to surgical resection and to investigate if combinations with systemic therapy may improve both local and systemic disease control.

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