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Stereotactic Body Radiotherapy for the Treatment of Adrenal Metastases – A Case-Based Radiosurgery Society Practice Guide and Review

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Running title

SBRT for Adrenal Metastases

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Adrenal gland, metastasis, stereotactic body radiotherapy, stereotactic ablative radiotherapy, SBRT, SABR

Abstract

Purpose: Adrenal metastases are frequently diagnosed in patients with common solid tumors. Surgical adrenalectomy has historically been used for their management. However, stereotactic body radiotherapy (SBRT) has emerged as a safe and effective alternative. Careful treatment planning is essential, considering multiple factors such as tumor size and location, motion management, dose and fractionation, and proximity to adjacent organs at risk. This case-based practice guide and review provides an overview of SBRT for the management of adrenal tumors, with a particular focus on adrenal metastases.

Methods and Materials: Three clinical scenarios were selected to illustrate the use of SBRT in managing adrenal tumors. These include a small right-sided metastasis treated with single-fraction, fiducial-based SBRT, a large left-sided metastasis treated with fractionated SBRT under magnetic resonance imaging guidance, and a case of bilateral metastases, which emphasizes the potential risk of adrenal insufficiency. We also address the limited evidence available regarding the management of primary adrenal gland tumors with SBRT.

Results: SBRT is an effective treatment modality for most adrenal tumors, demonstrating a favorable safety profile. Thoughtful treatment planning and an understanding of potential pitfalls, limitations, and risks are essential to ensure the appropriate use of SBRT.

Conclusions: This case-based guide and review provides a comprehensive overview of SBRT for treating adrenal tumors, specifically metastases. We present and discuss clinical cases and relevant literature, highlighting key considerations specific to adrenal SBRT.

Background

Tumors of the adrenal gland are reported in approximately 4.4 to 7.3% of adults, with most cases being benign adenomas [1, 2]. Due to their rich vascular supply, the adrenal glands are also a frequent site of metastatic disease from primary tumors of the lung, stomach, pancreas, liver, and kidney [3]. The prevalence of adrenal metastases in patients with metastatic disease is approximately 15 to 35%, with adrenal metastases accounting for approximately 7.5% of all adrenal masses [3-5]. The vast majority, roughly 85%, of all malignant adrenal lesions are metastases [5]. Patients with adrenal tumors should undergo a diagnostic work-up to determine whether the lesion is malignant or hormonally active, which can guide management [6]. A comprehensive diagnostic approach for this purpose is reported elsewhere [6]. Most cases of adrenal metastases are unilateral and often found during imaging studies obtained for cancer staging rather than incidentally [7].

Treatment options for managing adrenal gland metastases include surgery, interventional radiology techniques such as radiofrequency ablation and chemoembolization, and radiotherapy [8, 9]. Stereotactic body radiation therapy (SBRT), however, has become one of the primary treatment modalities for managing adrenal metastases, especially in patients with a limited metastatic disease burden, i.e., oligometastatic or oligoprogressive disease [10, 11]. A recent pattern of care analysis reported a considerable increase in adrenal metastases treated with SBRT compared to surgery [11]. SBRT allows for the delivery of ablative doses to a target using highly conformal techniques, while maximizing the sparing of surrounding healthy tissue and organs at risk (OARs). This ablative treatment achieves high local control rates with a favorable safety profile [10]. Careful treatment planning, accounting for the size and local extension of the metastases, their proximity to critical OARs, respiratory motion, and hormone status, along with close follow-up posttreatment, are all essential for the treatment's success. This case-based guide and review provides practical and concise information

for the use of SBRT in the management of adrenal metastases. Recommendations for treatment planning, dose and fractionation, motion management, and follow-up are provided, along with a discussion of potential pitfalls. Finally, we review the limited evidence regarding the management of primary adrenal tumors with SBRT.

SBRT for Adrenal Metastases

Conventionally fractionated external beam radiotherapy has been used for decades to treat metastases, including adrenal metastases. Technical advances have led to an increased availability and use of ablative radiotherapy, including SBRT, stereotactic radiosurgery, and fractionated stereotactic radiotherapy. SBRT has become one of the primary treatment modalities for adrenal metastases as a non-invasive and effective alternative to surgical resection, which usually involves total adrenalectomy [10-12]. The treatment indication for SBRT should be based on various factors, including but not limited to patient preferences, overall disease burden, and course of (oligo)metastatic disease, size of the metastasis, life expectancy, available systemic treatment options, and symptoms [13]. The increasing role of metastasis-directed treatment in patients with oligometastatic or oligoprogressive cancer provides further rationale for using SBRT [14-16]. The diagnosis of an adrenal metastasis is typically based on imaging, including contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) [17]. Positron emission tomography (PET) using ^{18}Fluorodeoxyglucose (FDG) as a tracer has gained popularity in cancer staging and response assessment and is helpful for the detection of adrenal metastases [17, 18]. Biopsy for tissue analysis can be justified in cases where a histopathological diagnosis is lacking.

Once the SBRT indication for treating an adrenal gland metastasis is confirmed, treatment planning consists of obtaining thin-slice four-dimensional (4D) or breath-hold CT. Due to the mobility

and the retroperitoneal location of the adrenal glands in the upper abdomen, intrafraction motion management must be considered. An internal target volume (ITV) should be created, accounting for target motion, using a 4D or breath-hold CT, either during inspiration or expiration. Using a maximum intensity projection, commonly referred to as MIP, can help in the ITV delineation, ensuring that all anatomical positions throughout the breathing cycle are considered. Intrafraction tracking and gating techniques may be utilized to safely apply ablative radiation doses [19-21]. While tracking techniques enable a continuous delivery of radiation focused on the target, gating techniques will deliver radiation only when the target is located in a prespecified anatomical position. Therefore, fiducial- and MRI-guided treatment techniques with tracking or gating can help minimize the total planning target volume (PTV) by reducing or eliminating the need for ITVs, while ensuring the accurate anatomical reproducibility of the target lesion [22, 23]. This helps to reduce the volume of gastrointestinal luminal structures, such as the stomach, small and large intestines, and duodenum, that receive high doses of radiation. Keeping an empty stomach during CT simulation and treatment can potentially increase the distance between the left adrenal metastasis and the stomach. Surface-guided techniques with breath-hold are also feasible and have been reported [12]. The use of abdominal compression to dampen respiratory motion is also an acceptable approach [24]. However, abdominal compression has the potential to push OARs, such as the small and large bowel, closer to the treatment target, which could make it more challenging to deliver ablative doses to the adrenal metastasis without exceeding dose constraints for OARs.

Adrenal SBRT prescription doses and the number of fractions have varied across reported studies and may depend on various factors, including, but not limited to, the size and extent of the metastasis, mobility, proximity to critical OARs, and patient performance status [10, 25]. Recent analyses highlight a dose-response relationship, favoring a high biologically effective dose (BED) [12, 25]. To achieve durable local control of metastases, a BED, assuming an α/β ratio of 10, of at least 80 Gy, but

ideally, ≥ 100 Gy, is recommended [25]. Therefore, acceptable ablative regimens may include 24-26 Gy in a single fraction, 39-45 Gy in 3 fractions, and 45-50 Gy in 5 fractions. The choice for fractionation is predominantly dictated by the size of the metastasis and proximity to OARs. Frequently used dose regimens are summarized in Table 1. The impact of tumor histology on local control remains elusive [26]. Therefore, there is insufficient evidence to adjust the dose based on histology alone. The prescription isodose line may range from 60 to 100%, depending on the treatment platform and desired dose heterogeneity within the PTV [12]. Doses exceeding 100% of the prescribed dose can be used for intratumoral dose escalation. Target delineation involves defining the gross tumor volume (GTV), which includes the macroscopic lesion and should incorporate all available imaging information prior to treatment, including CT simulation, PET-CT, and/or MRI, when applicable. Generally, the GTV comprises the full volume of the adrenal metastasis, often leading to irradiating the whole affected adrenal gland. A clinical target volume (CTV) expansion is typically not performed, given the inclusion of the entire adrenal gland in the GTV. However, a potential scenario in which a CTV expansion may be considered is when suspected or confirmed local invasion of adjacent organs, such as the liver or kidney, is present, most commonly in cases of large metastases. An ITV, which encompasses all positions in the entire respiratory cycle, is expanded from the GTV, depending on the treatment technique. In practice, for patients planned using a 4D CT approach, the ITV may often be first contoured on the MIP, then reviewed and checked on all of the individual phases of the respiratory cycle to ensure the entire lesion is included throughout breathing. This is especially important when the adrenal metastasis is adjacent to critical structures and the patient has a high respiratory rate, in which case contouring on the MIP alone may underestimate the target volume at the lesion margins compared to the composite of all 4D CT phases. To account for set-up uncertainties, a PTV margin of 3-5 mm is frequently used, depending on the treatment technique and onboard imaging verification [12, 22, 23]. OARs in proximity to the adrenal glands include the duodenum, jejunum, ileum, kidney, liver, stomach, and spinal cord. Careful treatment

planning and consideration of dose constraints are crucial to avoid treatment-associated high-grade toxicity. For non-adaptive approaches, a planning OAR volume, also known as PRV, can be created by adding a specific margin – typically 2-3 mm – to particularly sensitive OARs to account for residual setup uncertainties and organ motion with the goal of further decreasing the risk of treatment-associated complications. A summary of frequently used dose constraints for adjacent OARs is provided in Table 1.

The adrenal glands play a vital endocrinological role in the synthesis of multiple hormones, including catecholamines, mineralocorticoids, glucocorticoids, and androgens. Metastatic destruction with interventions, such as SBRT, can potentially cause insufficient hormone production, leading to adrenal insufficiency and, in severe cases, an adrenal crisis [7, 27, 28]. Therefore, a careful assessment of symptoms prior to and after SBRT is necessary to avoid unexpected and untreated hormone deficiencies, specifically in the case of bilateral adrenal metastases [7, 27]. While patients with unilateral adrenal metastasis in the presence of a healthy contralateral adrenal gland are at low risk, bilateral disease and unilateral disease in the absence of a contralateral healthy adrenal gland have a notable risk of developing adrenal insufficiency [10, 27]. As symptoms of adrenal insufficiency can be non-specific and vague, such as fatigue, weight loss, joint pain, and nausea, lab tests should be done regularly in patients with an expected risk of adrenal insufficiency [29]. In patients at risk, routine laboratory testing demonstrating hyponatremia, hyperkalemia, and/or hypoglycemia should raise suspicion for the development of an insufficiency [29]. Subsequent testing, including measurements of serum cortisol and plasma adrenocorticotropic hormone (ACTH), as well as utilizing an ACTH stimulation test, can confirm the diagnosis of a primary adrenal insufficiency [29]. A referral to an endocrine specialist is warranted in cases at higher risk for developing adrenal insufficiency and to ensure an adequate hormone replacement therapy is initiated without delay. The time from radiotherapy to adrenal insufficiency may be up to two years, with most patients developing hormone deficits within 12 months after treatment [27, 28, 30]. Other toxicities from SBRT for adrenal metastases may include fatigue, nausea, vomiting,

diarrhea, abdominal pain, and, rarely, hemorrhage, gastric ulcer, or vertebral fractures [10, 12, 22, 23, 28, 30].

Follow-up typically involves a review of the medical history, a physical examination, and restaging imaging, often using CT scans. In selected cases, imaging with PET-CT or MRI might be appropriate and provide additional information for further management. The follow-up intervals for patients with metastatic disease depend on various factors, such as the disease burden and performance status, with intervals of every 3 to 6 months being the most commonly used. Treatment response assessment is predominantly based on the RECIST criteria [31]. It is important to note that an unchanged volume of the treated adrenal gland metastasis does not automatically imply treatment failure. PET-CT to assess metabolic response may be helpful in such cases, especially when a pre-treatment PET-CT is available for comparison. The following cases will highlight modern SBRT principles for managing adrenal gland metastases.

Case-based Discussion and Review

Patient A

Patient A is a 71-year-old male with no history of any prior malignant disease who presented with unexplained weight loss. Ultrasound uncovered a right renal mass, verified by MRI, and he proceeded approximately one month after presentation to nephrectomy with the diagnosis of right renal cell carcinoma. Six months following his initial presentation, a routine CT of the chest, abdomen, and pelvis demonstrated a new right adrenal gland metastasis with no other locoregional or distant metastatic disease noted. The patient was referred to radiation oncology and given his oligometastatic disease and the size of the adrenal lesion, SBRT was recommended. The patient underwent single-fraction robotic

SBRT with a prescription dose of 24 Gy prescribed to the 70% isodose line, given the favorable location and size of the target and the distance to relevant OARs, rendering it possible to meet all dose constraints for a single-fraction treatment (Figure 1). Fiducials were placed for intrafraction motion tracking and alignment. The GTV was 6.0 cm^3, and the PTV was created by adding a 5 mm margin. The final PTV was 20.3 cm^3. Subsequent follow-up, including CT imaging, revealed no treatment-related toxicity at 3 and 9 months following SBRT. His last available follow-up, at 4 years and 4 months following SBRT, showed a complete response of his right adrenal metastatic lesion without any other metastases. This case highlights the ability to escalate the dose using a single-fraction fiducial-guided SBRT for small to medium-sized metastases with sufficient distance to OARs.

Historically, such cases may have been treated with prolonged courses with 2 Gy per fraction or moderately hypofractionated radiotherapy. SBRT allows for extreme hypofractionation, and although any tumor may be targeted with single-fraction SBRT, the selection of this regimen requires that a sufficient BED can be delivered, which is necessary for tumor cell kill without exceeding the tolerance of adjacent normal tissues (Table 1). This treatment approach is supported by radiobiological principles and extrapolation from other disease sites [12, 22, 25, 32, 33].

In the case of patient A, the adrenal metastasis was located between the liver and spine, remote from other dose-limiting gastrointestinal structures. The small size of this lesion, combined with our ability to deliver highly conformal treatment using robotic SBRT, resulted in a minimal dose being delivered to most of the liver and spine. At the same time, the bowel fell outside of the radiation field. Nevertheless, reliable motion management with fiducial placement for motion tracking was critical. With the tumor remote from OARs and motion adequately managed, dose escalation with a single fraction was possible, resulting in improved disease control while meeting the constraints of OARs. When lesion size, adjacent normal tissues, or respiratory motion make it unfeasible to deliver the required BED with a single fraction, fractionated regimens should be employed. In general, a target BED

of at least 80 Gy, and preferably ≥ 100 Gy, should be the goal to achieve durable local control [25]. In palliative settings, i.e., when symptoms are suspected to be caused by an adrenal metastasis in the context of widely metastatic disease, lower doses may be more appropriate.

Patient B

Patient B is a 58-year-old male with stage IV non-small cell lung cancer of the right upper lobe. He underwent palliative radiotherapy to 30 Gy in 10 fractions to the mediastinum for superior vena cava syndrome one month after his initial diagnosis. A colonoscopy and biopsy of an ileal mass confirmed the presence of a lung primary, with molecular testing revealing programmed cell death-ligand 1 (PD-L1) expression of 80%. He completed four cycles of carboplatin, pemetrexed, and pembrolizumab before starting maintenance pembrolizumab. Approximately 10 months later, he presented with an enlarging abdominal lymph node, which was resected and found to be consistent with a metastatic lesion. He resumed maintenance pembrolizumab. After an additional 17 months, he subsequently presented with a solitary oligoprogressive left adrenal gland metastatic lesion. The multidisciplinary consensus recommendation was to treat this left adrenal gland metastasis with SBRT. Due to its size and location, a total of 50 Gy in 5 fractions was delivered over 7 days using magnetic resonance-guided adaptive SBRT (MRgSBRT) (Figure 2). At the last available follow-up, one year after treatment, CT showed stable disease. The metabolic response was confirmed by comparing pre- and posttreatment PET-CT.

The treatment of larger adrenal gland metastases, especially left-sided lesions with SBRT, poses potential challenges due to the anatomical complexity of this location and the proximity of the adrenal gland to radiosensitive gastrointestinal OARs, such as the stomach and duodenum. Additionally, respiratory motion can further complicate accurate treatment delivery. The development of magnetic resonance-guided linear accelerators has advanced our ability to deliver SBRT to abdominal and soft tissue targets, such as adrenal metastases. MRgSBRT capitalizes on superior soft tissue resolution, real-

time imaging, and adaptive planning capabilities to enhance target accuracy and OARs sparing, thereby addressing some of the challenges associated with traditional CT-based SBRT [34]. Clinical implementation of MRgSBRT has enabled the delivery of higher BED in selected, anatomically challenging cases. In addition to delivering an escalated radiation dose while optimally sparing OARs, MRgSBRT allows for adapting a treatment plan in real-time, which can account for inter- and intrafractional anatomical variations [35, 36]. Growing evidence supports the efficacy and safety of MRgSBRT for the management of adrenal gland metastases [23, 37]. Patient B's case highlights the potential of adaptive MRgSBRT in managing complex adrenal metastases, particularly in patients with larger tumors or those with significant inter- and intrafractional variability (Figure 3). However, such tumors can also be efficiently and safely treated with carefully planned CT- or fiducial-guided treatments. The decision on which fractionated SBRT regimen is best suited for a specific case should be primarily based on the location, size, and motion of the metastasis, as well as its proximity to adjacent OARs.

Patient C

Patient C is a 68-year-old man with stage IB pT2a N0 poorly differentiated adenocarcinoma of the lung who underwent right upper lobectomy and mediastinal lymph node dissection, followed by adjuvant chemotherapy. Approximately 4 years later, follow-up CT imaging revealed a new 1.3 cm spiculated nodule in the right middle lobe, adjacent to the surgical suture, concerning for local recurrence. He received SBRT with 50 Gy in 5 fractions to his right middle lobe lesion. Unfortunately, 3 months later, he was noted to have metastatic progression, with PET-CT showing a good response at the treated right upper lobe recurrence, but new bilateral FDG-avid adrenal nodules and 2 additional bone metastases, one in the right ilium, the other in the sacrum. The patient underwent a left adrenal gland biopsy, confirming metastatic adenocarcinoma with PD-L1 expression of 50%. The patient proceeded with

pembrolizumab plus radiotherapy on a clinical trial investigating the efficacy of SBRT in patients with oligometastatic solid tumors. The patient received MRgSBRT targeting his bilateral adrenal metastases to 50 Gy in 5 fractions (Figure 4). In addition, ablative radiotherapy with 30 Gy in 3 fractions was also delivered to the 2 detected bone metastases. The patient was referred to endocrinology. During follow-up, at 43 months after SBRT, he did not experience any adrenal insufficiency and did not require hormone replacement therapy. Serial PET-CT scans showed a good response at all treated metastatic sites, with no additional distant disease progression.

Bilateral adrenal involvement is common, with around 25% of patients with adrenal metastatic disease presenting with bilateral metastases at the time of diagnosis [7]. In total, approximately 40% of patients will suffer from bilateral metastases during their disease, including metachronous lesions [7]. Therefore, it is of utmost importance to create and consider summation plans when treating both adrenal metastases with SBRT in synchronous and metachronous settings.

One concerning potential complication of SBRT targeting adrenal metastases is adrenal insufficiency. Primary adrenal insufficiency should be anticipated when more than 90% of the adrenal reserve is destroyed with subsequent failure of cortisol production [7, 38, 39]. Patients with adrenal insufficiency can present with a plethora of symptoms, including, but not limited to, fatigue, loss of appetite, nausea, vomiting, unintentional weight loss, muscle or joint pain, hypotension, and dry skin [29]. In addition, lab abnormalities, such as anemia, hyponatremia, and hyperkalemia, can occur [29]. Given the destruction of healthy adrenal gland tissue due to both the metastatic lesion itself and ablative radiotherapy, adrenal insufficiency must be anticipated and accounted for when bilateral adrenal SBRT is planned. According to one study, adrenal insufficiency was present in up to 12.4% of patients with bilateral adrenal gland metastases, with a prevalence of 20% in metastases larger than 4 cm [7]. In a retrospective multicenter study analyzing 366 adrenal metastases receiving radiation therapy, 4 cases of adrenal insufficiency were noted, two of them in the setting of bilateral disease [28].

Another single institution study of 49 adrenal metastases treated with SBRT found that 3 out of the 6 patients with bilateral disease developed adrenal insufficiency after treatment [30]. In another retrospective study with 56 patients, the risk of adrenal insufficiency was 80% in patients who underwent radiotherapy either to both adrenal gland metastases or to a single remaining adrenal gland following prior surgical resection of the contralateral gland [27].

In summary, studies have shown significant variability in the rates of adrenal insufficiency after SBRT. The risk of adrenal insufficiency appears to be considerable in patients with bilateral disease and those with a single adrenal gland metastasis treated with SBRT after surgical resection of the contralateral gland [27]. As the time from treatment to adrenal insufficiency may be up to two years, with most patients developing hormone deficits within 12 months after treatment, it is crucial to establish care with endocrinology to allow for the early detection of adrenal dysfunction and timely management of adrenal insufficiency or adrenal crisis [27-30]. Adrenal insufficiency treatment usually comprises the replacement of hormones, including glucocorticoids and mineralocorticoids [29].

SBRT for Adrenal Pheochromocytoma and Paraganglioma

While adrenal metastases represent the primary treatment indication for adrenal SBRT, there are other less common adrenal tumors for which SBRT may be appropriate. For instance, SBRT may be used for the management of adrenal pheochromocytomas (PCC) [40-43]. PCC are rare neuroendocrine tumors that arise from chromaffin cells in the adrenal medulla, in contrast with paragangliomas (PGL), which arise from extra-adrenal chromaffin cells. A minority of these tumors are malignant and can develop distant metastases. A variety of management strategies have been proposed for malignant PCC, which include observation for asymptomatic or slow-growing disease, surgery, systemic therapy with chemotherapy, targeted therapy, or I-131-labeled metaiodobenzylguanidine [44]. The evidence for external beam radiotherapy in managing malignant

PCC is limited. One study analyzed 24 patients with 47 malignant PCC and PGL lesions, demonstrating promising results with external beam radiation therapy [40]. Symptom control was achieved for 81.1% of treated lesions, with 86.7% demonstrating radiographic stability after radiotherapy [40]. A limitation of this study was that 85% of the treated lesions analyzed were bone metastases. Another study investigating radiotherapy for malignant or advanced PCC and PGL included 41 patients with a total of 107 lesions, comprising 69% bone metastases, 30% soft tissue metastases, and 1% liver lesions [42]. A 5-year local control of 81% for all lesions was observed. Lesions treated with a BED ≥ 53 Gy, assuming an α/β ratio of 10, resulted in a local control rate of 91%. Notably, all 11 lesions treated with SBRT or radiosurgery were controlled throughout the median follow-up of 3 years [42].

These results suggest the potential efficacy and safety of radiotherapy, including SBRT, in the local management of malignant PCC and PGL and their metastases, albeit with very limited available evidence. A recent case report described the use of SBRT in the treatment of a 27-year-old man with von Hippel-Lindau disease who developed an infiltrative, PET-avid right adrenal bed recurrence 7 years after right adrenalectomy for PCC with elevated free metanephrines and normetanephrines [41]. He had also undergone a right nephrectomy for renal cell carcinoma one year prior to the adrenalectomy. The patient developed hypertension with the need for intensified anti-hypertensive medication, with PET-CT confirming an infiltrative, FDG-avid nodule in the right adrenal bed. The case was discussed in a multidisciplinary tumor board, and the patient was deemed not a surgical candidate due to medical comorbidities and prior surgeries. Therefore, the consensus multidisciplinary recommendation was for radiation treatment. He received SBRT to a dose of 24 Gy in 3 fractions. During and after SBRT, the patient was monitored, demonstrating improvement in blood pressure, allowing a reduction of his anti-hypertensive medication. Given the potential of sudden catecholamine release during or shortly after treatment of hormonally functional tumors and metastases, premedication with α-adrenergic receptor blockers must be considered [45].

Unfortunately, the patient presented two weeks later with headaches, hypotension, and uncontrollable, generalized seizures. Clinical examination during the postictal state demonstrated the absence of vital signs, and no exact cause of death was identified [41].

Considering the limited evidence for the treatment of adrenal PCC and PGL with SBRT, it might be a potential treatment option in selected cases and for the management of metastases. Whether the favorable results of treating head and neck PGL with radiosurgery and SBRT can be extrapolated to adrenal PGL remains unclear [46]. Surgical extirpation remains the mainstay of treatment for good surgical candidates with adrenal PCC and PGL.

Conclusion

The adrenal glands are one of the most common metastatic tumor sites. Although surgery has been the historical gold standard, SBRT has become an effective and safe treatment alternative. The available evidence demonstrates favorable local control rates with a BED ≥ 100 Gy, assuming an α/β ratio of 10, with low rates of high-grade toxicity. SBRT planning requires careful consideration of tumor location and size, motion management, dose and fractionation, and adjacent OARs dose constraints. This case-based review serves as a practical and concise guide for SBRT for the treatment of adrenal metastases. The first case involved a patient with a small, right-sided adrenal gland metastasis, highlighting the potential use of high-dose, single-fraction SBRT in selected cases with favorable anatomy. The second case described a large, left-sided adrenal metastasis, calling for fractionated SBRT and careful motion management. MRgSBRT enabled the safe delivery of an ablative dose to achieve local control while minimizing toxicity. The final case described bilateral adrenal metastases, which were successfully treated with fractionated SBRT. This case highlighted the potential risk of adrenal insufficiency in the setting of bilateral adrenal involvement and emphasized the importance of establishing care with

endocrinology early on, whenever possible and deemed necessary. This allows for the early detection of adrenal dysfunction and the timely management of adrenal insufficiency or adrenal crisis. Finally, we briefly discuss the limited evidence for the use of SBRT in treating adrenal PCC and PGL, as well as related metastases.

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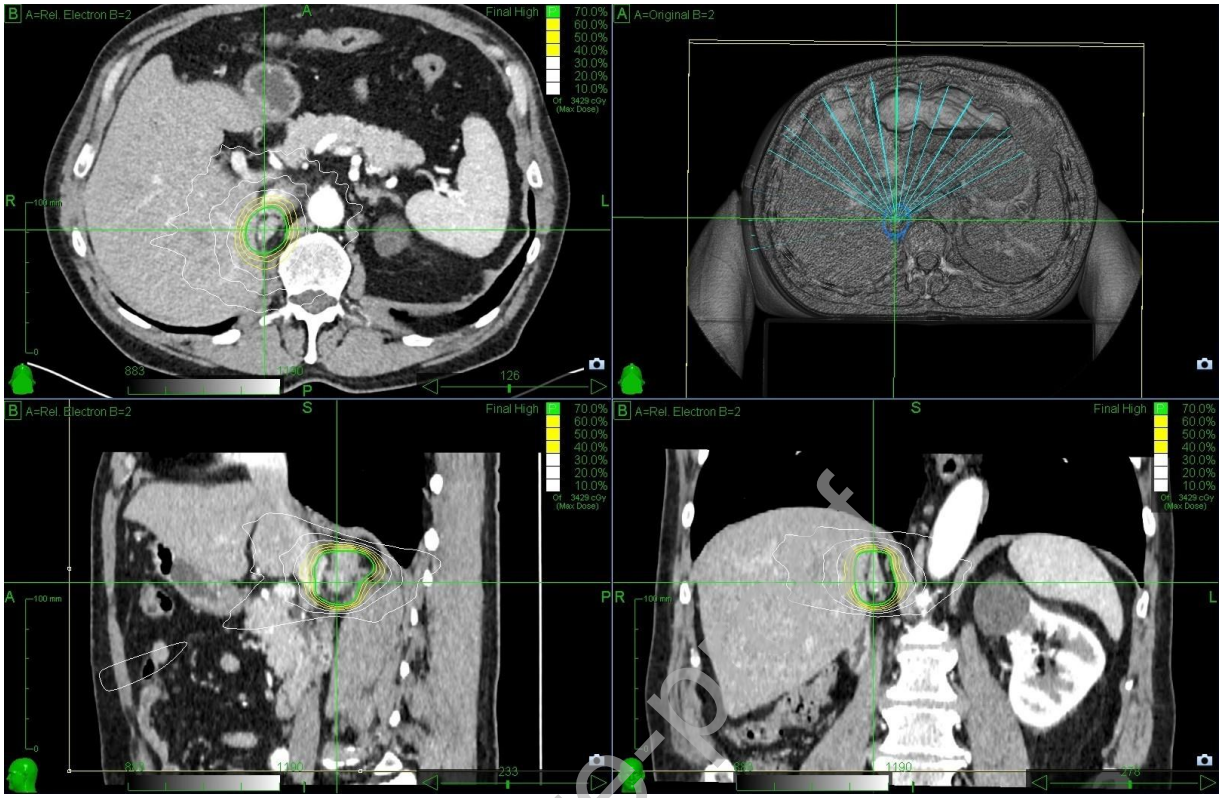

Figure 1. Treatment planning, right-sided adrenal gland metastasis. The prescription dose was 24 Gy, prescribed to the 70% isodose line. The PTV was 20.3 cm^3, created by adding a 5 mm margin to the 6.0 cm^3 GTV. The treatment was delivered in one fraction.

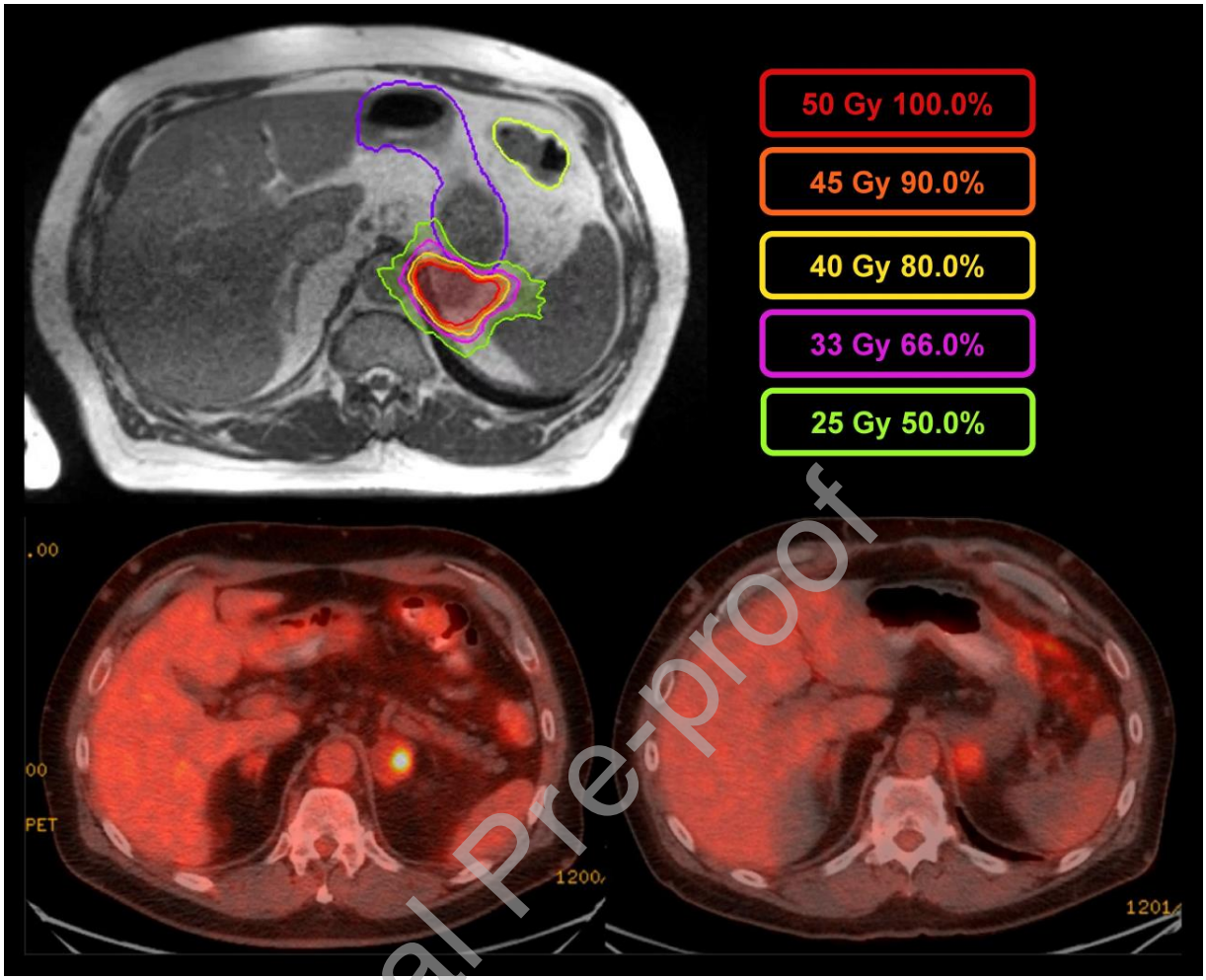

Figure 2. Top: SBRT treatment plan with isodose lines. The PTV was 80.6 cm^3, created by adding a 5 mm margin to the 23.1 cm^3 GTV. The colon and stomach are highlighted in purple and yellow. Bottom left: FDG-PET prior to SBRT. Bottom right: FDG-PET at 3 months after SBRT, demonstrating metabolic treatment response.

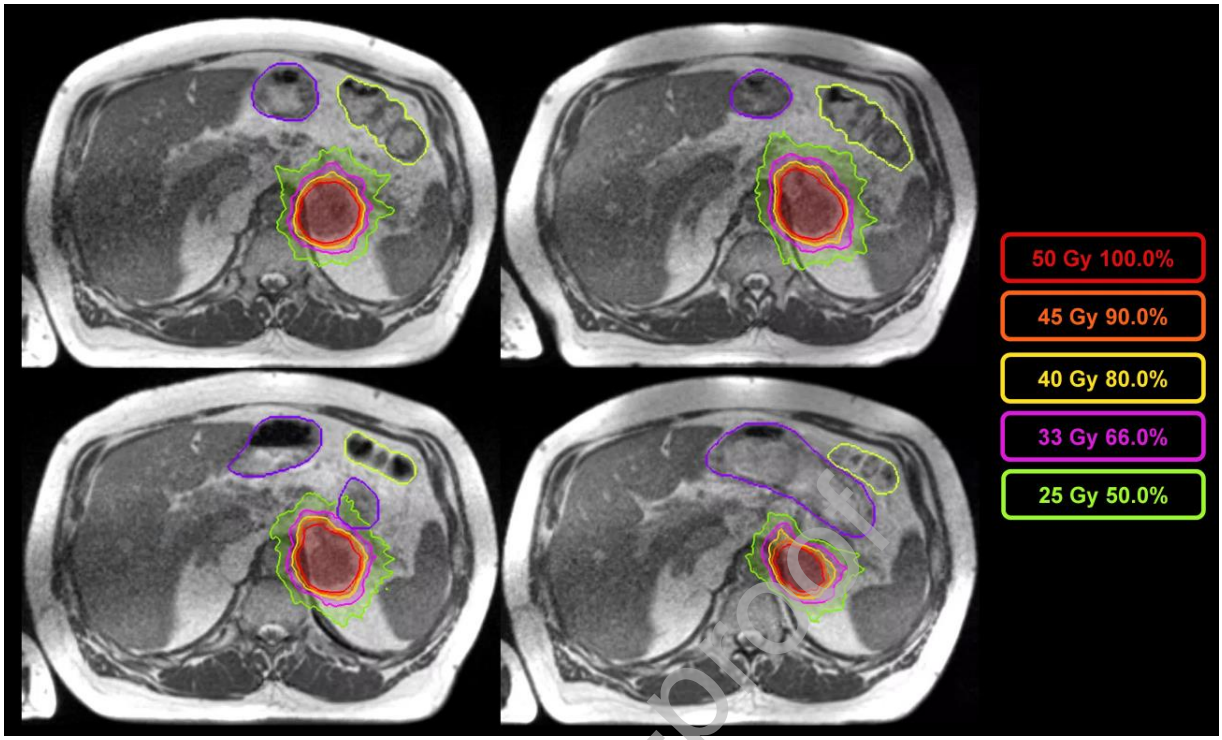

Figure 3. Four of the 5 adaptive treatment plans of Patient B, highlighting the notable inter- and intrafractional changes. The colon and stomach are highlighted in purple and yellow.

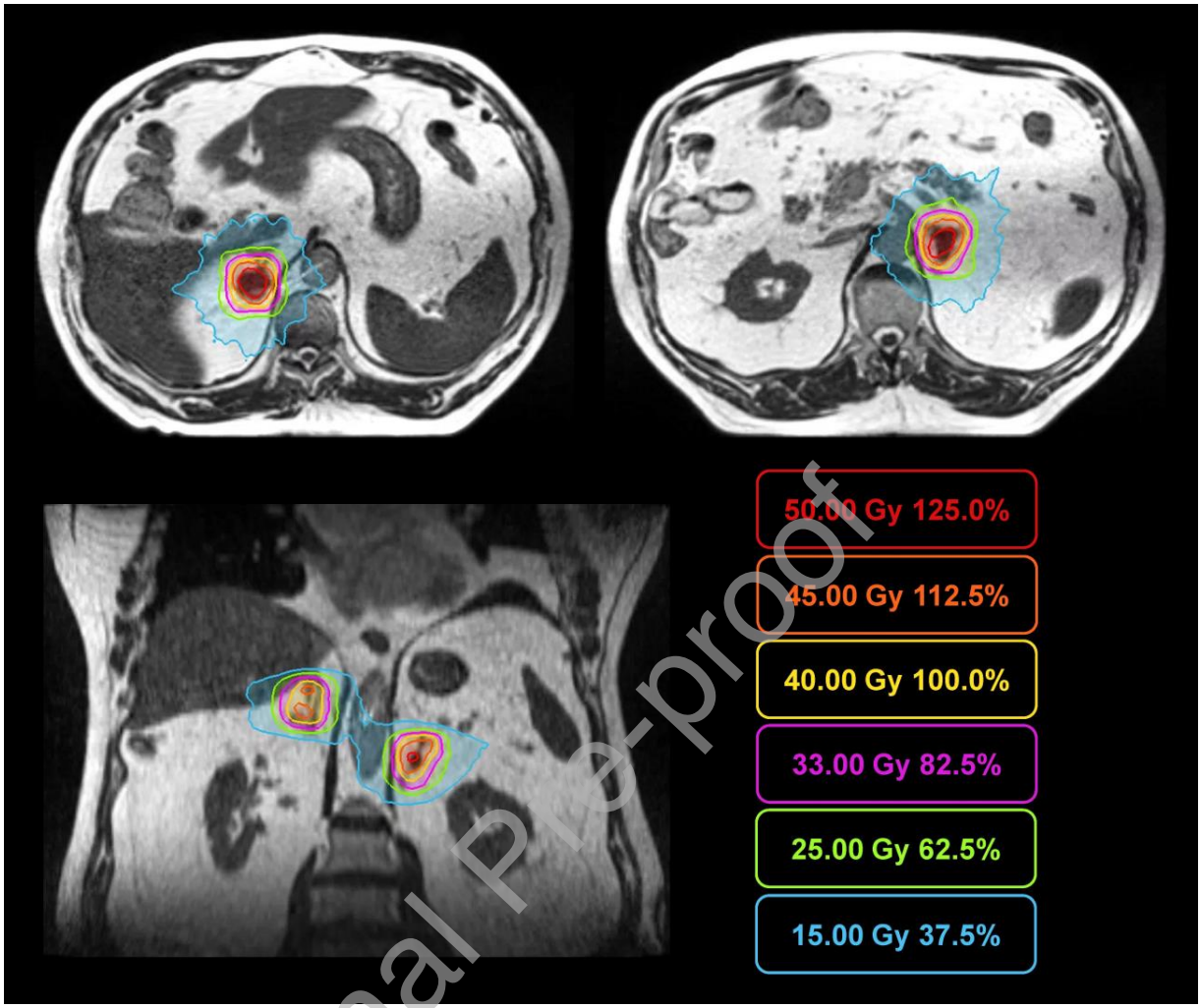

Figure 4. Top left and right: SBRT treatment plans for bilateral adrenal gland metastases with isodose lines, axial plane. The PTV for the right adrenal gland metastasis was 32.3 cm^3, created by adding a 5 mm margin to the 13.6 cm^3 GTV. The PTV for the left adrenal gland metastasis was 37.1 cm^3, created by adding a 5 mm margin to the 15.7 cm^3 GTV. Deep inspiration breath-hold was utilized for the treatment. Bottom: Combined SBRT treatment plans, coronal plane.

Table 1. Common adrenal stereotactic body radiotherapy dose concepts for metastases and organs at risk dose constraints.

SBRT dose regimens					
Fractions	**Dose per fraction (Gy)**	**Total dose (Gy)**	**Prescription isodose line[†] (%)**	**Biologically effective dose (Gy, α/β ratio: 10)**	**References**
1	24 – 26	24 – 26	60 – 100	81.6 – 93.6	[22, 23, 33]
3	13 – 15	39 – 45		89.7 – 112.5	[22, 23, 47]
5	9 – 10	45 – 50		85.5 – 100.0	[23, 26, 48]
8	6 – 7.5	48 – 60		76.8 – 105.0	[23, 49, 50]
10	5 – 7	50 – 70		75.0 – 119.0	[30, 49-51]

Dose constraints				
Organs at risk	**Fractions**	**Dose constraint references**		
		AAPM TG 101 [19]	**HyTEC [52]**	**Timmerman table [53]**
Stomach	1	Dmax: 12.4 Gy D10cm³: 11.2 Gy		Dmax: 22 Gy D5cm³: 17.4 Gy
	3	Dmax: 22.2 Gy D10cm³: 16.5 Gy		Dmax: 30 Gy D5cm³: 22.5 Gy
	5	Dmax: 32 Gy		Dmax: 35 Gy

		D10cm³: 18 Gy		D5cm³: 26.5 Gy
	8			Dmax: 42 Gy D5cm³: 31.2 Gy
	10			Dmax: 45 Gy D50cm³: 33.9 Gy
Duodenum	1	Dmax: 12.4 Gy D5cm³: 11.2 Gy D10cm³: 9 Gy		Dmax: 22 Gy D5cm³: 17.4 Gy
	3	Dmax: 22.2 Gy D5cm³: 16.5 Gy D10cm³: 11.4 Gy		Dmax: 30 Gy D5cm³: 22.5 Gy
	5	Dmax: 32 Gy D5cm³: 18 Gy D10cm³: 12.5 Gy		Dmax: 35 Gy D5cm³: 26.5 Gy
	8			Dmax: 42 Gy D5cm³: 31.2 Gy
	10			Dmax: 45 Gy D5cm³: 33.9 Gy
Jejunum/ileum	1	Dmax: 15.4 Gy D5cm³: 11.9 Gy		Dmax: 20 Gy D30cm³: 17.6 Gy
	3	Dmax: 25.2 Gy		Dmax: 28.5 Gy

		D5cm³: 17.7 Gy		D30cm³: 20.7 Gy
	5	Dmax: 35 Gy D5cm³: 19.5 Gy		Dmax: 34.5 Gy D30cm³: 24 Gy
	8			Dmax: 40 Gy D30cm³: 28.8 Gy
	10			Dmax: 41 Gy D120cm³: 33.9 Gy
Renal hilum	1	Dmax: 18.6 Gy D<2/3 of volume: 10.6 Gy		D15cm³: 14 Gy
	3			D15cm³: 19.5 Gy
	5	D<2/3 of volume: 23 Gy		D15cm³: 23 Gy
	8			D15cm³: 28 Gy
	10			D15cm³: 30.7 Gy
Renal cortex	1	D200cm³: 8.4 Gy		D200cm³*: 9.5 Gy
	3	D200cm³: 16 Gy		D200cm³*: 14.7 Gy
	5	D200cm³: 17.5 Gy		D200cm³*: 17.5 Gy
	8			D200cm³*: 20 Gy

	10			D200cm³*: 21 Gy
Liver	1	D700cm³: 9.1 Gy		D700cm³*: 11.6 Gy
	3	D700cm³: 19.2 Gy	Dmean: ≤ 13 Gy for primary liver tumors Dmean: ≤ 15 Gy D700cm³: ≤ 15 – 17 Gy for liver metastases	D700cm³*: 17.7 Gy
	5	D700cm³: 21 Gy		D700cm³*: 21.5 Gy
	8			D700cm³*: 24.8 Gy
	10			D700cm³*: 27 Gy
Spinal cord	1	Dmax: 14 Gy D0.35cm³: 10 Gy D<1.2cm³: 7 Gy	Dmax: 12.4 – 14 Gy	Dmax: 14 Gy D0.35cm³: 10 Gy
	3	Dmax: 21.9 Gy D0.35cm³: 18 Gy D<1.2cm³: 12.3 Gy	Dmax: 20.3 – 23.1 Gy	Dmax: 22.5 Gy D0.35cm³: 15.9 Gy
	5	Dmax: 30 Gy D0.35cm³: 23 Gy D<1.2cm³: 14.5 Gy	Dmax: 25.3 – 28.8 Gy	Dmax: 28 Gy D0.35cm³: 22 Gy
	8			Dmax: 33.6 Gy D0.35cm³: 26.4 Gy
	10			Dmax: 36 Gy D5cm³: 31 Gy
Great vessels	1	Dmax: 37 Gy D10cm³: 31 Gy		Dmax: 37 Gy

				D10cm³: 31 Gy
	3	Dmax: 45 Gy D10cm³: 39 Gy		Dmax: 45 Gy D10cm³: 39 Gy
	5	Dmax: 53 Gy D10cm³: 47 Gy		Dmax: 53 Gy D10cm³: 47 Gy
	8			Dmax: 62 Gy D10cm³: 55.2 Gy
	10			Dmax: 62.9 Gy D10cm³: 55.7 Gy

†: Depending on the treatment platform and desired dose heterogeneity, i.e., max doses over 100% of the prescription dose can be applied, *: One third of native total organ volume pre-resection or before disease-related volume reduction, whatever is larger, D = Dose, HyTEC = High Dose per Fraction, Hypofractionated Treatment Effects in the Clinic, AAPM = American Association of Physicists in Medicine, TG = Task group.