Diagnosis and treatment options including stereotactic body radiation therapy (SBRT) for adrenal metastases

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Abstract Adrenal metastasis is common in oncology but patients with this diagnosis are usually asymptomatic. The diagnosis can be challenging and delayed. Incidence, presenting symptoms and diagnostic modalities are reviewed. Various treatment options are also discussed, including open and laparoscopic surgery, local ablation (radiofrequency ablation, cryoablation, microwave thermal ablation, and chemical ablation) as well as radiation therapy. These treatment modalities were compared and contrasted in regards to their invasiveness, risks, side effects, outcomes, and patients' tolerance. Radiotherapy including stereotactic body radiation therapy (SBRT) is the only non-invasive approach, which is important as majority of the patients with adrenal metastases also receive systemic therapy, e.g., chemotherapy. The initial goal of conventional radiotherapy for metastatic adrenal lesion is for palliation which has been shown to be effective. With the advent of

technological advances in radiation oncology, e.g., image-guidance during radiation delivery, patient immobilization and patient re-positioning, tumor motion management, sophisticated treatment planning allowing rapid dose fall-off, accurate QA, etc., the clinical implementation of SBRT has been very successful. SBRT is defined as a "treatment method to deliver high dose of radiation to the target, utilizing either a single dose or a small number of fractions with a high degree of precision within the body". Adrenal metastasis, an example of oligometastases even from radioresistant primary, could be successfully treated with SBRT without significant toxicity as evidenced by various recently reported clinical trials. An additional advantage could be adrenal function preservation when compared to surgical intervention. The optimal total dose and fractionation scheme are yet to be determined. SBRT is an emerging non-invasive, safe, and effective treatment modality, and further research is warranted to define its role in the management of adrenal metastasis.

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Introduction

Adrenal gland is one of the most common organ sites of metastases. Metastasis is the second most common etiology of adrenal mass after adenoma [1]. Adrenal metastasis is a common finding on autopsies, reported to be between 13% and 35% [2–4]. The common primary malignancies which metastasize to the adrenals include cancers from lung (35%–59%) [5, 6], liver and bile duct (10%) [5], breast (30%–40%) [7], colon (14%) [5], and kidneys (7%–19%) [8]. Other less common primary cancers include skin cancer (melanoma) [9, 10], esophageal cancer [5], stomach cancer

[5], thyroid cancer (papillary [11], follicular, Hurthle [12]), anaplastic [13], prostate cancer [14], and gynecologic cancer [15].

The majority of adrenal metastases are carcinomas [5], that occur within a brief period after the diagnosis of the primary malignancy (latent period, 7 months), with only 2% of the cases metastasizing after 5 years [16]. The common prevalence of adrenal metastases, different diagnostic criteria, and different treatment modalities initiated this review. The purpose of this review is to look at the above-mentioned aspects and the emerging role of stereotactic body radiation therapy (SBRT) in the treatment of adrenal metastases.

Clinical presentations

The suspicion or detection of adrenal metastases solely based on symptomatic presentation is very rare since most adrenal metastases are silent or asymptomatic [5, 11]. Lam et al. studied data of 464 patients diagnosed with adrenal metastases for a 30-year period and found that the 96% (444 patients) were asymptomatic at detection [5]. Anyhow, the presenting symptoms include adrenal insufficiency [5, 7, 17], peritoneal hemorrhage [5], abdominal pain and pressure [10], and thrombosis of IVC [7, 15]. The fact that adrenal metastases are generally asymptomatic raises two questions:

1. What is the best way to detect adrenal metastases?
2. Is the goal of treatment palliative or curative?

Detection and diagnosis

The average age of patients with adrenal metastasis is 62 years. Even though biopsy remains the definitive diagnostic tool of adrenal metastases, imaging plays an important role [6]. Controversies still exist as to when a biopsy is needed. Harisinhgan et al. retrospectively examined 225 biopsies of adrenal masses performed from 1996 to 2001 with the purpose of testing the negative predictive value of negative biopsy [3]. Of the 225 biopsies in patients with primary non-adrenal malignancies and adrenal mass, 41 were determined negative and of these 13 did not have definitive diagnosis. A repeat biopsy was done and was negative for all 13, suggesting that the negative predictive value of CT guided biopsy was 100% [18]. In another study that examined 101 biopsies of adrenal mass, it was suggested that the positive predictive value of image-guided biopsy was 100%, with the diagnosis obtained in 86% of cases. Among 72 patients with proven outcomes, image-guided biopsy had an accuracy of 96%, sensitivity of 93%, and a negative predictive value of 91% [19].

Complication rate of fine needle biopsy (FNA) is reported to be around 3%. The complications include hemorrhage, infection, theoretical risk of tumor tract seeding, capsular disruption, and pheochromocytoma dynamic instability [20]. However, another study showed that complications such as pneumothorax, septicemia, and hemorrhage occurred in 8–13% of patients undergoing FNA [19]. The authors further suggested that since image-guided FNA biopsy cannot differentiate between an adrenal cortical carcinoma and an adrenal adenoma, but has sensitivity of 80% to 100% in detecting adrenal metastases, it should be reserved for adrenal masses suspicious for metastases [19].

CT has been used for the detection of adrenal metastases for more than 20 years. In one of the earlier reports in 1990, the authors studied the sensitivity and specificity of CT in detecting adrenal metastases from lung cancer in 91 patients. The results demonstrated that the sensitivity ranged from 20% to 41.4% and the specificity was much better ranging from 84.5% to 99.4% [21]. In recent years, special techniques such as high lipid density, enhancement after contrast, % absolute enhancement washout, and % relative enhancement washout have helped improve the specificity and sensitivity of CT [20]. Sensitivity and specificity have been reported to be as high as 100% with the use of <60% absolute enhancement washout on CT [22].

With conventional MRI, the sensitivity and specificity have been reported to be less than those of CT [23]. The intensity signal on T2 and single intensity index, have increased the sensitivity and specificity tremendously. Fujiyoshi et al. examined MRI's capability to characterize adrenal tumors using chemical shift, and found that single intensity index (cut off 11.2%–16.5%) was 100% accurate in determining metastatic adrenal lesions [24].

The use of 18F-FDG-PET in detecting systemic metastases and, specifically, adrenal metastases has shown very promising results. The role of PET imaging in cancer detection has been increasing in the last 10 years, and is now considered a part of the initial assessment of most cancer patients. PET offers an additional advantage over CT and MRI in determining the primary site of tumor and other possible metastatic sites [6]. Kumar et al. examined the sensitivity, specificity, and accuracy of recent studies using PET in detecting adrenal metastases, mainly from lung cancer, and reported 93–100% (sensitivity), 80–100% (specificity), and 92–100% (accuracy), respectively [6].

While biopsy has been historically the acceptable method in making the diagnosis of adrenal metastases, the advances made in imaging modalities in the last 20 years have challenged the role of biopsy. With sensitivity, specificity, and accuracy comparable to, if not better than, biopsy in detecting adrenal metastases, and unlike biopsy, no complications were reported. Currently, it is considered acceptable to use imaging as a diagnostic tool of adrenal metastases.

Treatment options

Surgery

The presence of metastatic lesions in adrenals has been associated with dismal prognosis and short survival period. Before the 1960s, adrenal metastases were treated conservatively as a part of disseminated process with poor outcome. In the 1970s, surgeons started to manage this problem with adrenalectomy, showing good results, but it was a big and traumatic operation that required careful selection of patients [4]. However, the introduction of laparoscopy has rendered surgery the primary treating modality of adrenal metastases. Laparoscopic approach has been proven to be as effective as open surgery [4, 25], with the former associated with less blood loss (63 ± 8 mL versus $2,207 \pm 1,067$ mL, $P=0.05$), a lower complication rate (0% versus 63%, $P=0.009$), and a shorter length of stay [26]. Contraindications to laparoscopic surgery include pregnancy, large tumors (>8 cm), or suspicion of primary invasive adrenocortical carcinoma on imaging. Other relative contraindications include morbid obesity, prior intra-abdominal surgery (adhesion was reported as the primary reason to convert a laparoscopic surgery to open surgery [27]), and large pheochromocytomas [7]. The majority of reports encourage surgical resection of adrenal mass measuring 5–6 cm [7] regardless of the cause, with the exception of nonfunctioning adrenal incidentaloma [28]. Surgical complication rate ranged between 4% and 29.4% [26, 27, 29, 30]. Complications include deep venous thrombosis, pulmonary embolism, stroke, pneumonia, hematoma, myocardial infarction, atelectasis, bowel perforation, lung infection, and wound infection [25, 27, 31]. Recurrence rate was reported to be between 0–21% [26, 30], and the 5-year survival between 22.5% and 47% [4, 26].

Surgical approach to adrenal metastases has been studied extensively and established as the primary treatment modality. Surgery has been shown to be effective, especially when the primary cancer is controlled and there is no evidence of other metastases besides the adrenals [21].

Percutaneous ablation

Tumor ablation is defined as the direct application of chemical or thermal therapies to a tumor to achieve eradication or substantial destruction of tumor [32]. Percutaneous ablative approaches that have been described and used in the treatment of adrenal tumors include percutaneous radiofrequency ablation, cryoablation, microwave ablation, and chemical ablation. Local tumor ablation in the adrenal gland presents unique challenges because of the unique anatomy and physiology of adrenal gland.[33]. Therefore, at present,

percutaneous ablation for adrenal neoplasms has primarily been applied in patients who are considered unresectable or poor surgical candidates, those who refuse surgery despite surgery being an option, or those who have multiple prior attempts at surgical debulking [33]. Risks and complications of adrenal ablation include bleeding, infection, hypertensive crisis, and in cases of thermal ablation, thermal injury to adjacent structures (including the kidneys, lungs, and pancreas) [33]. Of note, the reported studies involving local ablation had few patients and there was no prospective trials addressing these tumor ablative procedures.

Radiation therapy

The role of radiotherapy (XRT) in adrenal metastases was suggested more than 30 years ago. Earlier trials used XRT for palliative care of adrenal metastases and showed promising response. Soffen examined 16 patients treated between 1972 and 1988 for palliation of symptomatic adrenal metastases and found that 12 of 16 patients (75%) showed partial to full symptomatic pain relief after treatment with XRT [34]. Soejima et al. examined 14 patients with adrenal metastases treated between 1985 and 1995 with XRT for symptomatic relief. Seven of eight patients presenting with pain (87.5%) reported pain relief [35]. Short et al. examined 18 patients presenting with adrenal metastases in 1996 and reported complete pain relief after treatment with XRT in seven out of seven (100%) patients presenting with pain [36].

The first report of the role of XRT as primary treatment modality for adrenal metastases was suggested in a case report in 1999 [37]. Since then, the role of XRT of adrenal metastases has been primarily reported in the form of sporadic case reports. There have been two larger series of patients with adrenal metastases treated with XRT. Oshiro et al. examined 19 patients with adrenal metastases from lung cancer treated with by radiation therapy, seven of whom received external beam radiation therapy and 11 receiving SBRT. The mean age was 63 years. They were all symptomatic. The overall 1-, 2- and 5-year survival rates for all patients were 56%, 33%, and 22%, respectively. More favorable prognosis was observed for patients with a metachronous metastasis, with overall 1-, 2-, and 5- year survival rates of 83%, 56%, and 56%, respectively. Tumor size (>3 cm), pathology, location (right or left adrenal gland), method of radiotherapy (with or without SBRT), and radiation dose (>50 Gy) all had no significant effect on overall survival [38].

Zeng et al. examined 22 patients with adrenal metastases from hepatocellular carcinoma, treated by XRT. Eleven of 14 (78.6%) patients presenting with pain had complete pain relief after XRT and 2 patients had major relief of

Fig. 1 SBRT treatment plan for left adrenal metastasis showing very tight isodose distribution with rapid fall-off in an effort to reduce the volume of surrounding critical normal tissues (kidney, bowels, stomach, spinal cord and liver) receiving high-dose radiation

symptoms, but still required analgesics. Median survival was 10 months with none dying from adrenal metastases complication, and partial response was observed in 73% of patients. Minor toxicity including nausea and vomiting was noted [39].

Stereotactic body radiation therapy

SBRT is defined by the American Society for Radiation Oncology and the American College of Radiology as a

“treatment method to deliver a high dose of radiation to the target, utilizing either a single dose or a small number of fractions with a high degree of precision within the body” [40]. Some essential components needed for the clinical implementation of SBRT include patient immobilization and accurate reposition from simulation session to each treatment session, accounting for motion or tracking “moving target”, fusion of various imaging studies, construction of tight dose distributions covering tumor with rapid fall-off the adjacent normal tissues, as well as the availability of image-guidance during treatment delivery [41].

The most common indications for SBRT are the treatment of non-metastatic primary cancer and oligometastases, with primary goal of treatment being local control [42]. Patients who are more likely to benefit from SBRT for their oligometastases include those who are younger, and those who have higher performance status, controlled primary tumor sites, metachronous occurrence of metastatic disease, limited number of metastases, and radioresistant histologies such as renal cell carcinoma [43]. The advantage of SBRT is its ability to deliver high doses of radiation to the planning treatment volume (PTV) while limiting the radiation dose to organs-at-risk [42]. Figure 1 shows a SBRT plan where a highly conformal prescription isodose line is created around the adrenal metastasis while keeping high-dose radiation away from the adjacent normal tissues such as the kidney and small bowels.

There have been four reports that studied the treatment of adrenal metastases using SBRT as shown in Table 1. The Japanese study by Oshiro et al. described above under the section “Radiation therapy” was included. Eleven patients were treated with SBRT. Casamassima et al. studied 48 patients from 2002 to 2009 with adrenal metastases that were treated with

Table 1 Clinical studies of SBRT for adrenal metastases

	Oshiro et al. (2011). International Medical Center of Japan [38]	Casamassima et al. (2011). University of Florence [44]	Chawla et al. (2009). University of Rochester Medical Center [45]	Holy et al. (2011). RWTH Aachen [46]
Number of patients	11	48	30	18
Median age	63 years	62.7 years	61.8 years	61.5 years
SBRT dose	Median 30 Gy (30–60)	Median 36 Gy	Median 40 Gy (16–50)	Median 40 Gy (20–40)
# of fractions	1–5 fractions	3 fraction (except 8 patients 1)	4–10 fractions	5 fractions
Median follow-up	10.1 month	16.2 month	Until recurrence	21 month
Actuarial 1 year/2 year survival	56%/33%	39.7%/14.5%	44%/25%	66.7% at 1 year
1 year distant control		9%	13%	
1 year/2 year local control	79% over follow-up period	Both 90%	55%/27%	77% for single metastases
Presenting symptoms	All asymptomatic	4 pain/44 asymptomatic	3 pain/27 asymptomatic	
Toxicity	1 grade 2 toxicity peptic ulcer disease	1 adrenal insufficiency	No patient had toxicity	6 mild nausea, 2 peptic ulcers

Data compiled from source [38], [44], [45] and [46], respectively

SBRT. On univariate and multivariate analyses, no significant factor (primary tumor, synchronous versus metachronous, unilateral and bilateral, oligometastatic disease, PTV, and number of fractions) emerged as an independent prognostic factor for overall survival, local control and distant control ($P>0.05$) [44]. Among the four patients presenting with painful metastases, three were pain-free after SBRT and one had improved pain. Toxicity profile was excellent with only one patient having grade 2 adrenal insufficiency.

Chawla et al. examined 30 patients treated from 2001 to 2009. Fourteen patients with five or fewer metastatic lesions (including adrenal) underwent SBRT, with the intent of controlling all known sites of metastatic disease, and the other 16 patients underwent SBRT for palliation or prophylactic palliation of bulky adrenal metastases. Three patients with pain on presentation achieved complete pain relief after SBRT. None of the 30 patients treated with SBRT developed grade 2 or higher toxicity [45].

Holy et al. treated, between July 2002 and September 2009, 18 patients with adrenal metastases from non-small cell carcinoma with SBRT. An isolated adrenal metastasis was diagnosed in 13 patients, while 5 patients with multiple metastatic lesions had SBRT due to back pain. A median progression-free survival (PFS) of 4.2 months was obtained for the entire patient group, with a markedly increased PFS of 12 months in 13 patients with an isolated metastasis involving the adrenal gland. After a median follow-up of 21 months, 10 of 13 patients (77%) with isolated adrenal metastasis achieved local control. In these patients, median overall survival was 23 months. Overall survival was excellent and comparable to that of surgical approach. The advantage of SBRT is that it is a non-invasive approach and can be performed as an outpatient procedure. Acute side effects were mild [46].

A recent case report using SBRT to treat a remaining contralateral adrenal metastasis from renal cell carcinoma described adrenal function preservation as an added benefit of SBRT [47]. The patient reported had nephrectomy and adrenalectomy at the initial diagnosis. In addition to successful SBRT treatment achieving complete response on pain and imaging, he also had normal adrenal function at more than 3 years follow-up, despite one remaining adrenal gland. Adrenal function preservation will not be possible with surgery in this case.

Historically, adrenal metastases have been treated primarily by surgery because of the challenges that organ motion and location of sensitive small bowels poses for radiation treatment [28]. However, with the advent of advanced technology, SBRT, which can account for organ motion, protect function of surrounding organs by highly sophisticated planning and treatment techniques, and offer comparable local control, can be considered as one of the treatment options for the treatment of adrenal metastases. Based on the emerging data from the

literature, SBRT appears to be an effective non-invasive cancer treatment modality offering good palliation of symptoms and local control, with minimum toxicity [48–52]. Prospective trials are needed to better define the role of SBRT in this setting.

Conclusion

Adrenal glands are a common site harboring metastatic disease. The incidence, presenting symptoms, diagnostic modalities, and treatment options of adrenal metastases were reviewed. SBRT has emerged as a promising non-invasive treatment option for patient with adrenal metastasis. Limited data in the literature shows good symptomatic relief and local control. Adrenal function preservation may be an additional benefit with SBRT. More data from patients with longer follow-up are needed to define the role of SBRT for adrenal metastasis and it is best obtained in prospective clinical trials setting.

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