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Review

SBRT: A viable option for treating adrenal gland metastases

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ABSTRACT

The management strategy of adrenal metastases depends on different clinical situations. Adrenal metastasectomy in selected patients with isolated adrenal metastases is considered the treatment of choice, showing prolonged survival compared to chemotherapy alone.

More recently, Stereotactic Body Radiation Therapy (SBRT) has emerged as an alternative local ablative treatment modality although limited data are available on the use of SBRT in treating adrenal gland metastases. Preliminary results are, however, encouraging, especially in selected patients with oligometastatic disease. We herewith review and discuss the potential role of SBRT as a local ablative treatment modality for adrenal metastases.

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1. Introduction

The adrenal gland is a common site for metastasis from a variety of tumours.[1] The incidence of these metastases from autopsies is about 13–35%[2,3] in patients with malignant tumours. Lung, melanomas, breast, stomach and kidney cancers and lymphomas most commonly metastasize to the adrenal glands.[4]

The management strategy of adrenal metastases (AM) varies depending on the different clinical situations and can include palliative treatment, chemotherapy, surgery and local ablative treatments.[5,6] Historically, radiotherapy has been used with palliative intent with good response rates reported, especially in terms of pain relief (40–80%) defined as a reduction in the use of analgesics.[7–9]

However, in patients with oligometastatic disease, defined by the presence of one to five metastases,[10] aggressive local therapies may be a reasonable option to prolong progression-free survival.

Several studies have showed prolonged survival after an adrenal metastasectomy in selected patients with isolated adrenal metastases.[11,12] Surgery can be performed with an open resection or through laparoscopic approach. Laparoscopic adrenalectomy has been shown to improve patients' morbidity and to reduce hospitalization with a comparative oncological outcome compared to the open resection technique.[13] However, laparoscopic procedures are contraindicated in lesions larger than 6 cm.[14] Overall, the rate of major complication after surgery is around 1.8%.[15] Recently, Gunjar et al. in a systematic review reported a weighted 2y OS for patients undergoing adrenalectomy for

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adrenal gland metastases of 46%, representing a total of 655 patients.[16]

Other recently emerged treatment modalities include Radiofrequency Ablation (RFA), Microwave Ablation (MWA) and Stereotactic Body Radiation Therapy (SBRT).[17]

Limited data are available on the Percutaneous Catheter Ablation Technique due to a limited number of patients. The most common histology treated with this modality is renal cell carcinoma, where reported toxicity included hypertensive crisis and retroperitoneal haematoma.[16]

SBRT refers to the administration of large doses of highly conformal radiation with steep dose gradients towards the surrounding normal tissue over a limited number of fractions. SBRT usually provides much higher Biologically Equivalent Doses (BED) compared with conventional treatments and has been used as a non-invasive alternative to the gold standard of surgery in selected patients.[18,19]

Even though the majority of studies examining the role of SBRT have focused on lung and liver metastases, over the last years there has been an increasing interest in the use of SBRT for the treatment of adrenal gland metastases.

Consequently, the main objective of this review is to examine available clinical data supporting the potential role of SBRT in treating adrenal glands metastases and to outline inherent future challenges.

2. Materials and methods

A medline word search of literature undertaken for the period from 1 December 1994 to 30 November 2014, using the search terms "adrenal gland metastases" and "stereotactic body radiotherapy" was used. Reviews and case reports were excluded.

3. SBRT for adrenal glands metastases: clinical data overview

The review includes ten studies, of which nine were retrospective with the number of patients ranging from 7 to 48; all the studies were mono-institutional; the most common primary site of disease was lung cancer (44.4–100%); and in all studies chemotherapy was not given concurrently with SBRT. Data derived from these studies are summarized in Table 1.

3.1. Dose and fractionation

A large heterogeneity in total dose and fractionation was observed. Radiosurgery (SRS) was employed in only two studies,[20,21] with a median dose of 16–23 Gy (BED = 41.6–75.9 Gy, $\alpha/\beta = 10$). Most patients had fractionated SBRT with a total dose range of 25–48 Gy delivered in fractions of 3–18 (BED = 22.4–132, $\alpha/\beta = 10$), with a total number of 5 fractions (4/10, 40%) administered most commonly, followed by 3 fractions (3/10, 30%).

3.2. Pain relief

Four studies[20,22–24] evaluated pain control after SBRT in a total of 16 patients. A complete response to pain, following analgesic consumption interruption, was achieved in 12 patients (75%), notwithstanding the dose administered. In 2 patients (12.5%), a partial response was achieved (overall pain response 87.5%). No information on the duration of pain relief was provided.

3.3. Efficacy

Overall, the 1- and 2-year local control (LC) rate ranged from 44 to 100% and from 27 to 100%, respectively. However, in most of the studies (6/10, 60%), both 1 and 2 year local control was greater than 70%. It should be noted that in the four studies which showed a lower rate of local control, the median biologically equivalent dose delivered was lower than 60 Gy.[21,22,25,26]

In contrast, studies delivering higher biologically equivalent doses (BED median > 85 Gy, BED maximum value 132–137 Gy, $\alpha/\beta = 10$)[20,27,28] reported a 2-year local control $\geq 90\%$. These data are consistent with that indicating that a BED greater or equal to 100 Gy is necessary to control primary NSCLC.[29,30]

One- and 2-year overall survival (OS) rate ranged from 39.7 to 90% and 13 to 53%, respectively, and was largely influenced by the development of widespread distant metastases. However, the selection of patients seemed to have a strong impact on these data, especially with regard to the type of metastasis (isolated vs. not isolated), the state of oligometastatic disease as defined by Hellman and Weichselbaum[10] and the time of onset of the adrenal metastasis (synchronous vs. metachronous).

In effect, in the study by Holy et al.[24] patients with solitary metastasis (72.2%) had a median PFS of 12 months and a median OS of 23 months, comparable to some of the surgical series.[31] Furthermore, in the study conducted by Rudra et al.,[32] which included only patients with oligometastatic disease, the reported 1 year OS was 90% with a median survival of 17.3 months. Finally, in the study by Oshiro et al.,[27] patients with metachronous metastasis (with a disease free-interval > 6 months), when compared to the whole study population, showed an improved 2-year OS of 55.6% with median survival of 44.3 months.

3.4. Toxicity

In all the studies, toxicity was limited with no report of grade ≥ 3. The most commonly reported acute toxicity was nausea and fatigue G1–G2 with an overall incidence of 30–50%.

Among all the studies, 3 gastro-intestinal (GI) ulcers (1 duodenal, 1 gastric, 1 both duodenal and gastric) were reported, and were all treated successfully with a histamine-2 receptor antagonist. Particularly in the series by Oshiro et al.[27], patients who developed duodenal ulcer received 30 Gy in 3 fractions (BED 60 Gy, $\alpha/\beta = 10$) with a maximum dose of 30 Gy at the duodenum (BED 130 Gy, $\alpha/\beta = 3$). In contrast, in the series by Holy et al.[24] patients who were developing ulcers were treated with a BED of 72 Gy ($\alpha/\beta = 10$), but the corresponding dose–volume load to the stomach and the small intestine was below the tolerance level of these organs. The authors concluded that there might have been some uncertainties in dose–volume load because patients were not treated on an empty stomach, thus resulting in organ movement from different filling.[24]

Table 1 – SBRT for adrenal glands: clinical data.

Author	Patients	Primary	Volumes	Technique	Prescription	Dose (median/range)	N°fractions	BED 10	Response (evaluable pts) CR	PR	ORR	Toxicity	LC	OS	FUP
Katoh 2008[23]	8	67% Lung 25% Liver 8% Other	CTV = GTV + 3 mm PTV = CTV + 5 mm	RTRT	80% isodose	48 Gy (30–48)	8	78.8 (40.5–78.8)	5/8 52.5%	2/8 25%	77.5%	ACUTE: none LATE: none	1 y – 100% 2 y - 100%	1 y – 78%	16 months (3–21)
Chawla 2009[22]	30	66.7% Lung 13.3% GI 20% Other	GTV = CTV PTV = CTV + 7–10 mm	Conformal arcs	100% isodose	40 Gy (16–50)	10 (4–16)	56 (22.4–75)	1/24 4.16%	15/24 62.5%	66.7%	ACUTE: fatigue, Nausea G1 LATE: none	1 y – 55% 2 y – 27%	1 y – 44% 2 y – 25%	5–21 months
Holy 2011[24]	18	100% Lung	CTV = GTV + 2 mm PTV = CTV + 5–10 mm	Coplanar or non-coplanar static beams	100% isodose	38 Gy (15–40)	5 (3–12)	65.6 (22.5–72)	NR	NR	NR	ACUTE: nausea G1-G2 (6/18, 33.3%) LATE: stomach/duodenum ulcer (2/18, 11.1%)	1 y-94.4% 2y – 78.7%	Median 21 months	12 months (2–61)
Guiou 2012[26]	9	100% Lung	NR	NR	NR	25 (20–37.5)	5	47.0	NR	NR	NR	ACUTE: GI G2 2/9 (22%) LATE: none	1y-44% 2y-44%	1y-52% 2y-13%	7.3 months (0–26)
Scorsetti 2012[25]	34	64.7% Lung 8.8% Melanoma 26.5% Other	CTV = GTV + 3 mm PTV = CTV + 5 mm	Non coplanar arcs	isocenter	32 Gy (20–45)	4 (4–18)	(30–56.3)	3/28 11%	13/28 46%	57%	ACUTE: nausea G2 (6%) LATE: none	1 y-66% 2 y – 32%	1 y 64.8% 2 y -53% Median 22.8 months	41 months (12–75)
Ahmed 2013[28]	13	46.15% Lung 30.8% Kidney, Skin 23.05% Other	GTV = CTV PTV = ITV + 5 mm	IMRT and 3D conformal static beams	NR	45 Gy (33.75–60)	5	85.5 (53.62–132)	2/12 16.6%	9/12 75%	91.6%	ACUTE: fatigue G1 (6/1154.5%), nausea G1-2 (3/11, 27.3%) LATE: fatigue G2 (1/4) Nausea G1-G2 (2/4)	100% (crude)	1 y 62.9% Median 7.2 months	12.3 months (3.1–18)
Rudra 2014[32]	10	80% Lung 20% Kidney	GTV = CTV PTV = ITV + 5–10 mm	Non coplanar static beams	80–90% Isodose	36 Gy (24–50)	3 (3–10)	60 (43.2–79.2)	1/10 1%	4/10	50%	ACUTE: fatigue G1 (70%), G2 (10%); GI toxicity G1 (30%), G2 (10%) LATE: adrenal insufficiencyG2 (1/10, 1%)	1 y – 73% 2 y – 73%	1 y – 90% Median 17.3 months	14.9 months (5–45.8)

Casamassima 2010[20]	48 (8 pts SRS)	50% Lung 25% Colon 25% Other	GTV = CTV PTV = ITV + 3 mm	Conformal arcs	70% isodose	36 Gy (21–54) **SRS:** 23 Gy	3	60–137.7	5/48 10.4%	11/48 23%	33.4%	ACUTE: none LATE: G2 adrenal insuffi-ciency (1/48, 2%)	1 y – 90% 2 y – 90%	1 y – 39.7% 2 y – 14.5%	16.2 months (3–63)
Torok 2011[21]	7	71.4% Lung 28.6% Liver	GTV = CTV PTV = ITV	Cyberknife (71.4%)	80–94% isodose SRS 80%	27 Gy (24–36) **SRS:** 16 Gy (10–22)	3	51.3 (43.2-SRS = 41.4 (20–70.4)	1/6 16.6%	2/6 33.3%	49.9%	ACUTE: none LATE: none	1y-63%	Median 8 months	14 months
Oshiro 2011[27]	11	100% Lung	CTV = GTV PTV = CTV + 5–10 mm	Coplanar or non-coplanar static beams	isocenter	45 Gy (30–60)	5 (1–12)	85.5 (60.0–132)	6/11 54.5%	3/11 27.3%	81.8%	ACUTE: none LATE: G2 GI (5%)	6 months-94.7%	1y – 55.6% 2y – 33.4%	10.2 months (0.7–87.8%)

GI = gastrointestinal; GTV = gross tumour volume; CTV = clinical target volume; ITV = internal target volume; PTV = Planning Target Volume; RTRT = Real Time Tumour Tracking; BED10 = Biologically equivalent dose, $\alpha/\beta = 10$; SRS = Radiosurgery.

Table 2 – Constraints used for different SBRT schedules.

Author	No. fractions	Stomach/duodenum	Ipsilateral kidney	Bilateral kidney	Small bowel	Spinal cord
Katoh 2008[23]	8	1cc < 35 Gy	V20 Gy ≤ 50%	NA	NA	NA
Casamassima 2010[20]	3	V25 < 5%	V15 Gy < 50%	V15 < 35%	V27 < 2%	NA
Ahmed 2013[28]	5	Dmax < 42 Gy V38 < 5 cc V32.5 < 15 cc V20 < 30 cc	NA	NA	Dmax < 42 Gy V38 < 5 cc V32.5 < 15 cc V20 < 30 cc	Dmax < 30 Gy

Recently, Onishi et al.[33] reported a clinical case of fatal gastric ulcer occurring 5.5 months after receiving SBRT for a left adrenal metastasis. SBRT was delivered concurrently with vinorelbine (25 mg/m^2 days 1–8 every 3 weeks) and a daily CT scan was performed to verify the position of the gastric wall; the patient was treated with a total dose of 60 Gy delivered in 10 fractions (BED 96 Gy, $\alpha/\beta = 10$) with a very high maximum dose to the gastric wall of 61 Gy (BED 185 Gy, $\alpha/\beta = 3$).

Adrenal insufficiency can be caused by the tumour itself, as well as by local treatment. Despite high incidences of adrenal metastases in all malignancies, the incidence of symptomatic adrenal insufficiency remains low (4%),[34,35] which can be explained by the fact that over 90% of adrenal reserve must be destroyed before it becomes dysfunctional.

Among all the studies, two grade 2 adrenal insufficiencies were reported,[20,33] but no details were provided regarding the doses received by these patients, nor was it specified whether adrenal function was assessed before treatment. Recently, a clinical case of adrenal insufficiency after SBRT for bilateral adrenal metastases[36] was reported.

Constraints used in the studies for different fraction number are summarized in Table 2.

3.5. Technical issues

All patients underwent CT-based treatment planning in custom-made immobilization devices. Katoh et al.[23] investigated three-dimensional tumour motion of the fiducial marker inserted in the adrenal metastasis resulting in a large marker shift related to organ movement, greater in the cranio-caudal direction (1 cm). There was no statistically significant difference in the average amplitude between the supine and prone positions along the three axes, as well as with regard to the distance between the stomach, the duodenum and the tumour. For this reason, the authors recommended the supine treatment which is more reliable and comfortable for patients.

In order to manage target motion, either breath holding techniques or 4D CT scans or simulation CT scans in both inspiration and expiration phases were performed in almost all studies. Advanced IGRT devices were used in half of the studies during treatment, allowing smaller PTV margins.

3D treatment planning was used in almost all studies; however, Scorsetti et al.[37] in a previous report found intensity modulated techniques using either static fields or dynamic arcs and proton therapy superior to conformal solutions, thereby suggesting their use to increase the total dose administered.

4. Conclusions and future directions

As current studies available on treatment of adrenal metastases are few and extremely heterogeneous in terms of patient selection (primary tumours, previous treatment, performance status, disease extension), as well as with regard to dose and fractionation schedules used, the optimal SBRT regimen is yet to be determined and no comparative studies can be undertaken with other treatment options.

Overall, the reported toxicity rate was extremely low, but as all the studies were retrospective and the median follow-up time was limited, this could possibly cause the SBRT related side effects to be underestimated. An accurate baseline evaluation of patients' history should be undertaken prior to treatment, as some studies have shown that a history of gastro-duodenal ulcer is a significant risk factor for ulceration after conventional RT[38] and SBRT[39] and recommend that these patients be treated with considerable caution. Moreover, some clinical conditions such as portal hypertension cause functional abnormalities in the gastric mucosa and reduce the defensive and healing mechanism,[40] thus leading to an increased risk of gastrointestinal toxicity.

In the studies reviewed, GI toxicity occurred when the maximum biologically equivalent dose to the duodenum or gastric wall was ≥ 130 ($\alpha/\beta = 3$) and we therefore suggest that the maximum dose to either the gastric wall or duodenum be kept below this value, regardless of the number of fractions used.

Furthermore, adrenal function should be assessed before and after SBRT in order to provide glucocorticoids and mineralocorticoids replacement when needed, and careful attention should be paid when bilateral SBRT is administered as acute adrenal crisis requires urgent hospitalization as it is managed with intravenous fluids and steroid replacement.

Simulation and treatment should be performed on an empty stomach in order to reduce uncertainties regarding organ filling. Furthermore, due to adrenal gland organ motion, IGRT is also strongly recommended, when available. Treatment modalities such as IMRT/VMAT can be used in a dose escalation treatment protocol, leading to improved organ sparing compared with 3D techniques.[37]

Efficacy results also appear promising. An encouraging 2-year local control rate (>70%) can be achieved with different fractionation schemes (3, 5, 8 fractions) if total BED is greater than 60 Gy. An even higher local control rate (>90%) can be achieved using total BED ≥ 90 Gy. Based on the above considerations, we recommend that a total dose corresponding to a BED ≥ 90 Gy be administered, bearing in mind that a lower dose (minimum BED ≥ 60 Gy) might be considered if dose volume constraints are not satisfied.

For effective research to ascertain whether local control improvement can lead to extended progression-free survival or overall survival, patients included in SBRT studies should be carefully selected.

Moreover, patients selected for ablative SBRT should have a better prognosis, similar to those enrolled in surgical studies. Patients meeting these criteria are those with isolated metastases or oligometastatic disease (≤ 5 lesions, metastatic disease confined in ≤ 2 organs) and a prolonged disease-free interval (>6 months).

In conclusion, SBRT has shown promising results in selected patients with limited toxicity. For this reason, it can be considered an effective alternative for patients not eligible for surgical resection, although prospective clinical trials are necessary to establish the optimal SBRT regimen and to better define the role of SBRT compared to surgery and other local ablative therapies in the treatment of adrenal gland metastases.

Conflict of interest

None declared.

Financial disclosure

None declared.

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