Cancer Treatment and Research Communications 29 (2021) 100481

Contents lists available at ScienceDirect

Cancer Treatment and Research Communications

journal homepage: www.sciencedirect.com/journal/cancer-treatment-and-research-communications

Stereotactic body radiation therapy (SBRT) for patients with oligometastatic/oligoprogressive adrenal metastases: Outcomes and toxicities profile in a monoinstitutional study.

Giuseppe Facondo [1], Gianluca Vullo [1,*], Maurizio Valeriani [1], Anna Maria Ascolese [1], Vitaliana De Sanctis [1], Mattia Falchetto Osti [1]

Department of Medicine and Surgery and Translational Medicine, Sapienza University of Rome, Radiotherapy Oncology, St Andrea Hospital, Rome, Italy

ARTICLE INFO

Keywords:
Adrenal metastases
Oligometastatic
Oligoprogression
Radiotherapy
Stereotactic body radiation therapy

ABSTRACT

Aims: To evaluate survival outcomes and toxicology profiles in oligometastatic/oligoprogressive patients treated with SBRT for adrenal metastases.

Methods: We retrospectively analyzed 25 metastatic adrenal lesions in 24 oligometastatic/oligoprogressive patients undergoing ablative Stereotactic Body Radiation Therapy (SBRT) between February 2010 and November 2019 in our department. The primary endpoint was overall survival (OS). Secondary endpoints were local overall response rate (ORR), acute and late toxicities.

Results: The most common primary tumor was non-small cell lung cancer (54%). Twenty-one patients received chemo or immuno-therapy. The median planning target volume (PTV) was 41.7 cm^3. Median SBRT dose was 36 Gy. Median dose per fraction was 15 Gy. Median survival was 35-months with OS outcomes ranging from 6-months (100%), 1-year (87.5%) and 2-years (66.7%). ORR based on RECIST criteria was 66.5%. 12 patients experienced acute toxicities, mostly grade 1–2 (8 patients, 32%).

Conclusions: SBRT for oligometastatic/oligoprogressive patients with adrenal metastases showed acceptable survival outcomes and a safe toxicity profile.

Introduction

The adrenal glands are a common site affected by metastatic cancers. The majority of adrenal metastases develop from the following cancer sites: lung cancer (35%), particularly non-small cell lung cancer (NSLC), gastric cancer (14%), esophageal cancer (12%) and hepatobiliary primary carcinomas (10%). Such metastases are characteristically asymptomatic and show up as incidental imaging findings [1]. The widespread use of abdominal computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) during staging and follow-up of metastatic diseases has generally increased the rate of detection of adrenal gland metastases [3]. A recent analysis of 464 patients with metastatic cancers demonstrated that only 4% of adrenal metastases presented with symptomatic lesions, with the overall incidence of adrenal metastases on autopsy being up to 33% [2].

The first adrenal metastases resections started as early as the mid-1970s [4]. Thereafter, several studies demonstrated significant outcomes of metastasectomies for patients with adrenal metastases isolated from different primary tumors [5]. One study in particular being in 1996, when Luketich and colleagues demonstrated significantly improved survival outcomes for patients following resection of adrenal metastases from non-small cell lung cancers (NSCLC) and for those who were treated conservatively; subsequently, adrenal resections became a recognized treatment for adrenal metastatic cancers [6]. To date, adrenalectomy using open or laparoscopic approach is widely considered the standard of care for adrenal metastases in oligometastatic/oligoprogressive patients, as it offers long-term (≥5 years) overall survival (OS) rates that range between 22% and 45%. [7–8].

Local radiotherapy for non-adrenal metastases is conventionally reserved for palliative treatments for symptomatic metastases [9]. In contrast to conventionally fractionated radiotherapy, stereotactic body radiation therapy (SBRT) allows the administration of highly compliant

* Corresponding author at: Department of Medicine and Surgery and Translational Medicine, Sapienza University of Rome, Radiotherapy Oncology, St Andrea Hospital, Via di Grottarossa 1035, 00189, Rome, Italy.
E-mail address: gianluca.vullo@uniroma1.it (G. Vullo).
[1] These Authors contributed equally to this study.

https://doi.org/10.1016/j.ctarc.2021.100481

Available online 21 October 2021

radiation doses, enabling tumor reduction/ablation. SBRT is also a non-invasive treatment option for patients, characterized by the rapid dose-reduction outside the target volume, accurately sparing surrounding organs at risk (OARs) while achieving excellent localized tumor coverage and control [10–11]. Therefore, the aim of the current study was to evaluate survival outcomes in oligometastatic or oligoprogressive patients with adrenal metastases targeted by SBRT therapy.

Methods

Patients. This study is a retrospective, single-institution analysis of oligometastatic or oligoprogressive (1–5 metastases) patients treated for adrenal metastases with ablative SBRT between February 2010 and November 2019. A total of 24 patients with 25 metastatic adrenal lesions were treated with SBRT.

Before treatment all patients were subjected to physical examination, blood chemistry test including liver function, thorax and abdomen CT scan with i.v. contrast and, selected patients did MRI and whole body 18-F-fluorodeoxyglucose (FDG) PET-TC scan. Written informed consent was obtained before beginning radiation therapy.

Treatments. All patients underwent CT simulation taking the supine position. All patients were immobilized in a vacuum-assisted body mold to recreate patient positioning during daily sessions of radiotherapy.

If the target lesion was not readily identified on the CT images, the planning data set was registered to a pre-treatment diagnostic MRI or PET-CT, using a mutual information algorithm from our in-house treatment planning system, to facilitate gross tumor volume (GTV) delineation. A 3 mm isotropic expansion was generated from GTV to obtain PTV. The OARs included liver, spinal cord, kidneys and bowel bag.

The Eclipse 4.5.5 (Varian) treatment planning system, and VMAT/IMRT technique on a 6-MV linear accelerator Varian were used for SBRT. All patients underwent image-guided radiotherapy (IGRT) using a cone-beam computed tomography (CBCT) system as daily pre-treatment imaging. Pre-treatment imaging allowed evaluators to correct set-up errors $\geq$ 2 mm prior to any clinical treatment. Radiation dose was prescribed to the isodose surface covering 95% of the maximum PTV dose. The schedules of dose were different and they were chosen by treating radiation oncologist. Details of target and organs at risk delineation and an example plan are shown in Fig. 1.

Results and follow-up. The primary endpoint of our study was OS, calculated from the date of diagnosis to the date of death from any cause, or date of the last follow-up. Secondary endpoints were local overall response rate (ORR), acute (< 3mo) and late (> 3mo) toxicity. ORR was defined as the absence of progression of the treated metastasis, while treatment response was scored using the Response Evaluation Criteria in Solid Tumors (version 1.1) [12]. Acute adverse effects were reported according to the RTOG/EORTC scoring system during SBRT, 5–6 weeks post-SBRT, and 3 months post-SBRT. Late toxicities where scored after a 6-month minimum follow-up period according to the SOMA (symptoms, objective, management, analytic) scoring system [13–14]. CT scan with contrast medium or FDG/PET-CT were performed every three months for the first two years following SBRT and every six months afterwards as follow-up to asses local failure or systemic progression.

Statistical analysis Statistical analysis was performed using the SPSS statistical software package version 13.0. The Kaplan-Meier method was used to estimate the rate of OS.

Results

Patients' characteristics are summarized in Table 1. Median age was 73 years (range, 45– 91 years). The statistical analysis included 24 patients with adrenal metastases with a total of 25 adrenal gland metastases treated. Most of the metastases originated from non-small cell lung cancer (54%), followed by small cell lung cancer SCLC (17%), renal carcinoma (12%) and other tumors (16%). For 16 patients (67%), adrenal metastases were considered metachronous (i.e., identified later than 6 months following primary cancer diagnosis) with a median interval time of 21 months (range: 7–78 months) between primary tumor and adrenal metastasis diagnoses. Neoadjuvant chemotherapy was defined as systemic therapy given before SBRT treatment. Concurrent chemotherapy was defined as within 1 month from SBRT treatment.

The median time between the diagnosis of the primary tumor and the occurrence of adrenal metastases was 10 months (range: 0–78 months). Overall, 21 (88%) patients received systemic tumor therapy, either chemo- or immuno-therapy. The median planning target volume (PTV) was 41.7 cc (range: 5.8–178 cc). The median GTV was 13.9 cc (range: 1.6–95.4 cc). For 10 metastases (40%), a 3-fraction SBRT regimen was used with a median total dose of 15 Gy (range: 10–18 Gy). Five patients were treated with a single fraction of a median total dose of 23 Gy (range: 23–30 Gy). Additional dosimetric and planning parameters are shown in Table 2.

Clinical response after SBRT was evaluated using RECIST criteria and revealed a local overall response rate (ORR) of 66.5% (CR = 50%, PR

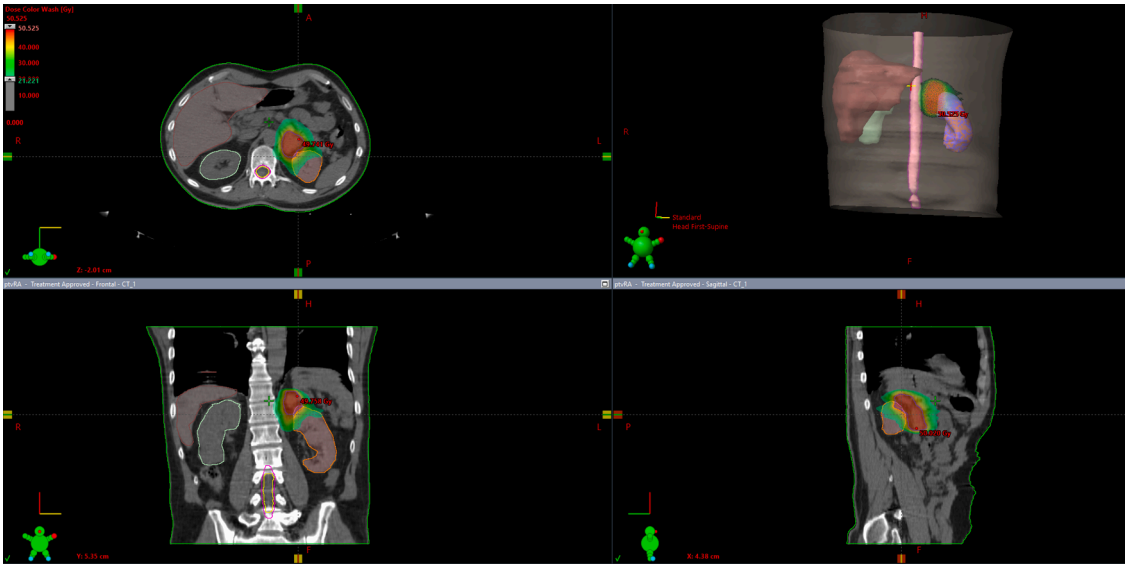

Fig. 1. Stereotactic body radiation therapy with the Eclipse 4.5.5 (Varian) treatment planning system.

Table 1
Patient characteristics.

	N(%)median
Age	73 (45 - 91)
Gender	
Female	9 (38%)
Male	15 (62%)
ECOG	
0	5 (21%)
1	17 (71%)
2	2 (8%)
Primary histology	
NSCLC	13 (54%)
SCLC	4 (17%)
Renal carcinoma	3 (12%)
Gastrointestinal	2 (8%)
Endometrial carcinoma	1 (4%)
Melanoma	1 (4%)
Adrenal metastases location	
Left	18 (72%)
Right	7 (28%)
Oligometastatic (5 or fewer lesions)	
Yes	22 (92%)
No (Oligoprogressive)	2 (8%)
Timing of metastasis	
Synchronous	7 (29%)
Metachronous	17(71%)
Systemic therapy	
Neoadjuvant	17 (71%)
Concurrent	4 (17%)

NSCLC: Non-small cell lung cancer; SCLC: Small cell lung cancer.

Table 2
Treatment characteristics.

Characteristic	No.Median (range)
SBRT treatments:	25
Total dose (Gy)	36 (10 - 60)
Fractions (n)	3 (1 - 18)
Dose per fraction (Gy)	10 (3 - 30)
BED_{10} (Gy)	76.8 (48.0 – 151.2)
Gross tumor volume, (cm3)	13.9 (1.5 – 95.4)
Planning target volume, (cm3)	41.7 (5.1 - 177)
Planning technique:	
VMAT	19
IMRT	6

BED: Biologically effective dose; IMRT: Intensity-Modulated Radiation Therapy; SBRT: Stereotactic body radiation therapy; VMAT: Volumetric-Modulated radiation therapy.

=12.5%), stable disease in 6 patients (25%) patients, and progression of disease in 3 patients (12.5%). Among patients achieving local response, one patient experienced local recurrence after 7 months and was treated again with the same SBRT fractionating schedule of 45 Gy/3 fractions and showed complete response (Table 3).

The median follow-up after adrenal SBRT was 9 months (range: 1–101 months). The median survival was 35 months (range: 8–171 months) with 6 months, 1-year, and 2-year OS at 100%, 87.5% and 66.7% respectively. Progression of disease occurred in 10 patients. Among those patients, sites of initial progression included the brain (20%), bone (50%), liver (10%), lung (10%), and other sites (40%). Survival curves are presented in Fig. 2.

Table 3
Treatment outcomes based on RECIST.

	TotalNo. (%)
Local overall response rate (ORR)	24
CR	12 (50%)
PR	3 (12.5%)
SD	6 (25%)
PD	3 (12.5%)
Distant recurrence	
Yes	10 (40%)
No	15 (60%)

CR: complete response; PD: progressive desease; PR : partial response; SD : stable desease.

Patients with synchronous adrenal metastases (i.e., diagnosed within six months from primary diagnosis) had worse outcomes regarding overall survival compared to patients with metachronous (i.e., identified later than 6 months following primary cancer diagnosis) adrenal metastases. The 1-year and 2-year OS for the metachronous group was 94% and 70% compared to 71% and 57% for those with synchronous metastases (CI 95%: 45.15–100.20 $p = 0.76$) (Fig. 3).

Twelve patients (48%) experienced acute toxicities, mostly grade 1–2 (8 patients, 32%). The most common side-effects included mild nausea, fatigue, loss of appetite, and abdominal pain (Table 4). All acute symptoms were well treatable and were already decreasing after a short time.

Discussion

Multiple approaches may be used as definitive treatment for adrenal metastases. Open or laparoscopic adrenalectomy is widely considered the first-line treatment. Unfortunately, many patients cannot undergo surgical resection due to comorbidities or may reject surgery. For this reason, radiation therapy has been used as a noninvasive alternative to surgery in the management of adrenal metastases. The role of SBRT as ablative treatment in an oligometastatic patients (defined as ≤ 5 lesions in ≤ 2 organ sites) is well established, especially for pulmonary and hepatic oligometastases [15–17]. Conversely, there are only limited heterogeneous data on adrenal SBRT as an ablative treatment in oligo-progressive patients. (Table 5) [18–25].

In this study, 24 patients were treated with SBRT for adrenal metastases, which allowed encouraging survival outcomes with a tolerable toxicity profile. Consistent with other studies, a 1-year and 2-year OS rate of 87.5% and 66.7% was observed. According to RECIST criteria, a complete response was achieved in 12 lesions (50%), a partial response was achieved in 3 lesions (12.5%), with overall disease stability for 6 patients (25%). Only one patient was diagnosed with local relapse at 7 months.

In 2008, Katoh and collaborators published the first study of SBRT for adrenal metastases, prescribing 48 Gy in eight fractions. No symptomatic adverse effects were reported within the median follow-up period. No local progression during a 12-month period was also reported [18].

One study by Scorsetti and associates evaluated 34 patients treated for adrenal metastases with SBRT in a median dose of 32 Gy, delivered in 4 fractions. After a median follow-up time of 41 months, the actuarial local control rates [LC] at 1 and 2-years was 66% and 32%, respectively;

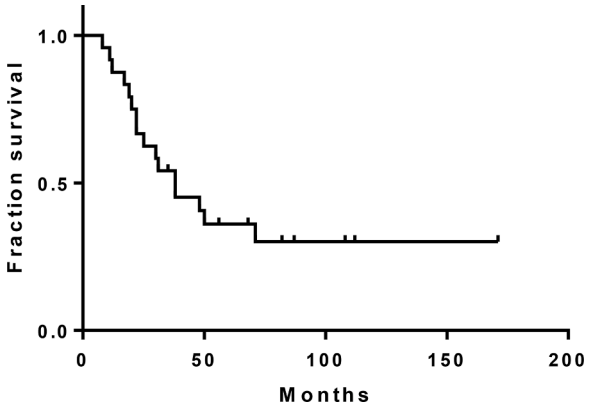

Fig. 2. Overall Survival considering all 24 patients.

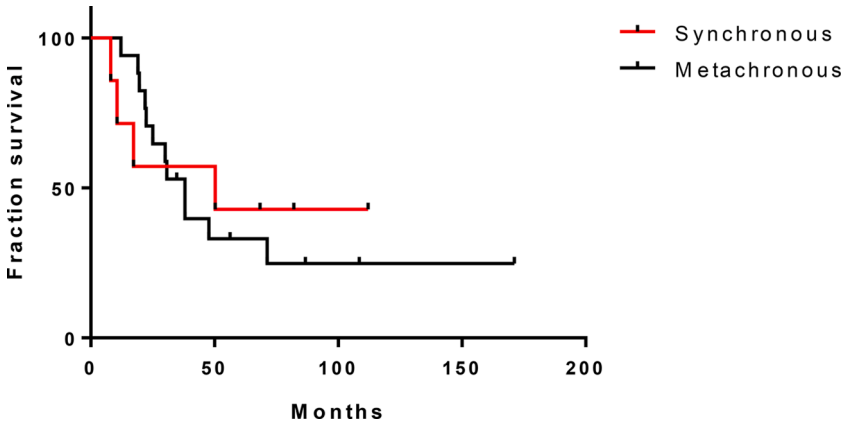

Fig. 3. Overall Survivor between patients with synchronous (1) and metachronous (2) adrenal metastases.

Table 4
Treatment acute toxicity ($n = 25$).

	Grade 1–2No. (%)	Grade 2–4No. (%)	TotalNo. (%)
Toxicities related in 25 cases (xx%)	8 (32%)	5 (20%)	12 (48%)
Asthenia	4 (16%)	0	4 (4%)
Abdominal pain	2 (8%)	2 (8%)	4 (16%)
Nausea	0	1 (4%)	1 (4%)
Vomiting	1 (4%)	1 (4%)	2 (8%)
Diarrhea	1 (4%)	0	1 (4%)

no grade (G) ≥ 3 toxicity was reported. [19].

A.Helis et al. treated 29 lesions in 27 SBRT patients from 2005 to 2018 with a median dose of 50 Gy in 10 fractions. Actuarial 1 and 2-year local control was 86% and 76% respectively. Only 2 patients developed late G3 gastrointestinal toxicity [20].

In another study, Voglhuber et al. analyzed 34 adrenal gland lesions in 31 patients treated with low-dose SBRT. Median follow-up for all patients was 9.8 months, and for patients still alive at the time, 14.4 months. At 9.8 months follow-up, 14 patients were still alive with the following resulting adrenal metastatic disease courses: 7 adrenal gland metastases (20.6%) faced local failure, and 80.6% of patients has been affected by distant metastases. No treatment-related side-effects greater than grade 2 occurred [21].

According to Toesca et al. SBRT offers excellent local control (median OS of 19 months) of adrenal gland metastases with very low toxicity rates (no case of grade ≥3 toxicity). Moreover, comparing the glomerular filtration rate (GFR) before and after stereotactic treatment, kidney function is minimally affected or not affected by SBRT [22]. Konig et al. analyzed 28 oligometastatic patients who received ablative SBRT to adrenal gland metastases, reporting a 2 years LC of 84.8% [23].

The concept of synchronous versus metachronous metastases emerged in both surgical and SBRT literature. Similar to data from several other studies, our study suggests that survival outcomes for patients with metachronous disease are significantly better when compared to synchronous disease. Celik et al. examined 15 oligometastatic patients with adrenal metastases treated with the Cyberknife® system, a robotic SBRT device. With the Cyberknife® system,1-year and 2-year local control rates for metachronous and synchronous groups

Table 5
Published series on patients with adrenal metastases treated with stereotactic body radiation therapy.

Authors (year)	Patients (n)	Histologies	Technique	Dose (Gy)	N Fractions	Local control	Survival	Toxicities
Katoh et al. (2008) (18)	9	Lung, live, kidney and prostate	SBRT	48	8	1 year 100%	1 year: 78%	No toxicities
Scorsetti *et al.* (2012) (19)	34	Different histologies	SBRT	32	4	1 year: 66% 2 year: 32%	22 months (median)	Not significative toxicities
Helis *et al.* (2020) (20)	39	Lung, liver	3D-CRT/SBRT	30–50	5–10	1 year: 87% 2 year: 69%	22.8 months (median)	Acute GI Grade 2: 9pts Late GI grade 2: 3 pts
Voglhuber *et al.* (2020) (21)	31	Lung, breast, melanoma	SBRT	25–57	5–14	1 year progression: 25.9%	18.7 months (median)	No toxicities > grade 2
Toesca et al. (2018) (22)	35	Lung, liver, other gastrointestinal tracts	SBRT	30–50	1–5	Local recurrence: 7.6%	19 months (median)	Grade 2: 7 pts
Konig *et al.* (2020) (23)	28	Lung, kidney	3D-CRT/ IMRT/VMAT	30–54	3–12	2 years: 84.8%	1 year: 46.6% 2 years: 32%	Grade 1–2: 32%
Burjakow *et al.* (2018) (24)	33	Lung, melanoma, colonrectal, breast, esophagus.	SBRT	28–68	na	LFFS 1 year: 58.1	11 months (median)	Only grade 1
Scouarnec *et al.* (2019) (25)	31	Lung, melanoma, kidney, breast, liver, bladder, stomach, merkel cell carcinoma	SBRT	30–55	3–9	1 year: 96.5% 2 year 92.6%	33.5 months (median)	Grade 3: 9pts
This study	24	Lung, kidney, gastrointestinal, endometrial, melanoma	SBRT	10–18	1–8	ORR: 66.5% Local recurrence 1pt	35 months (median)	Grade 1–2: 8 pts (32%) Grade 2–4: 5 pts (20%)

CRT: Conventional Radiotherapy; Pts: patients; SBRT: Stereotactic Body Radiation Therapy; IMRT: Intensity Modulated Radiation Therapy; GI: gastrointestinal; ORR: Local overall response rate; VMAT: Volumetric Modulated Arc Therapy; LFFS: Local failure-free survival; Na: not avaible.

were 60% and 46.6%, respectively ($p = 0.00028$). [26].

Limitations of our study are represented by the retrospective nature of this analysis. The low number of patients is similar to other studies. Primary tumor site and histology heterogeneity may represent another limitation. In order to increase the strength and homogeneity of our study, we analyzed only oligometastatic or oligoprogressive patients and excluded all patients treated with palliative intent or dose.

Conclusion

Even though the limited number of patients investigated in our study, SBRT technique as ablative treatment for oligometastatic or oligoprogressive patients with adrenal metastases showed acceptable survival outcomes and a safe toxicity profile. Although adrenal metastasis resections still represent the standard of care, SBRT may prove to be a feasible alternative, especially for patients who are not candidates for surgical resection.

More clinical data is required to define the role of SBRT in the management of adrenal metastases as compared with surgical resection, as well as the best radiation dose regimen to be used. Nevertheless, the good toxicity profile and the promising clinical outcomes should encourage the scientific community to further prospective clinical studies with the aim of optimizing local control and evaluating a potential benefit.

Authors' contributions

G. Facondo, G. Vullo: Made substantial contributions to conception of the study, wrote the manuscript, analyzed the data and drafted the article. M.Valeriani: performed the analysis and analysed the data. M. Valeriani, A.M. Ascolese, V. De Sanctis and M.F. Osti: Made substantial contributions to revising the article critically for important intellectual content. All Authors critically revised the article, approved the final version to be published, and agree to be accountable for all aspects of the work.

Declaration of Competing Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Acknowledgments

Not applicable.

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