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Original Research Article

Total dose, fraction dose and respiratory motion management impact adrenal SBRT outcome

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ABSTRACT

Purpose/Objective(s): Stereotactic body radiotherapy (SBRT) is an effective treatment for oligometastatic disease in multiple sites. However, the optimal radiation dose for long-term local control of adrenal metastases has yet to be determined. The aim of this study is to evaluate outcomes of adrenal SBRT and to evaluate factors that correlate with local control.

Materials/Methods: After IRB approval, a retrospective data review of patients treated with SBRT for adrenal metastases at a medical center in Israel between 2015 and 2021 was conducted. A biological effective dose was calculated using an alpha beta ratio of 10. Kaplan Meier and Cox regression were calculated using SPSS software to describe the hazard ratio for local control and survival.

Results: 83 cases of adrenal SBRT were identified. The average age was 67 (range 42–92 years old). Non-small cell lung cancer was the primary site in 44 % of patients. A total of 70 % of the patients had oligometastatic disease (less than five lesions), and the rest were polymetastatic, responding to systemic therapy with oligo progression in the adrenal. The average gross tumor volume (GTV) was 42 ml. Respiratory control was applied in 88 % of cases; 49.3 % used 4-D/ITV, and 38.5 % used breath-hold or continuous positive airway pressure (CPAP) with free breathing. On multivariable analysis, Dose above 75 Gy (biological effective Dose) (HR = 0.41, p = 0.031), Dose above 8 Gy per fraction (HR = 0.53p = 0.038), and breath-holds or CPAP (HR = 0.65, p = 0.047) were significant for local control. From multivariable analysis, we computed a predicted nomogram curve using seven clinical parameters to evaluate local control odds.

Conclusion: In this single institution series reported to date, we found unilateral adrenal SBRT safe, yet bilateral treatment harbors a risk of adrenal insufficiency. Biological effective Dose > 75 Gy (BED), motion management with breath-hold or CPAP, and Dose per fraction > 8 Gy were the enhanced local controls. We propose a nomogram to help in decision-making regarding total Dose and Dose per fraction when treating adrenal SBRT.

Introduction

The adrenal glands are a common metastatic site, with an incidence ranging from 9 % to 27 % [1]. Most lesions are asymptomatic and are typically discovered incidentally during routine imaging. Aggressive local treatment for oligometastatic disease has been associated with an overall survival advantage in some studies [2]. Stereotactic body radiotherapy (SBRT) is a non-invasive technique that delivers ablative radiation doses to discrete lesions, typically in one to five fractions. Since the adrenal gland moves significantly with respiration, it is crucial to account for respiratory motion to achieve higher local control rates without increasing toxicity [3,4].

While data on SBRT to the adrenal gland is available, much of it is limited due to small cohort sizes. Doses reported in the literature vary widely, and there is a paucity of data on which dose regimen is adequate for local control [5,6].

The aim of the current study is to explore the relationship between the BED, Dose per fraction, and respiratory motion in relation to the local control of adrenal metastases.

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Materials and Methods

Institutional Review Board (IRB) approval for a retrospective review was obtained. Inclusion criteria encompassed patients treated with SBRT to the adrenal gland between 2015 and 2022, specifically those with an oligoprogression or oligometastatic disease. Patients with follow-up durations of less than two years were excluded. Additionally, patients who were either deceased or were lost to follow-up were excluded from the study.

Background demographics, pathologic and radiographic data, prior oncologic therapies, and detailed information related to adrenal radiotherapy were extracted from electronic medical records and institutional radiotherapy databases. Patients were classified as oligometastatic if they presented with five or fewer sites of metastasis at the time of treatment. Local failure was defined as tumor growth within the treated adrenal gland, according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria (version 1.1). Time to failure was calculated from the completion of radiotherapy.

Toxicity was evaluated and graded using the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 criteria. By standard practice, radiation doses were converted to biologically effective doses using an α/β ratio of 10 for tumor tissues and 3 for normal tissues. Dose constraints were evaluated using strict published protocols [7].

Statistical analysis

Descriptive analyses were performed using the mean and standard deviation (SD) for parametric variables, while the median and range were employed for non-parametric variables. The chi-squared (X^2) test was used for categorical variables. Time-to-event outcomes were estimated using the Kaplan–Meier method. BED and Dose per fraction were analyzed as continuous and categorical variables at different thresholds. A Cox regression model was applied to investigate variables that demonstrated the impact of local control. A nomogram was created from the Cox regression model. All Data was analyzed using statistical software SPSS v26 (IBM SPSS®, SPSS Inc, Chicago, Illinois).

Results

Patients demographic

Between 2015 and 2022, 83 cases of adrenal SBRT were treated. The average age was 67 years, ranging from 42 to 92 years. Of the patients, 54.3 % were males. Non-small cell lung cancer accounted for 44 % of the total patients, followed by Melanoma at 14 %, Colon carcinoma at 12 %, Breast cancer at 9.6 %, Bladder cancer at 4.8 %, Small cell lung cancer at 4.8 %, Ovarian cancer at 3.6 %, and other malignancies at 3.6 %. The distribution between the right and left adrenal glands was almost equal, with 40 cases on the left and 37 on the right side; 6 patients received bilateral SBRT. Oligometastatic disease was present in 70 % of the patients (oligo metastatic disease was defined with less than five lesions). At the same time, the rest had polymetastatic disease yet responded to systemic therapy with oligo progression in the adrenal gland. None of the lesions found were symptomatic.

SBRT was delivered with a median BED of 75 Gy (ranging from 48 Gy to 105 Gy). The median number of fractions was 5 (ranging from 3 to 10), and the median Dose per fraction was 8 Gy (ranging from 5 Gy to 12 Gy).

The median GTV and PTV were 42.2 ml (ranging from 3.2 ml to 124 ml) and 138.3 ml (ranging from 23.1 ml to 350 ml), respectively. All cases were treated using the Volumetric Modulated Arc Therapy (VMAT). Respiratory motion was addressed in 88 % of cases.

All treatments were delivered on Varian machines with Cone Beam CT capabilities, and the dose prescription was 100 % of the PTV. In 88 % of treatments, dose painting techniques were utilized to spare high doses to the bowel and stomach. The dosage for analysis was given to the most significant volume for each plan. For example, in plan number 14, a PTV of 78 ml was defined, and the dosage was distributed as follows: 45 Gy in 5 fractions to 17.4 ml, 40 Gy for 46 ml, and 35 Gy for 14.6 ml. Therefore, for the analysis, a dosage of 40 Gy was used (see Table 1).

Local control

All radiation dose schedules with respect to BED and local control are shown in Table 2. Local control at the two-year mark was 74.6 %.

Impact of total dose and dose per fraction

During univariate analysis, we noticed distinct differences in BED and Dose distribution per fraction between patients who achieved local control and those who failed locally ($P = 0.011$ and $P = 0.007$, respectively). The correlation between BED and Dose per fraction was 0.49 ($P < 0.001$).

We analyzed to assess the impact of varying BED levels (using a dichotomous cut-off ranging from 50 Gy to 100 Gy BED, with increments of 5 Gy each time) and different Dose per fraction (ranging from 6 Gy to 10 Gy with 1 Gy increments) on local control. Each univariate analysis was tested using Cox regression. Dose above 75 Gy BED ($HR = 0.27$, $P = 0.008$) and a Dose above 8 Gy per fraction ($HR = 0.23$, $P = 0.004$), both were significantly associated with local failure.

Kaplan Meier curves for those parameters are presented in Fig. 1.

We performed multivariable analysis using Cox regression to study local control as a function of BED and Dose per fraction. We computed seven clinical parameters in the model. When including age, PTV, BED

Table 1
(a) Patients characteristics.

Total (N)	83
Age	67.1 y (42–92)
Gender (female)	38 (45.7 %)
Primary histology	
Non small cell lung	37 (44 %)
Melanoma	14 (16.8 %)
Colon	10 (12 %)
Breast	8 (9.6 %)
Others	14 (16.8 %)
Side	
Left	40 (48.1 %)
Right	37(44.5 %)
Bilateral	6 (7.2 %)
Oligometastasis (<5 mets)	58 (70 %)
Oligoprogression	25 (30 %)

(b)

Radiation treatment characteristics	
GTV ml (mean, range)	42.2, 3.2–124
PTV ml (mean, range)	138.3, 23.1–350
High dose PTV ml (mean, range)	82.5, 2.9–234.8
ITV ml (mean, range)	42.2, 7.6–131
BED (median, range)	75 Gy 48–105
Number of fractions (median, range)	5, 3–10
Dose per fraction (median, range)	8, 5–12
Motion management	
Breath hold	22 (26.5%)
CPAP	20 (24%)
4D/ITV	31 (37.3%)
CBCT only	10 (12%)

Table 2
All dose regiments.

Total dose (dose per fraction)	Biological effective dose(α/β = 10)	Number of patients in cohort	Local control at 2 year %
30(6)	48	6	**50 %**
27(9)	51.3	3	**66 %**
32(6.4)	54.48	2	**0 %**
32(8)	57.6	4	**100 %**
36(6)		2	**0 %**
35(7)	59.5	6	**66 %**
34(8.5)	62.9	2	**100 %**
37.5(7.5)	63.75	4	**50 %**
42(6)	67.2	4	**25 %**
40(8)	72	8	**100 %**
50(5)	75	6	**66 %**
48(6)	76.8	3	**100 %**
42(8.4)	77.28	4	**100 %**
40(10)	80	2	**100 %**
49(7)	83.3	3	**100 %**
45(9)	85.5	10	**80 %**
44(11)	92.4	2	**100 %**
50 (10)	100	7	**100 %**
60(7.5)	105	4	**50 %**
48(12)		1	**100 %**

> 75 Gy, Dose per fraction > 8 Gy, oligo metastatic status, and breath-hold versus other respiratory techniques, we found that BED > 75 Gy was significantly correlated with local control (HR = 0.41 (0.2–0.81), P-0.031), in addition dose per fraction above 8 Gy was significant for local control (HR = 0.53 (0.32–0.88), P = 0.038).

Local control was not associated with GTV, PTV, and primary cancer type. Similarly, there was no difference in local control in oligo-metastatic versus oligo-progression patients (77.5 % vs.68 %, p = NS). (Table 3).

Respiratory motion control

In 88 % of cases, respiratory motion was addressed by 4D (49.3 %) or breath-hold (38.5 %).

Local control was 84.3 % for patients planned and treated with the breath hold strategy versus 68.8 % for those treated with 4d only. Fig. 1 presents a Kaplan Meir curve for local control stratified by motion management Technique.

On multivariable analysis, we found that breath hold improves local control even when adjusting to the different variables in the model. (HR = 0.65 (0.43–0.910, P = 0.047). (Table 3).

Nomogram

From the Cox regression model analysis, we computed a nomogram for the prediction of local failure using seven clinical parameters. We included age, total PTV, clinical presentation (oligometastatic, oligo-progression), histology, total Dose, Dose per fraction, and respiratory motion management. We expanded the data for external validation and included 49 more cases from a second hospital for 132 cases. Fig. 2.

Toxicity

Within this cohort, 24 % of patients experienced bowel toxicity, with the majority (75 %) presenting with G1 toxicity. A single patient exhibited G4 toxicity, characterized by bowel perforation, which manifested as acute peritonitis three months post-completion of radiation therapy. This patient needed an emergency intervention and was still alive at the last follow-up of this analysis.

We performed a univariate analysis and found no correlations between BED, Dose per fraction motion management, and bowel toxicity. Notably, the patient who experienced G4 toxicity received a radiation regime of 35 Gy delivered in 5 fractions, adhering to established bowel constraint seven, as verified during a second-look retrospective quality assurance review. Cone-beam CT scans confirmed compliance with the treatment plan.

Additionally, we identified one patient (1.5 %) who developed

Table 3
Multivariable comparison local control vs local failure.

Variable	**Local control (n = 62) 74.6 %**	**Local failure (n = 21) 25.4 %**	**HR**
Age (y) **(mean, range)**	66.2 (51–79)	69.68 (42–92)	1.003 (0.91–1.22) p = 0.87
Fraction Dose > 8 Gy	83.8 %	16.2 %	**0.53(0.32–0.88) p**
Fraction Dose ≤ 8 Gy	65.3 %	34.7 %	**= 0.038**
Dose > 75 Gy	88.8 %	11.2 %	**0.41(0.2–0.81) p**
Dose ≤ 75 Gy	59.5 %	40.5 %	**= 0.031**
Melanoma/Colon CA	57.1 %	42.9 %	1.4 (0.89–2.4) p =
others	78.2 %	21.8 %	0.71
PTV(CC) mean	136.7 cc	143.03 cc	1.02 (0.93–1.3) p = 0.91
Breath hold/free	84.3 %	15.7 %	**0.65 (0.43–0.91) p**
breathing + CPAP	68.8 %	31.2 %	**= 0.047**
4d/CBCT only			
Oligo-metastases	77.5 %	22.5 %	0.8(0.64–2.1) p =
Oligo-progression	68 %	32 %	0.34

Highlight variables were statistically significant.

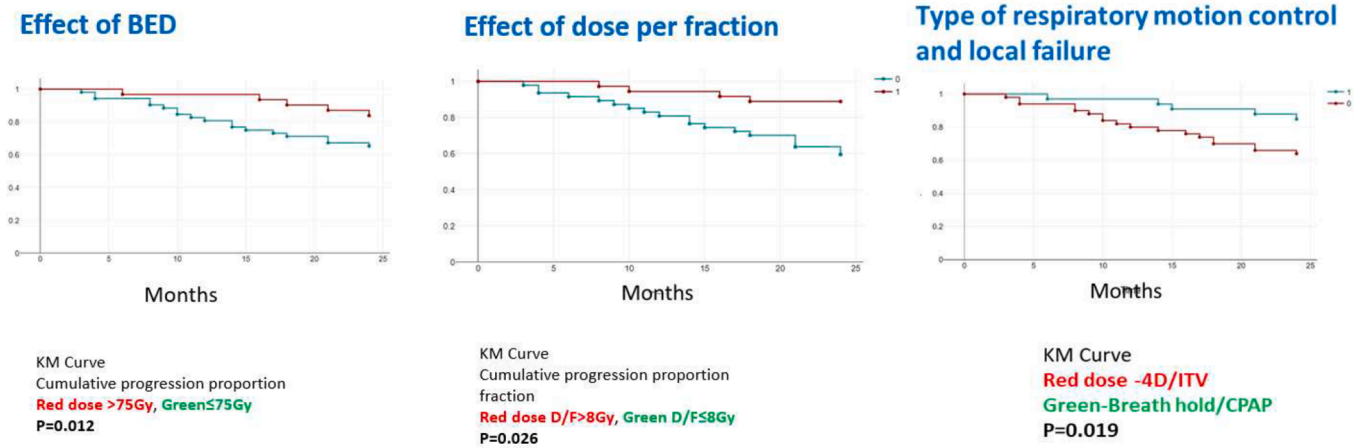

Fig. 1.

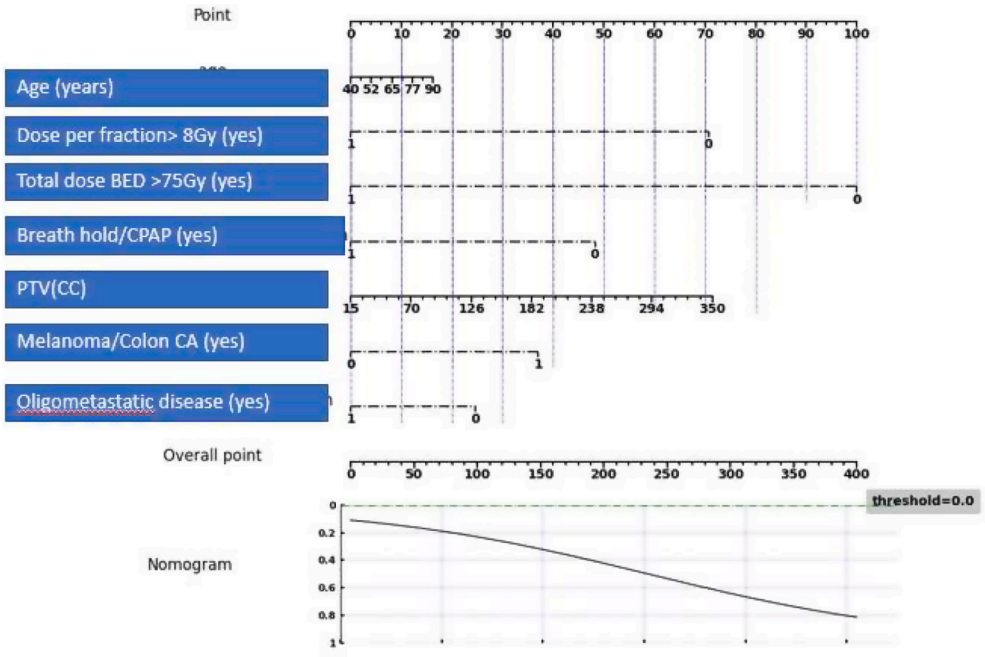

Fig. 2. Nomogram (n-132).

adrenal insufficiency. This patient had received bilateral adrenal radiation, with the right adrenal gland receiving 50 Gy in 5 fractions and the left adrenal gland receiving 45 Gy in 5 fractions. Five months after the second radiation course, the patient presented with general weakness, prompting cortisol level assessment as part of a general evaluation. Following the initiation of prednisone 5 mg per day, the patient experienced an improvement in general weakness with no other complications. It is noteworthy that the patient did not undergo immunotherapy and was not on long-term steroid use, suggesting a likely relationship between adrenal insufficiency and radiation therapy.

Discussion

SBRT for adrenal metastasis has emerged as a viable alternative to surgical metastectomy. Nevertheless, the current literature on adrenal SBRT remains relatively limited. We analyzed disease and treatment variables influencing local control and toxicity in this retrospective cohort study.

In our study of 83 patients, adrenal SBRT demonstrated promising local control with only mild toxicity. We achieved a two-year local control rate of 76.4 %, which compares favorably to other published studies [14].

In multivariate analysis, both size per fraction (>8Gy) and BED (>75 Gy) were statistically significant, even when adjusting to standard clinical variables. It is noteworthy that our median tumor volume matched that reported by König et al. at 42 ml for GTV. However, our PTV was slightly larger at 112 ml compared to 96 ml in the König et al. study [6].

Previous investigations have highlighted that adrenal SBRT with a BED $\geq$ 85.5 Gy correlated with superior local control [8]. While König et al. detected a non-significant trend for improved local control, a BED $\geq$ 75.0 Gy. A recent meta-analysis by Franzese et al. concluded that a BED > 72 Gy combined with using 4DCT for motion control should be considered for high-quality ablative adrenal SBRT [9,14]. Additionally, a multicenter database analysis indicated that achieving a significant improvement in Local Recurrence Rate (LRR) for adrenal SBRT necessitates a BED > 73.2 Gy (adenocarcinoma: 69.1 Gy) [15].

In this cohort, patients received varying doses chosen by the primary physician, with due consideration of Organ-At-Risk (OAR) constraints. Our findings suggest that doses exceeding 75 Gy correlate with excellent local control, with no observed advantage of doses greater than 100 BED.

Furthermore, our study revealed a notable correlation between dose per fraction and local control, a finding that holds even when adjusting for BED. We also showed a correlation between dose per fraction and local control, even when adjusting to the BED. A fraction size above 8 Gy appears pivotal for optimizing local control. Although an 8 Gy size may seem arbitrary, it aligns with experimental evidence showing that this dose level induces substantial vascular injury within tumors, subsequently leading to secondary tumor cell death and boosting antitumor immunity [10].

In addition, the seminal laboratory data from Fuks et al. have shown activation of the acid sphingomyelinase pathway at a fraction above 8 Gy, which in turn activates tumor endothelial cell apoptosis, disrupts tumor vasculature, and increases cell death [11].

Regarding motion management, the adrenal glands have been reported to show extensive respiration-induced motion of more than 20 mm in several directions [12]. 88 % of patients were treated with deep inspiratory breath hold or abdominal compression with an internal target volume (ITV) derived. We found improved local control when a breathhold technique was used. This could be explained by the variable inter-fraction respiratory motion difference shown previously by different studies [13].

Our study is not without Limitations. First, the retrospective nature of this analysis and a modest sample size, yet with a large sample size compared to other studies of adrenal SBRT [5,6]. The heterogeneous population, both in the state of disease (oligo progression, oligo metastatic, extensive metastatic), the purpose of treatment (palliative, ablative), and the histologic type of primary tumor are typical of this condition and are unlikely to be different in future series.

Another area for improvement is our inability to link overall survival data to our study. We are now collecting the survival data for this cohort and would like to add this to our analysis shortly.

The Strengths of this study are the large, relatively robust follow–up, a significant number of the patients still alive after two years, and the fact that for the majority of them, a PET-CT scan was done. In addition, the validation of the nomogram and creation of the ROC curve can help predict local control for adrenal SBRT in future studies.

Conclusions

SBRT for adrenal metastases is a highly effective local therapy and alternative to surgery with mild toxicity. We demonstrated that a dose above 8 Gy a total BED above 75 Gy and breath hold/CPAP enhanced local control. For our knowledge this is the first study that showed the importance of Dose per fraction when treating adrenal SBRT and in addition the first time that breath hold Technique was showed to improve local control versus 4D/ITV method.

We propose a treatment regimen with a fraction size of at least 8 Gy and a BED of at least 75 Gy BED (for example 42GY in 5 fractions) with incorporation of breath hold or using MR-LINAC for evaluation in a prospective clinical trial. In addition, we created a nomogram which can help improve individual dos regiment, we suggest to evaluate our nomogram in larger cohorts.

Author contribution

OH- study conception and design, data collection, statistical analysis
ZS, YL, SA, OPK- analysis and interpretation of results
MJ-grammar check
MBA, SD-physics dosimetry analysis
IW-data collection.

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Patient consent

Informed consent was obtained for experimentation with human subjects by the IRB.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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