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Modeling of Tumor Control Probability in Stereotactic Body Radiation Therapy for Adrenal Tumors

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Abstract

Purpose: Stereotactic body radiotherapy (SBRT) in the management of adrenal metastases is emerging as a well-tolerated, effective method of treatment for patients with limited metastatic disease. SBRT planning and treatment utilization is widely variable, and publications report heterogeneous radiation dose fractionation schemes and treatment outcomes. The objective of this analysis was to review the current literature on SBRT for adrenal metastases and to develop treatment guidelines and a model for tumor control probability (TCP) of SBRT for adrenal metastases based on these publications.

Methods: A literature search of all published studies of SBRT for adrenal metastases from 2008–2017 was performed and outcomes in these studies were reviewed. Local control (LC) rates were fit to a statistically significant Poisson model using maximum likelihood estimation techniques.

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Conflicts of Interest:

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Results: One-year LC greater than 95% was achieved at an approximated biological equivalent dose with $\alpha/\beta=10$ Gy (BED_{10}) of 116.4 Gy.

Conclusion: While respecting normal tissue tolerances, tumor doses greater than or equal to a BED_{10} of 116.4 Gy are recommended to achieve high LC. Further studies following unified reporting standards are needed for more robust prediction.

Summary

Based on the published literature on outcomes of SBRT for adrenal tumors, a model for the tumor control probability (TCP) was developed, and an optimal dose/fractionation schema is recommended to achieve high tumor control while respecting nearby organs at risk.

Keywords

SBRT; tumor control probability; adrenal; metastasis

1. Clinical Significance

The most common tumors involving the adrenal gland are metastases from other primary cancers. An autopsy study of patients with metastatic carcinoma revealed that approximately one-quarter of patients had metastatic involvement of the adrenal gland by the primary cancer, most commonly from lung, gastric, and renal cancer (1). Surgery has historically been the primary treatment modality for patients with adrenal metastases, predominantly in the setting of oligometastatic disease (limited metastases to typically one to five sites/lesions).

Radiotherapy (RT) in the treatment of adrenal metastases has gained traction in recent years, although conventional RT techniques were typically only employed for palliation of pain (2–4). In the modern era, the development and utilization of stereotactic body radiotherapy (SBRT) has expanded the use of RT in treatment of adrenal tumors (5, 6). SBRT delivers a very conformal, high dose of radiation in a reduced fractionation scheme.

In patients who are ineligible for surgery (due to medical co-morbidities, sub-optimal anatomy, local tumor invasion) or patients who refuse surgery, SBRT can be considered a reasonable alternative. With advances in management of tumor motion, imaged-guided treatments, and more sophisticated treatment planning software, SBRT can be delivered safely to intra-abdominal tumors including malignancies of the adrenal gland. No randomized controlled trials have been conducted comparing surgery to SBRT for adrenal malignancies; however, recent studies that report SBRT outcomes are encouraging. Utilization of SBRT has classically been focused on patients with limited disease who are poor surgical candidates in an attempt to increase progression-free survival (PFS) (6).

With the increasing use of SBRT for many sites and the growing interest in using SBRT as an alternative to surgical resection in patients with oligometastatic disease, there has been an attempt to quantify the benefit of this approach and to establish appropriate dose and fractionation schemes. Although SBRT for adrenal metastases is less commonly performed than for liver and lung tumors, there is a move toward using this approach for

patients with oligometastatic disease and there have been multiple recent additions to the literature on SBRT for adrenal tumors. The objective of this work was to review the existing publications of primarily single institution, retrospective studies reporting the use of SBRT for adrenal metastases and to model tumor control probability (TCP) with SBRT in this particular clinical scenario. Despite the variation in the available datasets, there appeared to be sufficient discrete data points for outcomes and a range of doses and fractionations to develop a model encompassing these differing dose and fractionation schema to allow for an evaluation of the efficacy of these regimens.

2. Endpoints

Several endpoints have been reported in the literature including overall survival (OS) (median, one- and two-year survival), local control (LC) at similar time points, or PFS. The most commonly reported outcomes were LC and OS (5, 7–16). These were the endpoints selected for analysis and modeling. LC is generally defined as no evidence of locally progressive disease. All the studies reported in Table 1 employed Response Evaluation Criteria in Solid Tumors (RECIST) to evaluate the objective response of solid tumors after treatment (17) except for studies by Torok, Desai, and Chance which stated that radiographic progression on follow-up PET and CT studies was used. For example, Chance, *et al*, characterized failure by “CT evidence of progressive abnormalities over time that corresponded to PET-avid areas (18).” While RECIST criteria are the most commonly used assessments of response, they may be limited in evaluating response to SBRT where tumors are less likely to change in size, and treatment response can evolve over time with initial increase in size of lesions followed by gradual reduction in tumor size.

Dosimetric data were also reported in the studies and included median total dose, number of fractions, target dose coverage, and target volume size. For patients whose outcomes were reported at 1 year, data were recorded, and the equivalent dose in 2 Gy fractions ($\alpha/\beta=10$ Gy) (EQD2₁₀) was calculated and used for analysis.

3. Challenges Defining and Segmenting Volumes

The delineation of target volumes when utilizing SBRT can be complicated and necessitates multiple imaging modalities and optimal CT simulation with intravenous contrast if possible and immobilization of the patient. If diagnostic imaging studies including PET/CT, CT, and MRI are available they can be fused with the CT scan obtained during simulation of the patient and reviewed by the treating physician prior to contouring. The gross tumor volume (GTV) is defined by the axial images from the simulation and diagnostic images. Although the studies in Table 1 primarily used CT for tumor delineation, 5 of them (5, 7, 8, 13, 18) also fused PET and/or MR scans from staging imaging to aid this task. As evidenced in the reported retrospective data (Table 1), frequently no expansion for microscopic disease is applied to the GTV; in such cases, the GTV and clinical target volume (CTV) are identical (8, 15). It is common in the practice of SBRT to omit a CTV expansion as microscopic disease is not the intended target. Given high dose and planning techniques with SBRT, tighter margins are typically employed. Nonetheless, contouring adrenal tumor volumes remains challenging and a source of uncertainty despite multiple

diagnostic imaging modalities available, thus the input of a diagnostic radiologist may be helpful to accurately delineate the GTV.

An important component of SBRT is the consideration and management of motion typically driven by respiration. Adrenal tumor motion is marked in the cranio-caudal dimension, ranging from 5–12mm in one report (19), but less so in the left-to-right or antero-posterior dimensions (20, 21). In the reported series in Tables 1 and 2, motion was accounted for in a myriad of ways including the use of four-dimensional CT (4DCT), deep inspiration breath hold (DIBH), and abdominal compression. In most cases an internal target volume (ITV) was contoured based on the 4DCT. Lastly, a planning target volume (PTV) was created by adding an approximately 3–5 mm margin to the CTV or ITV in most cases. This volume accounts for daily setup error, breathing pattern variations, and motion of the target (if an ITV had not previously been defined).

In the literature, a large range of PTV sizes (see Table 1) is reported; median reported PTVs in these studies ranged from 41 cc to 306.6 cc. The size of the target volume and presence of nearby organs at risk pose limitations to the total dose and number of fractions that can be safely delivered to these mobile, intra-abdominal tumors.

Fiducials are commonly used to improve target localization when delivering SBRT. However, in this report, a minority of the published experiences utilized fiducial markers for adrenal tumors (12, 22, 23). This is likely due to the relative ease in identifying an adrenal mass with the difference in Hounsfield Units of surrounding fat and other nearby organs on cone-beam CT (CBCT), which was used for image guidance in many of the reviewed studies. Fiducials remain an option for optimizing treatment delivery, though are not essential per the summarized reports here and remain institutionally dependent. Further discussion on this topic is included in the American Society for Radiation Oncology (ASTRO) quality and safety considerations in SBRT (24) and in the report of AAPM Task Group 101 on stereotactic body radiation therapy (25).

4. Review of Outcomes

A literature search using Pub Med was undertaken to identify publications capturing patients treated with SBRT for adrenal malignancies with available outcomes. Specifically, the search criteria included keyword in the Title/Abstract of “stereotactic” or “radiotherapy” and “adrenal” published from January 01, 2007 through March 01, 2017. Results were limited to those in the English language. This yielded 250 relevant results. These results were manually reviewed. Studies were excluded if not pertaining to adrenal SBRT. Those that were reviews only were excluded. Studies with available outcomes (LC or OS) were included. One study, Guiou *et al*, was not available in the Pub Med database. However, this was later included when referenced in another included source.

Captured in Table 1 are important clinical and treatment parameters. The studies themselves were fairly small. The number of treated lesions ranged from 6–49 total tumors (6–48 patients) per study. Multiple primary sites were included with different histologies. As aforementioned, publications often included information regarding PTV and GTV with

typically in the setting of early stage NSCLC, have supported the finding of increased LC with BED_{10} greater than or equal to 100 Gy with SBRT (29, 30).

5. Factors Affecting Outcome

Many factors that have the potential to influence outcomes in this population of patients and the data are reported in Table 1. As described above, there is considerable heterogeneity in the datasets regarding target delineation, dose prescription (dose per fraction, prescription isodose, number of fractions), primary histology, types of outcomes analysis and treatment intent (palliative or definitive). It is also important to realize that target coverage for each patient depends on many factors including treatment planning and delivery technique, respiratory motion control, proximity to critical structures, and previous treatments. The planning target volume (PTV) definition differed from study to study; the PTV had a margin of as little as zero ($PTV = GTV$) (15) or as large as 10 mm expansion from CTV or ITV (11, 13, 27). Given variability in the available data, we are unable to establish a clear correlation between margin size and LC. Margin adequacy could impact tumor control and a standardized margin would be desirable for future studies. Finally, all of these studies had small patient numbers with competing risks of death from other sites of metastatic disease, thus impacting the reliability of the local control data. Despite these caveats, there was a clear dose response in terms of LC and OS in patients with adrenal metastases treated with SBRT.

6. Mathematical/Biological Models

Analyzing the publications in Table 1, we found no correlation of PTV margin with LC. Prescription isodose lines (IDL) varied from 70% to 100%; these did not seem to correlate with the observed LC rate based on the crude observation. We did not perform statistical analysis of the IDL effect due to very limited data points available.

The 1-year LC rates of the suitable studies in Table 1 were fit to a statistically significant Poisson model, shown in Equation 1 (31), using maximum likelihood estimation techniques. The 95% confidence intervals of the parameters were estimated using profile likelihood. The Poisson model for TCP is among the most commonly used in the literature due to its radiobiological relevance. To account for the variety of fractionations, doses were converted into the equivalent dose in 2 Gy fractions with $\alpha/\beta=10$ ($EQD_{2,10}$) (32).

$$TCP = \left(\frac{1}{2}\right)^{\exp\left[2\gamma_{50}\left(1 - \frac{EQD_{2,10}}{EQD_{2,10}}\right)/\ln(2)\right]} \quad \text{Equation 1}$$

where TCP is 50% at $EQD_{2,10}$ and γ_{50} is the normalized slope at 50% TCP.

Because detailed DVH data were not available, we used the median prescription dose, isodose line, and number of fractions from each publication to estimate the median $EQD_{2,10}$ encompassing the tumor; the dose was adjusted accordingly, if the prescription IDL was known. The fit to these data was statistically significant using chi-squared test ($\chi^2 = 57.5$, χ

< 0.0001) (the p value rejects the null hypothesis that the fit is has a zero slope (horizontal line)).

Figure 1 shows the model fit (solid curve), the 95% confidence intervals (dotted), and the data points. The circle size is proportional to the number of patients in the study and the error bars are calculated using Agresti–Coull approximation for binomial proportions (33). It is noted that LC at 95% is achieved with an approximate BED_{10} of 116.4 Gy ($EQD2_{10} \sim 97$ Gy). In addition, a dose-response model using equation 1 for the published OS rates at year 1 is presented (Figure 2). This fit is also statistically significant (χ^2 is 44.7, $p < 0.001$), though we note that its confidence intervals are quite wide compared to LC, given that many factors other than dose may also contribute to OS.

Three additional studies have been published during the write up of this work which were not included in the present model as the manuscripts were not available at the time of this analysis. One recent study (31 patients, 33 lesions) fit this model very well. It treated to a median BED_{10} of 112.5 Gy with 96.5% LC at 1 year (34). The two additional publications showed a high LC at 1 year with 30 patients and a BED_{10} of 85.5 Gy (35) and one with 35 patients and median BED_{10} of 72 Gy (36). The one-year LC for all three studies fell within the 95% CI of the model. The LC dropped off in the two studies with the lower BED_{10} at two and three years suggesting that the durability of LC may be impacted by dose (35, 36). Most recently, a meta-analysis of outcomes for SBRT of adrenal metastases is in press(37). The authors extracted data from 39 of an initially identified 569 published between 2009 and September 2019. They also report that LC is strongly correlated with BED_{10} . Their analysis, based on 22 studies, predicts LC at 1 year of 70.5% for BED_{10} of 60 Gy, 84.8% at BED_{10} of 80 Gy and 92.9% for BED_{10} of 100 Gy, which is well within the CI of our model. They also found BED_{10} to be significantly correlated with 2 year LC (19 studies) and 2 year OS, though not with 1 year OS.

7. Special Situations

A recently published review of the literature compared surgical adrenalectomy, SBRT, and percutaneous catheter ablation (PCA) (38). Reported OS and LC were greater in patients undergoing surgery. However, the manuscript aptly reports significant selection biases amongst patients. Tumor histology, performance status, extent of uncontrolled extra-adrenal disease, and co-morbidities were among some of the biases noted. For example, patients in the SBRT group tended to more often have lung primary histology as compared to the surgery or PCA groups (68% vs 33% and 27%, respectively). The authors assert that patients with lung primary metastases have an overall poorer prognosis than other malignancies. Another observation made was that patients offered surgery tended to have isolated adrenal disease (75% vs 48% in the surgical and SBRT cohorts, respectively). Given these heterogeneities in patient cohorts, it remains unclear whether adrenalectomy, SBRT, or other local ablative treatment options offer the most effective approach for adrenal metastases. When considering patients for localized therapy and critically evaluating the literature, these selection biases should be considered. Finally, all but one study that we reviewed included only patients who had not received prior radiation to the adrenal gland. Chawla *et al*/included two patients who underwent re-irradiation and were both still alive at

the time of publication with LC of 16 and 5 months (5). However, given the low number of patients represented, our results may not be applicable to patients undergoing re-irradiation to the adrenal disease.

8. Recommended Dose/Volume Objectives

As discussed, there were a range of doses reported in the studies analyzed in this model. The median dose prescribed was 40 Gy, and the median fraction number was 5. In Table 1, the results of the largest retrospective institutional analysis by Casamassima *et al* are presented (9). In this report, patients received a BED_{10} of just over 139 Gy to isocenter (100% isodose) with an actuarial LC rate of 90% at 1- and 2-years. This corresponded to a dose of 36 Gy prescribed to the 70% IDL over 3 fractions, and it yielded acceptable toxicities with no acute gastrointestinal, hepatic, or renal issues reported. Within the PTV, the BED_{10} varies between 79.2 to 139 Gy (EQD₂₁₀ between 66–116.3 Gy).

The LC model of Figure 1, which incorporates the reviewed studies with dosimetric and LC information, suggests that at 1 year LC over 95% is achieved at an approximate BED_{10} of 116.4 Gy (EQD₂₁₀ ~ 97 Gy). Clinical examples of fractionation schema providing this BED_{10} include (though are not limited to) 45 Gy delivered in 3 fractions (BED_{10} 112.5 Gy) or 55 Gy in 5 fractions (BED_{10} 115.5 Gy). Providing normal tissue tolerances are respected, tumor doses at or above this range are a desirable goal. However, larger studies with more consistent dosimetric reporting and longer follow-up are needed for firm recommendations.

A current ongoing clinical trial, NRG-BR001, may provide further information on TCP for adrenal metastases. This is a phase 1 study of SBRT for the treatment of oligometastases arising from the breast, lung or prostate to various sites (39), prescribes 45 Gy delivered in 3 fractions (acceptable variation of 42.5–45Gy) with a plan to decrease dose to 42 Gy in 3 fractions should dose limiting toxicities be reported. The protocol defines prescription dose as the dose covering 95% of the PTV with the 80–90% IDL generally used, but a range of 60–90% is acceptable. In this protocol, hot spots are to be restricted to within the target unless the target is overlapping with an organ at risk. OAR constraints are provided in the protocol. Normalization is employed such that 100% prescription dose corresponds to the maximum dose in the PTV. Of note, our suggested dose-volume objectives are based on studies which all included respiratory motion management (Table 2). Many techniques are available, as described in the references, and clinicians can adopt motion management techniques in accordance with their available resources.

9. Future Studies

Prospective studies comparing the efficacy and toxicity of adrenal SBRT to adrenal metastectomy could provide essential data to assist in selecting the optimal modality based on individual patient and disease characteristics. Studies should clearly describe the patient characteristics (number of metastases, other sites of disease, performance status) and treatment details (for radiation therapy, motion management and prescription methods are key) and provide data by which future analyses can more confidently determine the optimal dose and fractionation of SBRT. The results of the aforementioned NRG trial will also help

elucidate LC rates and outcomes for patients with oligometastatic disease (39). This study includes various histologies which would be representative of typical adrenal metastases. The overall disease response to SBRT in this study will provide prospective data to assist in establishing more standard fractionation patterns for adrenal metastases.

10. Reporting Standards for Outcomes

In an effort to standardize reporting of outcomes for adrenal SBRT, we propose recording and publishing the following parameters, making use of electronic supplements if necessary:

- Primary tumor histology
- Volume of GTV (or ITV) and PTV
- GTV (or ITV) to PTV margin including methods used to mitigate target motion and daily set-up verification measures
- In addition to summary dose and outcome statistics, at least have electronically available
 - Prescription dose and IDL and fractionation for each individual patient together with patients' failure and survival endpoints reported in published data (use of supplementary data if necessary).
 - Dose to organs at risk and reported toxicities
- Criteria used to determine LC (e.g. RECIST- Response Evaluation Criteria in Solid Tumors used to evaluate the objective response of solid tumors after treatment (17))
- Outcomes to consider include but are not limited to cancer-specific survival, LC, time to local progression, time to distant progression
- Follow-up protocol (frequency, imaging and other methods)

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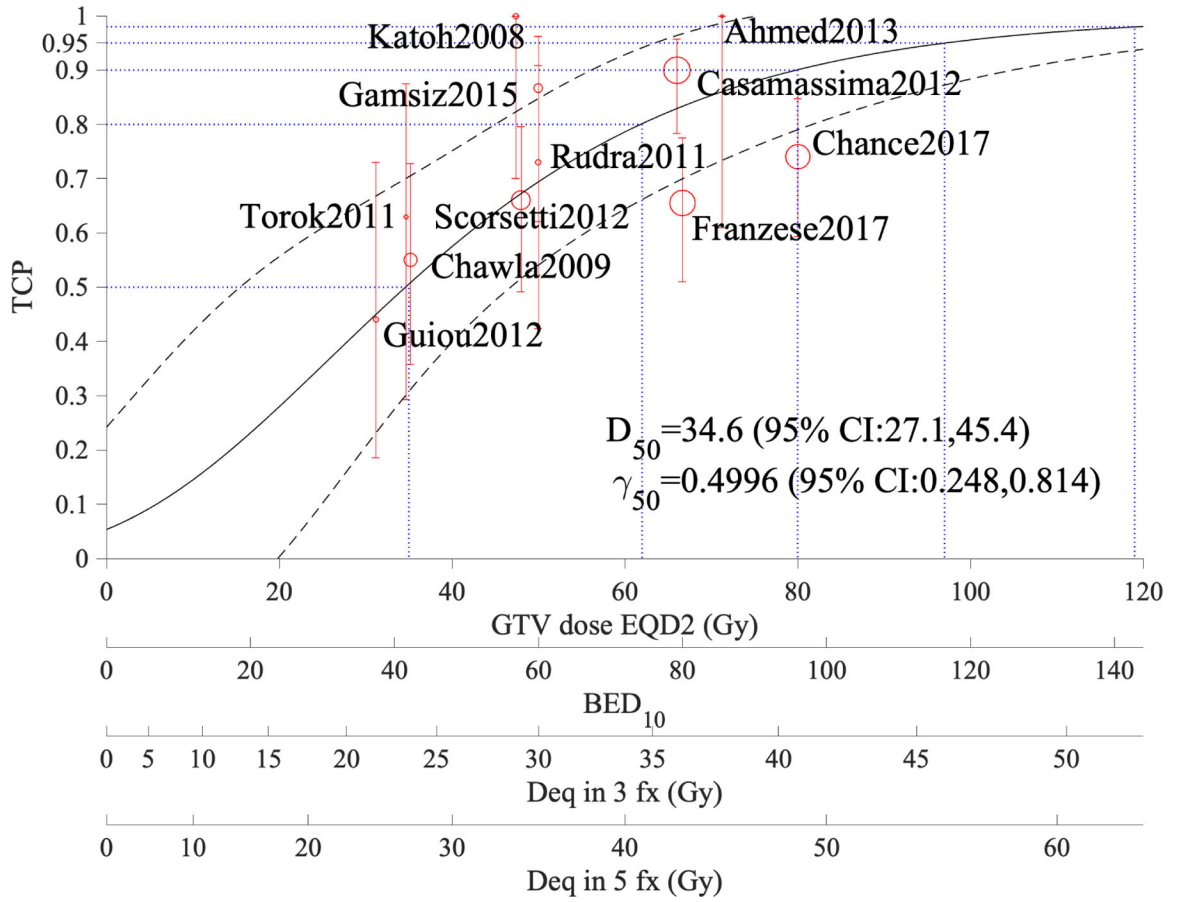


Figure 1: Tumor control probability of adrenal metastases treated with SBRT based on one-year local control; $\alpha/\beta=10$ Gy in this model. The figure shows TCP estimates at 50%, 80%, 90%, and 95% (blue dotted horizontal lines). The black dashed curves show the 95% confidence band and the GTV coverage dose scales are for EQD2₁₀, BED₁₀, and equivalent doses in 3 and 5 fractions.

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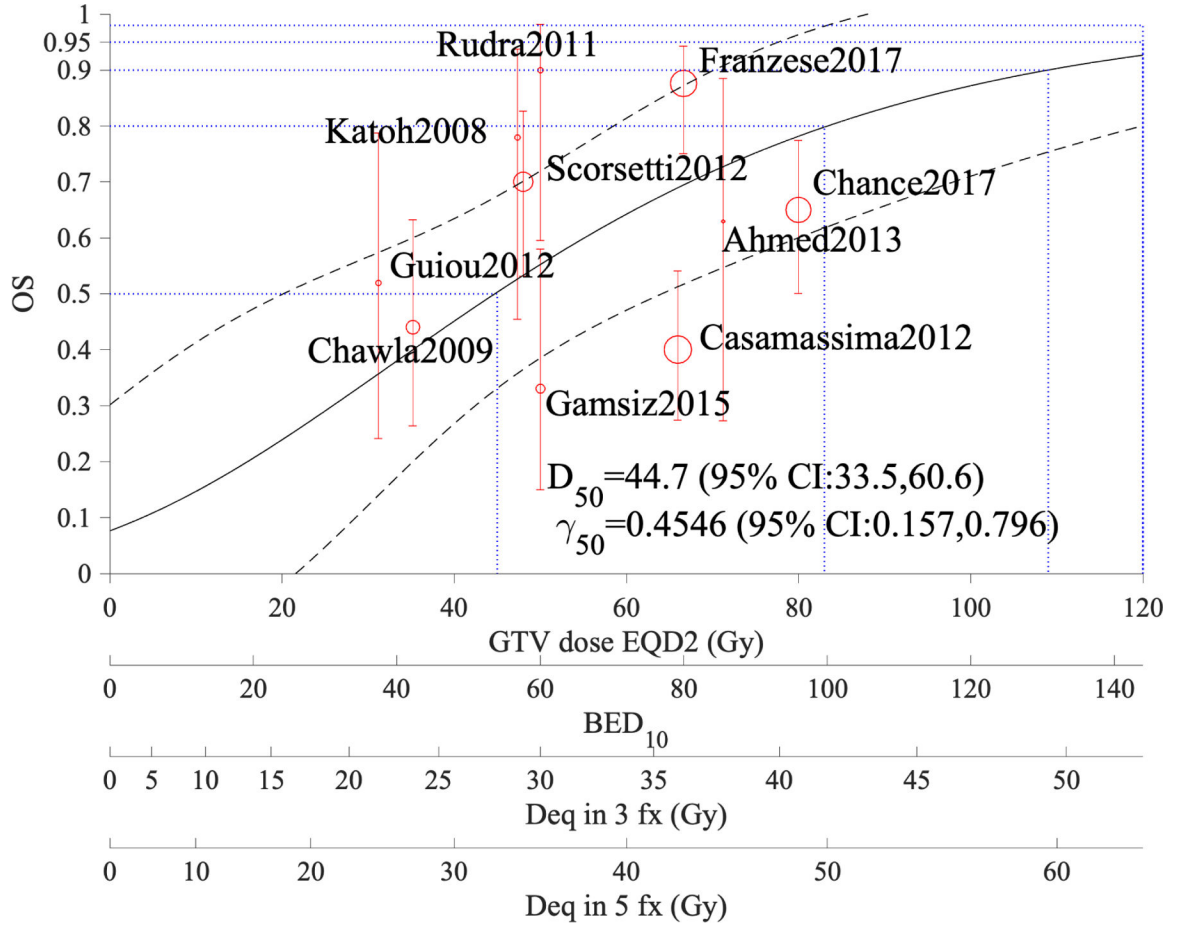


Figure 2:

Overall survival of patients with adrenal metastases treated with SBRT based on one-year estimates; $\alpha/\beta=10$ Gy in this model. The figure shows OS estimates at 50%, 80%, 90%, and 95% (blue dotted horizontal lines). The black dashed curves show the 95% confidence band and the GTV coverage dose scales are for EQD2₁₀, BED₁₀, and equivalent doses in 3 and 5 fractions.

Table 1: Adrenal SBRT studies reviewed in the study. Ones included in the adrenal tumor control probability model are shown in Figure 1.

Author (citation)	No. of Patients	Median FU (m) [range]	No. of Lesions	Primary Site	Volumes (mm)	Median Total Dose (Gy) [range]	No. of Fractions	Local Control	Overall Survival	Rx type	Target Dose Coverage	GTV size (cc) [range]	PTV size (cc) [range]
*Ahmed, 2013 (7)	13	12.3 [3.1–18]	13	Lung, Kidney, Skin, Other	GTV=CTV PTV=ITV+5	45 [33.75–60]	5 (all)	12.3mo-100%	12 mo- 62.9%	NR	NR	NR	88.4 [37.7–379.6]
Barney, 2012 (8)	6 (subgroup of 50 abdo/pelvic mets: numbers quoted are for entire patient cohort).	12 [2–28]	6	GI, Lung, Kidney, Other	GTV=CTV PTV=ITV+5	45 [20–60]	5 [1–5]	6 mo- 98%; 12 mo-87%	6 mo- 90% 12 mo- 62%	95% IDL	99% target received at least 90% dose	NR	NR
*Casamassima, 2012 (9)	48	16.2 [3–63]	48	Lung, Colon, Melanoma, Other	GTV=CTV PTV=ITV+3	36 [21.69–54.09]	3 [1–3]	12 mo- 90% 24 mo- 90%	12 mo- 39.7% 24 mo- 14.5%	70% IDL	NR	103.4 [6.6–497]	NR
*Chawla, 2009 (5)	30	9.8 [3.2–28.3]	35	Lung, Liver, Breast, Other	GTV=CTV PTV=CTV+7–10	40 [16–50]	10 [4–16]	6 mo- 91% 12 mo- 55% 24 mo- 27%	12 mo- 44% 24 mo- 25%	100% IDL	80% to PTV	18.6 [7.5–156]	NR
*Guiou, 2012 (10)	9	7.3 (mean) [0–26]	10	Lung	ITV PTV=ITV+ expansion	25 [20–37.5]	5 (all)	12 mo- 44% 24 mo- 44%	12 mo- 52% 24 mo- 13%	NR	NR	163 [22.3–599.7]	306.62 [127.5–953.6]
Holy, 2011 (11)	18	12 [2–61]	18	Lung	CTV=GTV+2 PTV=CTV+5–10	40 [24–40]	5 [3–6]	Median PFS- 4.2 mo	Median- 21 mo	100% IDL	~100%	NR	176 [20–422]
*Katoh, 2008 (12)	9	16 [5–21]	10	Lung, Prostate, Kidney, Liver	CTV=GTV+3 PTV=CTV+5	48 [30–48]	8 (all)	12 mo- 100%	12 mo- 78%	iso	80% to PTV	NR	NR
Oshiro, 2011 (27)	19 (11 underwent hypofractionation and 8 underwent conventional fractionation)	10.1 [0.7–87.8]	19	Lung	CTV=GTV PTV=CTV+5–10	45 [30–60]	10 [1–27]	NR	For synchronous mets: 12 mo- 55.6% 24 mo- 33.4% 60 mo- 22.3% Metachronous mets: 12 mo- 83.3% 24 mo and 60 mo- 55.6%	NR	NR	NR	NR

Author (citation)	No. of Patients	Median FU (m) [range]	No. of Lesions	Primary Site	Volumes (mm)	Median Total Dose (Gy) [range]	No. of Fractions	Local Control	Overall Survival	Rx type	Target Dose Coverage	GTV size (cc) [range]	PTV size (cc) [range]
*Rudra, 2011 (13)	10	14.9 [5-45.8]	13	Lung, Kidney	ITV PTV=ITV+5-10	36 [24-50]	3 [3-10]	12 mo- 73%	12 mo- 90%	80-90% IDL	V95%>95%	NR	NR
*Scorsetti, 2012 (14)	34	41 [12-75]	36	Lung, Melanoma, Other	CTV=GTV+3 PTV=CTV+5	32 [20-45]	4 [4-18]	12 mo- 66% 24 mo- 32%	24 mo- 53%	NR	NR	NR	NR
*Torok, 2011 (15)	7	14 [1-60]	9	Lung, Liver	GTV=CTV PTV=ITV	16 (for 5 lesions) [10-22] 27 (for 4 lesions) [24-36]	16 Gy in 1 fx 27 Gy in 3 fx	12 mo- 63%	Median- 8 mo	1fx: 80% 3fx: 94%	86%	63.8 [5-123.6]	NR
Desai, 2015 (22)	14	NR	14	Lung, Renal, Other	NR	25 [13-30]	3 [1-5]	NR	Median- 7 mo	NR	NR	NR	NR
*Chance, 2016 (18)	43	16 [3-94]	49	Lung, Ovary, Esophagus, Other	ITV PTV=ITV+3-5	60 [40-70]	10 [4-15]	12 mo- 74% 24 mo- 57%	12 mo- 65% 24mo- 42%	95% IDL	97% (median)	13 [3-90]	41 [11-262]
*Franzese, 2017 (26)	46	7.6		Lung, Other	CTV PTV = CTV + 5	40 (all)	4 (all)	12 mo- 66% (±12%) 24 mo 41% (±16%)	12 mo- 87.6%	V95%>90% (for PTV)	V95%>90%	NR	63 (mean) (±34)
*Gamsiz, 2015 (16)	15	16	17	Lung	GTV=CTV (DIBH) PTV=CTV+3-5	30 (all)	3 (all)	16 mo- 86.7%	16 mo- 33%	90-100% IDL	NR	28.4 (mean) [6.6-101.5]	57.4 (mean) [16.5-143.8]
Li, 2013 (23)	26	NR	26	Various	PGTV=GTV+3 CTV=GTV+8 PTV=CTV+2-3	43 [30-50]	5 [3-5]	NR	Median- 17 mo	Median- 70% IDL (58-80%)	95%	NR	NR

Abbreviations: No. (Number); Gy (Gray); NR (not reported); mo (months); PFS (progression-free survival); fx (fraction); DIBH (deep inspiration breath hold);

* studies used in TCP model

Summary of motion management and image guidance utilized in Adrenal SBRT studies at the time of simulation, planning, and treatment.

Table 2:

Author (citation)	Motion Management: Simulation and Planning	Motion management: Image Guidance for Treatment
Ahmed, 2013 (7)	4DCT/ITV	¹ Daily CB (2 nd confirming CB for shifts > 3 mm)
Barney, 2012 (8)	Compression for diaphragm motion 5 mm + 4DCT to construct ITV	¹ Daily CB (2 nd confirming CB for shifts > 3 mm)
Casamassima, 2012 (9)	ITV from free-breathing, end inhale and end exhale CT scans at simulation	Daily CB (matched on bone)
Chawla, 2009 (5)	End Exhale Breath-hold	NR
Guiou, 2012 (10)	Compression if tolerated (5/9 pts); 4DCT for ITV	Daily CB
Holy, 2011 (11)	Compression (14/18 pts); SI margins from fluoroscopy of diaphragm	Daily orthogonal radiographs compared to DRR
Katoh, 2008 (12)	One implanted fiducial; Planning CT at end-exhale.	RTRT fluoroscopic tracking system, tracking fiducial
Oshiro, 2011 (27)	End exhale gating (9/11 pts)	Gating with modified Microtron
Rudra, 2011 (13)	Simulation with free-breathing, 4DCT and end exhale scans; plan for ITV ('not significant tumor motion') or end exhale	Daily orthogonal radiographs (match on bone) followed by ungated CB to verify PTV margin
Scorsetti, 2012 (14)	Population based	Orthogonal KV radiographs (2D-2D)
Torok, 2011 (15)	4DCT for the 2/7 gating patients	5/7 pts CK (<i>Synchrozy system</i>); 2/7 pts Trilogy with gating
Desai, 2015 (22)	(single fiducial placed; free-breathing CT; margins NR	CK (<i>Synchrozy system</i>)
Chance, 2016 (18)	4DCT; ITV for 86% of pts, voluntary deep-inhale breath-hold for tumor motion > 1 cm (14% pts)	Daily CB or CT on Rails
Franzese, 2017 (26)	Abdominal compression and 4DCT for construction of ITV (union of CTVs on all phases)	Daily CB compared to simulation scan
Gamsiz, 2015 (16)	Moderate deep inhale using ABC™ device	Daily CB
Li, 2013 (23)	3 fiducials placed; generic margins	CK

Abbreviations: ITV (internal target volume); CB (cone beam); NR (not reported); DRR (digitally reconstructed radiograph); KV (kilovoltage); CK (CyberKnife); RTRT (Real-time Tumor-tracking radiotherapy) (40)

¹ matching structure not stated