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FULL PAPER

Stereotactic body radiotherapy for adrenal oligometastasis in lung cancer patients

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Objective: To report our experience on stereotactic body radiotherapy (SBRT) in adrenal metastases from lung cancer.

Methods: 37 oligometastatic lung cancer patients with 38 adrenal metastases submitted to SBRT were retrospectively analyzed. SBRT was delivered by volumetric modulated arc therapy (VMAT) or helical tomotherapy (HT). Primary study end point was local recurrence-free survival (LR-FS) and secondary end points were distant-progression free survival (d-PFS) and overall survival (OS).

Results: Median age was 67 years and primary tumor was non-small-cell lung cancer in 27 (73%) and small-cell lung cancer in 10 (27%) patients. Adrenal metastases were in the left side in 66% cases. Median prescribed dose was 30 Gy in 5 fractions for a median biologically equivalent dose (α/β ratio 10 Gy, BED10) of 48 Gy. Most patients (62%) were submitted to SBRT alone, while the

others (38%) received chemo-, immune- or target- therapies. Median follow-up was 10.5 months, median OS 16 months and median d-PFS 3 months. 27 (70%) patients obtained a local control with a median LR-FS of 32 months. LR-FS was significantly related to BED10 with a better LC with BED10 ≥ 72 Gy, 1- and 2-year LR-FS rates were $54.1 \pm 11.6\%$ and $45 \pm 12.7\%$ vs 100 and 100% for BED ≤ 59.5 Gy and BED ≥ 72 Gy, respectively ($p = 0.05$). There was no severe toxicity.

Conclusion: SBRT was effective and safe in lung cancer adrenal metastases. A dose-response relationship was found between BED10 ≥ 72 Gy and better local control. No significant toxicity was registered thanks to the respect of dose constraints and suspension of chemo- and target-therapies.

Advances in knowledge: SBRT with a BED10 ≥ 72 Gy is an effective treatment for adrenal oligometastatic lung cancer patients.

INTRODUCTION

Adrenal metastases are common in lung cancer patients and in some cases, their detection is synchronous with diagnosis of the primary tumor.¹ Positron emission tomography-computed tomography (PET-CT) has an excellent sensitivity and specificity in identifying adrenal metastases and differentiate malignant from benign lesions.² The PET-CT accuracy permitted to detect the so-called oligometastatic disease, a setting of patients who has neither localized nor a diffusely metastatic disease.³ This paradigm suggests that oligometastatic patients (defined as patients with ≤ 5 lesions in ≤ 2 organs sites) should be amenable to a curative treatment approach.^{4,5} Actually, several studies reported that the treatment of oligometastatic disease with metastasis directed therapy can lead to better-than-expected survival compared with the general population of patients with metastatic disease.⁶

Overall survival (OS) of metastatic lung cancer patients has clearly improved with the advent of targeted therapy and immunotherapy.⁷ Despite these advances, drug resistance remains the biggest problem and an effective local treatment could allow ongoing therapy to continue. In selected oligometastatic lung cancer patients with isolated adrenal metastases, adrenalectomy has been considered the standard of care with a 5-year OS rates of 22–45%, but it may result in adrenal insufficiency and surgical complications, many patients are unable to undergo surgery due to poor performance status or severe comorbidities.⁸

Percutaneous ablative therapies such as radiofrequency, microwave, and cryoablation have also been used to treat adrenal metastatic tumors with local control rates ranging between 67 and 88% at 1 year.⁹

Stereotactic body radiotherapy (SBRT) as a non-invasive, ablative modality has emerged as a promising alternative option for the local treatment of oligometastatic disease.¹⁰ It allows to administer external beam accelerated hypofractionated doses to the tumor, sparing the surrounding healthy tissues by a rapid fall of dose outside the target.^{11,12} Although there is a rising evidence that oligometastatic lung cancer patients benefit from local treatments, there is a lack of studies investigating the role of SBRT in the treatment of adrenal metastases and there is not a consensus regarding overall radiation dose and fractionation scheme.^{13,14}

The aim of this retrospective study is to report our experience on SBRT with volumetric modulated arc therapy (VMAT) and helical tomotherapy (HT) for adrenal metastases in lung cancer patients.

METHODS AND MATERIALS

Patients characteristics

Between January 2010 and June 2019, 37 adrenal gland oligometastatic lung cancer patients submitted to SBRT at the Radiotherapy Oncology Centres of Perugia and Terni (Italy) were retrospectively analyzed.

Synchronous oligometastasis was defined as the development of metastatic adrenal disease within 6 months after diagnosis of primary lung cancer (including patients with oligometastatic disease at the time of diagnosis). Metachronous oligometastasis was defined as the development of metastatic adrenal disease more than 6 months from primary diagnosis. In this last group, there were oligorecurrent patients so defined for the appearance of a single lesion in absence of systemic antitumor therapy, and oligoprogressive ones, metastatic patients who had a single escape lesion diagnosed during systemic antitumor therapy.¹⁰ In our institutions (Terni and Perugia Radiotherapy Oncology Centres), the criterion for receiving SBRT to the adrenal gland was the presence of a limited metastatic disease burden (≤ 5 lesions in ≤ 2 organs sites) detected at CT and/or CT-PET. Patients undergoing chemotherapy, target therapy and immunotherapy were included in this analysis.

Treatment

The decision whether to continue or discontinue systemic therapy during SBRT was determined case-by-case by the Radiation-Oncologist. Generally, chemotherapy and/or target therapy were discontinued 5–7 days before and after SBRT, while immunotherapy was not discontinued. The written consent was obtained from all patients before treatment planning.

Patients were in supine position with their arms overhead using a Wing system immobilization prior to CT simulation scan. CT scan was performed with a slice thickness of 2 mm, with the scan range 15–20 cm below and above the target. The gross tumor volume (GTV) was the whole adrenal gland and planning target volume (PTV) was created by adding 5 mm margin to the GTV in all directions. Stereotactic body radiotherapy was delivered by HT (TomoTherapy Inc., Madison, WI) or VMAT (Elekta Ltd, Crawley, UK).

Treatment planning with HT was performed as described elsewhere.¹⁵ For VMAT treatment planning, the dose was prescribed to the isocenter and the stereotactic plan was optimized, so that at least the 95% isodose line encompassed the 95% of the target volume and treatment schedule was chosen based on target volume, laterality and closeness to organs at risk (OARs). Dose constraints related to five administered fractions were as follows: spinal cord maximum dose 30 Gy; stomach and small bowel maximum dose 35 Gy; kidneys were allowed to receive a mean dose of 10 Gy and the dose to ≥ 20 cc was kept < 16 Gy; liver mean dose < 15.2 Gy. All these constraints are similar to those reported by Hanna *et al* in a recent review.¹⁶ Treatment appropriateness was daily controlled by a kV cone beam CT or MV CT in those treated with VMAT or HT, respectively.

The biological equivalent dose (BED) was calculated from the prescribed dose and fractionation by applying the standard linear quadratic formula, $BED_{10} = nd \times (1 + d/[a/b])$, where $a/b = 10$ and n and d represent the number of fractions and dose per fraction, respectively.¹⁷ An α/β ratio of 10 Gy (BED_{10}) was assumed for the adrenal metastasis.

Follow-up and response evaluation

Follow-up included CT and/or CT-PET 3 months after treatment for response assessment. Additional CT and/or CT-PET scans were performed every 4–6 months for the first 2 years and every 6 months thereafter.

Treatment response was evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) and/or with CT-PET Response Criteria in Solid Tumors (PERCIST 1.0).^{18,19}

Primary study end point was local control (LC) defined as no growth and/or increase in standardized uptake value $> 25\%$ of the treated adrenal gland, while a tumor increase of at least 20% and/or an increase in standardized uptake value $> 25\%$ were defined local recurrence (LR). The local recurrence free survival (LR-FS) was calculated from SBRT to the imaging evidence of LR.^{18,19} Secondary end points were distant-progression free survival (d-PFS), interval between SBRT and radiological evidence of disease progression outside the adrenal gland) and OS which was calculated from SBRT to patient death or last follow-up.

Toxicity, graded according to Common Terminology Criteria for Adverse Events (CTCAE v. 3.0), was assessed during SBRT, 1–3 months after completion of treatment, and then each 3–4 months.²⁰ Toxicity was recorded as acute when occurred during SBRT and within 3 months after completion of treatment. When the time interval was higher than 3 months, toxicity was defined late.

Statistical analysis

A software package (MedCalc 19.0.3 Broekstraat 52, B-9030 Mariakerke Belgium, 2019) was used for statistical analysis. OS, d-PFS and LR-FS were estimated for the entire population using the Kaplan–Meier product-limit method.²¹ Histology [(non-small cell lung cancer (NSCLC) vs small cell lung cancer (SCLC)], PTV (continuous), BED_{10} (continuous), presence of

other disease beyond the adrenal metastases (yes vs no) and time of adrenal metastases diagnosis (synchronous vs recurrent vs progressive) were analyzed as possible prognostic factors for LR-FS, d-PFS and OS rates. In a univariate analysis, variables associated with LR-FS, d-PFS and OS were assessed using the long rank test, and *p* values < 0.05 were considered statistically significant.

RESULTS

Patient and adrenal metastasis characteristics are summarized in Table 1. A total of 38 adrenal metastases were treated in 37 patients. The median age was 67 years (range, 43–83). Primary tumor was NSCLC in 27 (73%) and SCLC in 10 (27%) patients. 14 (38%) patients had adrenal metastases synchronous to the primary lung tumor; 16 (43%) and 7 (19%) patients were defined oligorecurrent and oligoprogressive, respectively. The median time to develop adrenal metastasis was 14 months (range, 0–108). 23 (62%) patients had solitary adrenal metastasis at the time of SBRT. Adrenal metastases were in the left and right side in 25 and 12 cases, respectively; 1 patient had bilateral lesions. Treatment characteristics are shown in Table 2. The median prescribed dose was 30 Gy administered in 5 daily fractions for a median BED10 of 48 Gy for all patients. Particularly, patients treated with VMAT and HT received a median dose of 40 and 30 Gy for a median BED10 of 72 and 48 Gy, respectively. The median GTV and PTV were 16 and 43.5 cc, respectively. Most patients (62%) were submitted to SBRT alone, while the others (38%) received chemotherapy, immunotherapy or target therapy according to already specified timing.

Median follow-up after SBRT was 10.5 months (range, 4–100) for all patients and 17 months (range, 4–100) for patients who were alive at the time of this analysis. At last follow-up, 14/37 (38%) patients were alive, 7 without radiological evidence of disease; 23/37 (62%) had died because of lung cancer progression. Median OS was 16 months (95% CI: 9–28) and the 1-, 2- and 3 year OS rates were 53±8.6%, 41.1±9%, 27.4±8.8%, respectively (Figure 1). Patients with NSCLC and SCLC had a median survival of 20 and 9 months, respectively.

Distant progression was observed in 29 (78%) patients with new metastases identified in other organs. The sites of distant progression included liver, lungs, bones and/or brain. Median d-PFS was 3 months (95% CI: 2–5), and the 1- and 2 year d-PFS rates were 19.5±7.3% and 13±7.2%, respectively (Figure 2).

26 (70%) patients obtained a LC of the treated adrenal metastasis, but 11 (30%) experienced a LR at a median time of 7 months (range, 4–32). Median LR-FS was 32 months (95% CI: 12–32) with a 1-, 2- and 3 year LR-FS rates of 63.5±10%, 54.4±12% and 40.8±14.9%, respectively (Figure 3).

At univariate analysis, LR-FS was significantly related to BED10 with a better LC with BED10 ≥72 Gy (*p* = 0.05). Particularly, 8/21 (38%) and 3/6 (50%) lesions receiving a BED10 of 48y and 59.5 Gy, respectively had a LR, while no LR was evidenced in 11 lesions treated with a BED10 ≥72 Gy. Median LR-FS was 23 months for adrenal metastases receiving a BED10 ≤59.5 Gy,

Table 1. Patient and lesion characteristics

Parameter	Number	%
Patient treated		
Total	37	
V-MAT	17	46
Helical tomotherapy	20	54
Lesions treated	38	
V-MAT	17	45
helical tomotherapy	21	55
Male/female ratio	27/10	73/27
Primary tumor		
NSCLC	27	73
SCLC	10	27
Adrenal metastasis appearance		
Synchronous	14	37
Metachronous	24	63
Oligoprogressive	17	45
Oligorecurrent	7	18
Median time between diagnosis of primary	14 months	
and adrenal metastasis	(0–108)	
Additional site of metastasis		
Yes	14	38
One	8	
More than one	6	
No	23	72
Adrenal metastasis diagnosis		
Biopsy	0	
PET	29	76
CT	9	24
Adrenal metastasis laterality		
Left	25	66
Right	13	34
Bilateral	1	

CT, computed tomography; NSCLC, non-small-cell lung cancer; PET, positron emission tomography; SCLC, small-cell lung cancer; VMAT, volumetric modulated arc therapy;

NSCLC, non-small-cell lung cancer; PET, positron emission tomography; SCLC, small-cell lung cancer; VMAT, volumetric modulated arc therapy.

while in patients treated with a BED10 ≥72 Gy the median LR-FS was not reached because no LR were observed in this subgroup. The 1- and 2 year LR-FS rates were 54.1±11.6% and 45±12.7% vs 100 and 100% for BED ≤59.5 and ≥72 Gy, respectively (Figure 4).

Adrenal metastases from NSCLC had a higher but not significant median LR-FS compared with adrenal metastases from SCLC (32 vs 10 months). The 1- and 2 year LR-FS rates were 68±11%

Table 2. Treatment characteristics

Parameter	Value (range)
Dose and fractionation of all lesions	
Median total dose	30 Gy (30-50)
Median dose per fraction	6 Gy (6-10)
Median number of fractions	5
Median BED10	48 Gy (48-100)
Dose and fractionation with V-MAT	
Median total dose	40 Gy (30-50)
Median dose per fraction	8 Gy (6-10)
Median number of fractions	5
Median BED10	72 Gy (48-100)
Dose and fractionation with HT	
Median total dose	30 Gy (30-40)
Median dose per fraction	6 Gy (6-8)
Median number of fractions	5
Median BED10	48 Gy (48-72)
Volumes of irradiation	
Median GTV	16cc (0.91–123)
Median PTV	43.5cc (8-236)
Concomitant treatment	
Chemotherapy	2
Target therapy	5
Immunotherapy	5
No systemic therapy	25

BED10, biological equivalent dose with an α/β ratio of 10 Gy; GTV, Gross tumor volume; HT, helical tomotherapy; PTV, Planning target volume; SBRT, Stereotactic body radiotherapy; V-MAT, volumetric-modulated arc radiotherapy.

and $56\pm14\%$ vs $47\pm22\%$ and $47\pm22\%$ for NSCLC and SCLC, respectively.

Another variable which was not significant but with a trend of difference is the time of adrenal metastasis diagnosis. In metachronous-oligoproggressive patients, the 2 year LR-FS rate was 100% compared with 53% for synchronous and 45% for metachronous-oligorecurrent patients.

No statistically significant differences in LR-FS were registered according to PTV and presence of other disease beyond the adrenal metastases. Moreover, all examined prognostic variables did not have a significant impact on d-PFS and OS.

After treatment, seven patients (19%) developed Grade 1 or 2 acute nausea lasted for 3–7 days. No patient developed late toxicity.

DISCUSSION

Outcome of metastatic lung cancer patients has recently improved with target therapy and immunotherapy.⁷ The probability of adrenal metastatic disease increased as well as the indication to a metastasis directed therapy for selected oligometastatic patients who can have a longer survival.^{6,13}

Adrenalectomy is currently the standard of care and percutaneous ablative therapies have also been used to treat adrenal metastatic tumors.^{8,9} SBRT is a non-invasive ablative modality which can be a promising alternative option for the local treatment of oligometastatic disease. The advent of SBRT has permitted to accurately deliver high doses of irradiation in one or few treatment fractions with the aim to eradicate the local disease by the ablative effect associated to high single dose, sparing the surrounding healthy tissues by a rapid fall of dose outside the target. This approach can be performed using a body frame-based patient setup with external stereotactic co-ordinates and/or internal stereotactic co-ordinates with the help of image-guidance procedures which can either visualize and locate the

Figure 1. Kaplan-Meier plot of overall survival probability from SBRT. Censored data are marked on the graph. The number of patients at risk is presented as well. SBRT, stereotactic bodyradiotherapy.

Figure 2. Kaplan–Meier plot of progression free survival probability from SBRT. Censored data are marked on the graph. The number of patients at risk is presented as well. SBRT, stereotactic bodyradiotherapy.

target itself and anatomical structures that are closely correlated to the target.^{10,11} There are various possible modalities to give this special radiotherapy technique, VMAT and HT were the two approaches used in the present study.

Most of the published studies on SBRT for adrenal metastases have mixed histologies of primary tumors, while there are few studies focusing on the role of SBRT on lung cancer adrenal metastases.^{22–27} Table 3 reports an overview of published trials on SBRT for lung cancer adrenal metastases, inclusive of our experience.^{28–33} Each trial analyzed less than 20 patients apart from Zhao's and our trials in which were studied 30 and 37 patients, respectively.³³ The majority of patients had NSCLC and all underwent SBRT. Administered doses ranged from 22.5 to 120 Gy BED10 and a better 2 year-LC was obtained with BED10 ≥ 72 Gy. These findings were underlined by Zhao et al who reported a 2 year LC rate of 72.7% when BED 10 was ≥ 85.5 Gy

and by our experience in which a significant difference on 2 year LC was registered comparing lower with higher administered doses (45% with a BED10 of 48–59.5 Gy vs 100%, with a BED10 of 72–100 Gy; $p = 0.05$).³³ This dose/response relationship was evidenced in other publications on SBRT for adrenal metastases due to different primary histologies.^{24,25}

Although in Zhao's trial a correlation between smaller adrenal tumor size and higher LC was reported, in our experience this relationship was not found. The reason can rely on the prevalence of small volumes of adrenal metastases we have treated.³³ Otherwise, if we compare LC obtained in Zhao's trial and in our patients who received higher doses of SBRT, values are similar (1 year LC was 96.9 vs 100%, see Table 3).³³ So, as already stated, higher doses on smaller adrenal metastases were the best association to have a better LC.

Figure 3. Kaplan–Meier plot of local recurrence free survival probability from SBRT. Censored data are marked on the graph. The number of patients at risk is presented as well. SBRT, stereotactic bodyradiotherapy.

Figure 4. Kaplan-Meier plot of local recurrence free survival probability from SBRT as a function of BED 10 Gy, median survival times for BED 10 Gy ≤ 59.5 Gy versus median survival times for BED 10 Gy ≥ 72 Gy, ($p = 0.05$). Censored data are marked on the graph. The number of patients at risk is presented as well. BED, biologically effective dose.

Lesions at risk

Group: ≤ 59.5 Gy

27 6 3 2 2 0

Group: ≥ 72 Gy

11 1 0 0 0 0

Less data exist in oligometastatic SCLC patients regarding the effectiveness of a metastasis directed therapy. However, three trials showed a prolonged time to progression and an increased OS in extensive stage SCLC if thoracic and extra thoracic radiotherapy was offered to patients with less than four metastases.^{34–36} In our 10 oligometastatic SCLC patients submitted to adrenal metastases SBRT, an OS of 9 months was reached. It is impossible to draw conclusions about the impact of SBRT in this setting of patients, so we discuss in our multidisciplinary lung team the appropriate therapy to offer.

Targeted therapy and immunotherapy have favorably modified the prognosis of Stage IV NSCLC patients.^{7,37} Despite this, after a certain period, a proportion of disease develops drug resistance becoming less responsive to therapy. In these cases, SBRT can play an important role to eradicate resistant disease, allowing ongoing systemic therapy to continue.^{38–41} A recently published prospective Phase II study has demonstrated that the addition of local consolidative SBRT to standard of care in oligometastatic NSCLC patients significantly prolonged PFS and OS compared to maintenance therapy or observation (PFS 14 months and OS

41.2 months).³⁸ Our experience, with a median LR-FS, d-PFS and OS of 32 months, 4 months and 20 months, respectively, seems to confirm the benefit of SBRT in selected oligometastatic NSCLC patients.

There is lack of literature addressing the treatment of primary NSCLC patients based on the time of adrenal metastasis diagnosis (*i.e.* synchronous, metachronous-oligorecurrent and metachronous-oligoprogressive). In our trial 14 (38%), 7 (19%) and 16 (43%) patients were defined synchronous, metachronous-oligoprogressive and metachronous-oligorecurrent. In metachronous-oligoprogressive patients, the 2 year LR-FS rate was 100% compared with 53% for synchronous and 45% for metachronous-oligorecurrent patients. All metachronous-oligoprogressive patients received target therapy and/or immunotherapy. The longer LR-FS rate in this setting of patients could be conditioned by the effectiveness of over said new emerging therapies and possible synergism with SBRT.

Late toxicities reported in literature include adrenal insufficiency and gastric/duodenal ulcers.^{22,29,42} In our trial, despite

Table 3. Overview of stereotactic body radiotherapy for lung cancer adrenal metastases

Trial	Patients / lesions	Median follow-up (months)	NSCLC/ SCLC	Metachronous/ Synchronous	Total dose/ fractions	Median BED10 (Gy)	Median PTV (cc)	LC	OS
Oshiro ²⁸	19/19	10.1	14/5	13/6	30-60/1-27	48-120	GTV 14.1 (0.52-113)	79%	1-y 56% 2-y 33%
Holy ²⁹	13	12	13/0	-	20-40/3-8	22.5-72	176	1-y 77%	1-y 66.7%
Guoioi ³⁰	9/11	7.3	4/5	6/5	20-37.5/5	37.5	306.62	1-y 44% 2-y 44%	1-y 52% 2-y 13%
Gamsiz ³¹	15/17	16	15/0	-	30/3	60	57.4	1-y 86.7%	1-y 33.3%
Celik ³²	15/15	24	15/0	8/7	42/6	71.4	74.4	1-y 60% 2-y 46.6%	1-y 93.3% 2-y 66.6%
Zhao ³³	30/32	10.7	25/5	-	Median 44.4/5	85.5	GTV 23.9 (2.5-115.3)	1-y 96.9% 2-y 72.7%	1-y 58.1% 2-y 54%
Our trial All cases	37/38	10.5	27/10	23/14	30-50/5	48	43.5	1-y 63.5% 2-y 54.4%	1-y 53% 2-y 41.1%
Lower dose	26	12	19/8	17/10	30-35/5	48-59.5	49	1-y 54.1% 2-y 45%	1-y 54% 2-y 40%
Higher dose	11	8	9/2	7/4	40-50/5	72-100	33.5	1-y 100% 2-y 100%	1-y 53% 2-y 53%

BED, biologically effective dose; NSCLC, non-small-cell lung cancer; PTV, planning target volume; SCLC, small-cell lung cancer.

most (66%) of adrenal metastases were localized on the left close to the stomach and small bowel, a low toxicity rate was registered. The explanation of this better clinical outcome, could be related to accuracy we had in respecting OAR dose constraints (*i.e.* 35 Gy for stomach and small bowel), in daily verifying the correct patient positioning and gastric filling with image-guided cone beam kV-CT or MV-CT.

In conclusion, SBRT was effective and safe in lung cancer adrenal metastases. Based on our study, a dose-response relationship was found between higher administered dose ($BED_{10} \geq 72$ Gy) and better local control. No significant toxicity was registered. For lesions in close proximity to the stomach and small bowel, new techniques, such as simultaneous integrated protection,

may allow to enhance SBRT prescribed dose limiting iatrogenic risk.^{43,44}

PATIENT CONSENT

Informed consent was obtained from all individual participants included in the study.

ETHICS

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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