Original Study

Inoperable Pulmonary Carcinoid Tumors: Local Control Rates With Stereotactic Body Radiotherapy/Hypofractionated RT With Image-Guided Radiotherapy

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Abstract

Pulmonary carcinoid tumors are rare and generally treated surgically. Hypofractionated radiotherapy, delivered in a precise manner via stereotactic body radiotherapy (SBRT), is a good alternative for patients not amenable to surgery. We treated 10 patients with 12 lesions using 5- to 10-fraction SBRT/hypofractionated regimens with excellent local control rates. SBRT appears to offer a promising approach for patients with inoperable pulmonary carcinoid tumors, which needs further investigation.

Introduction: Surgery is the standard of care for pulmonary carcinoid tumors; however, options for inoperable patients are few. We report the outcomes of inoperable pulmonary carcinoid patients treated with stereotactic body radiotherapy (SBRT). **Patients and Methods:** From an institutional database, we retrospectively identified patients treated with SBRT for pulmonary carcinoid tumors from 2007 to 2017. Additional inclusion criteria were previous histopathologic diagnosis, age older than 18 years and Karnofsky performance status $\geq$ 70. **Results:** Ten patients were treated for 12 pulmonary carcinoid lesions with 5 to 10 fractions of SBRT. Their median age was 66.5 years (range, 40-83 years) and most presented with nonspecific symptoms of cough, shortness of breath, or hemoptysis. Pathology revealed typical carcinoid for 9 patients, with the 10th with atypical histology. The median prescription dose for all patients was 50 Gy in 5 to 10 fractions (range, 40-60 Gy) with SBRT/hypofractionated radiation with daily image-guided radiotherapy (IGRT) delivered using a linear accelerator with respiratory monitoring. Four patients received 10-fraction hypofractionated radiation with daily IGRT and 6 others received 5-fraction SBRT. The follow-up after SBRT/hypofractionated IGRT ranged from 6 to 56 months (median, 25 months). Four patients were alive with stable disease at their last follow-up. Two patients died from disease progression in the mediastinal lymph nodes as well as in the lung. Both opted for palliative treatment. The other 4 patients died from their comorbid medical conditions, but had stable disease at their last follow-up. Median overall survival was 27.1 months (range, 5.5-56 months). **Conclusion:** Pulmonary carcinoid tumors treated with SBRT have a promising tumor control rate and survival.

Clinical Lung Cancer, Vol. 20, No. 3, e284-90
Keywords: BED, IGRT, PET-CT, SBRT, Survival

Introduction

Pulmonary carcinoid tumors are relatively rare, constituting less than 1% to 2% of lung neoplasms.[1] Pulmonary neuroendocrine tumors, which arise from neuroendocrine cells, include well differentiated low-grade typical carcinoid, intermediate-grade atypical carcinoid, poorly differentiated/high-grade large-cell neuroendocrine, and high-grade small-cell neuroendocrine tumors.[2] Typical and atypical carcinoid tumors (grouped together as pulmonary carcinoid tumors) arise de novo and are morphologically distinct from higher-grade neuroendocrine tumors.[3] As opposed to

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Submitted: Aug 29, 2018; Revised: Jan 29, 2019; Accepted: Feb 6, 2019; Epub: Feb 14, 2019

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1525-7304/$ - see frontmatter
https://doi.org/10.1016/j.cllc.2019.02.003

small-cell lung cancers,[4] pulmonary carcinoid tumors have no association with smoking and approximately 5% of cases can be associated with multiple endocrine neoplasia type 1.[5]

Pulmonary carcinoid tumors might present incidentally and asymptomatically or might present with nonspecific symptoms.[6] Generally, typical carcinoid tumors are located centrally within the trachea/main stem bronchi (10%) or lobar bronchi (75%) as opposed to atypical carcinoid tumors, which are more peripheral and more likely to be asymptomatic and incidentally discovered.[3,4] Histologically, typical carcinoid tumors have low mitotic rates (< 2%) and no necrosis whereas atypical carcinoid tumors have mitotic rates of 2% to 10% with presence of necrosis.[3] Typical carcinoid tumors tend to present in younger patients with a central location and without nodal or distant metastases.[7-9] Routine staging includes computed tomography (CT) imaging, but functional imaging such as octreotide scans and/or Ga-68 positron emission tomography (PET) imaging is often done as well.

Surgery remains the standard of care for early stage pulmonary carcinoid tumors. However, some patients might decline surgery and/or are not suitable candidates for resection because of underlying medical comorbidities. Historically, pulmonary carcinoid tumors were considered relatively radiation-resistant. Although this remains plausible with the use of standard, conventionally fractionated radiation, high-dose hypofractionated radiotherapy (RT) might act via novel biologic mechanisms[10] and could conceptually be considered a means to overcome radiation resistance of slow-growing tumors. Hypofractionated RT, delivered in a precise manner via stereotactic body RT (SBRT), facilitates the delivery of high biologically effective doses (BEDs) or radiation in few treatments while minimizing the normal tissue exposure.[11] Although SBRT/hypofractionated radiation with daily image-guided RT (IGRT) is well suited for delivering potentially ablative doses of radiation to pulmonary carcinoid tumors; to our knowledge, only 1 study of 4 patients has been published to date.[1]

We sought to review the treatment and outcomes of pulmonary carcinoid patients treated with SBRT/hypofractionated RT at our institution. We hypothesized that tumor control rates would be relatively high in our cohort of patients.

Patients and Methods

Patient Population

Using a department-maintained institutional database, we retrospectively identified 10 patients treated for pulmonary carcinoid tumors between 2007 and 2017. These 10 patients had 12 lesions treated with 5- to 10-fraction SBRT/hypofractionated radiation with daily IGRT. This study was approved by our institutional research subject review board.

All patients had to have histological confirmation of pulmonary carcinoid tumor; patients with higher grade tumors were excluded. Additional inclusion criteria included age older than 18 years, Karnofsky performance status $\geq$ 70, CT-defined tumor diameter < 6 cm, and no extrathoracic metastatic sites. Patients with 2 parenchymal lung lesions were also included if both lesions were treated with SBRT. All patients were deemed ineligible for surgical resection and/or refused surgery for personal reasons (Table 1). Two had a history of surgery: patient 9 had received right upper lobe video-assisted thoracoscopic surgery wedge resection (WR) in 2011 and the pathology showed low-grade carcinoid, pT1B, Nx, and patient 10 had a history of right middle lobe WR in 2004; pathology showed carcinoid. Subsequently, the patient received evaluation for pulmonary embolism in September 2016 and CT angiography showed a right hilar soft tissue density around bifurcation of the right mainstem bronchus that corresponded to abnormal radiotracer uptake seen on octreotide scan. The workup before SBRT/hypofractionated radiation included pulmonary function tests, contrast-enhanced CT of the chest and abdomen, and/or fluorodeoxyglucose PET/CT.

Table 1 Reasons for Inoperability

Patient	Reasons for Being Inoperable
1	Two lung nodules Severe oxygen-dependent COPD Cardiomyopathy with ejection fraction <30%
2	Cirrhosis with coagulopathy Congestive heart failure
3	Central tumor involving right hilum needing pneumonectomy
4	Severe COPD with FEV1 0.6 L (34%)
5	Post wedge resection and XRT 64.8 Gy
6	Nonalcoholic cirrhosis, and psychiatric disorders
7	Aortic and mitral valve dysfunction
8	Two separate nodules needing lobectomy
9	DLCO 13%; history of right upper lobe VATS wedge July 20, 2011
10	Cushing syndrome, central tumor needing pneumonectomy

Abbreviations: COPD = chronic obstructive pulmonary disease; DLCO = diffusing capacity of the lungs for carbon monoxide; FEV1 = forced expiratory volume; VATS =video-assisted thoracoscopic surgery; XRT = radiation treatment.

Stereotactic Body RT Technique

The SBRT techniques used in our study have been described in detail in previous publications from our group[12] and are briefly summarized herein. At the time of initial simulation, all patients were immobilized with a vacuum cushion device. Respiratory motion was minimized by using relaxed expiratory breath hold techniques in most patients. Patients unable to comply with breath-hold used shallow breathing in conjunction with 4-dimensional CT. The gross tumor volume (GTV) was delineated using CT and fused PET imaging in most cases. The planning target volume (PTV) was generated using a 7-mm circumferential and 11-mm superior–inferior expansion of the GTV for breath-hold patients and 5 mm for patients when 4-dimensional CT was used. There was no expansion for the clinical target volume. The use of arcs and noncoplanar beams was encouraged. Dose volume histograms (DVH) were calculated for the lung (defined as total lung minus GTV), heart, esophagus, spinal cord, and liver.

The 80% isodose line encompassed the PTV, with isocenter dose defined as 100% of the prescribed dose. When our institution began using SBRT techniques > 15 years ago, most patients were treated with a 10-fraction schedule. More recently, patients have been treated with 5-fraction schedules. The prescribed target dose was determined on the basis of the DVH of normal (uninvolved) lung and surrounding organs. The median prescription dose was 50 Gy in 5 to 10 fractions (range, 40-60 Gy) to isocenter with 80% to 100% isodose covering 99% to 100% of PTV. Generally, 95% of

Table 2 Patient Characteristics

Variable	Value
Number of Patients	10
Median Age (Range), y	66.5 (40-83)
Median Follow-up (Range), mo	25.2 (5.5-56.0)
Characteristic	
Sex	
Male	50 (5)
Female	50 (5)
Symptoms	
Cough	60 (6)
Shortness of breath	60 (6)
Hemoptysis	20 (2)
Incidental	20 (2)
Histology	
Typical carcinoid	90 (9)
Atypical carcinoid	10 (1)
CT Size of Primary Tumor	
10 mm	20 (2)
11-20 mm	30 (3)
21-30 mm	10 (1)
31-40 mm	20 (2)
41-50 mm	10 (1)
>50 mm	10 (1)
RT Characteristics	
Median BED (range)	100 (75-115.5)
Median EQD2 (range)	83.3 (62.5-96.5)

Data are presented as % (n) except where otherwise noted.
Abbreviations: BED = biologically effective dose; CT = computed tomography; EQD2 = equivalent dose in 2-Gy fractions; RT = radiotherapy.

the PTV was covered by the 85% to 95% isodose line. Patients were required to have 1000 mL of tumor-free lung, with < 12% of the lung volume receiving > 20 Gy. The spinal canal maximum was required to be < 25 Gy in 5 fractions and < 30 Gy in 10 fractions. The dose for smaller peripheral tumors was mostly 50 to 60 Gy and the dose for larger central tumors was mostly 40 to 50 Gy.

All patients were positioned and monitored in real time using our precision linear accelerator-based stereotactic system with respiratory monitoring using infrared reflecting body fiducial markers monitored using 2 ceiling-mounted infrared cameras. Those patients treated with 10-fraction schedules underwent a pretreatment and midtreatment verification CT scan as a quality assurance measure of setup accuracy. With 5-fraction SBRT, patients underwent daily cone beam CT for positional verification.

Outcomes/Statistics

Per our institutional standard, patients were followed with CT or PET-CT imaging every 3 to 6 months for post-treatment surveillance. Actuarial tumor control and overall survival (OS) were calculated using Kaplan–Meier actuarial survival analyses. OS was defined as months from date of completion of SBRT/hypofractionated RT until death or last follow-up. Patient local control (LC) was scored as an event if recurrence was confirmed pathologically or if any treated lesion grew by ≥ 20%, on the basis of the Response Evaluation Criteria In Solid Tumors (RECIST) criteria. LC was analyzed per patient, meaning that if a patient had more than 1 lesion treated, progression of any of the treated lesions was considered a local recurrence. LC was analyzed according to tumor size; among patients with more than 1 lesion, the largest tumor size was used. Excel for Mac version 14.7.7 (Microsoft, Redmond, WA) and R version 3.3.3 with survminer version 0.4.2 (R Project for Statistical Computing, Vienna, Austria) were used for all data analyses.

Results

The characteristics of the 10 patients treated with SBRT/hypofractionated RT for pulmonary carcinoid tumors are shown in Table 2. Two patients within this cohort had 2 parenchymal lesions, both treated with SBRT/hypofractionated radiation with daily IGRT. Thus, a total of 12 lesions were treated in 10 patients.

There were equal numbers of male and female patients. The median age was 66.5 years with a range of 40 through 83 years. Seven patients had a history of smoking > 20 pack-years. Most patients initially received evaluation for symptoms of cough and shortness of breath, but 2 patients presented with hemoptysis and 2 were diagnosed incidentally on routine chest imaging (Table 2). Nine patients had pathological diagnoses of typical carcinoid tumors and 1 had an atypical carcinoid tumor. Histopathologic characteristics of the tumors (including synaptophysin, chromogranin, CK7, CD56, TTF-1, and Ki-67) are shown in Table 3. The tumor size was < 20 mm in 5 patients, 21 to 40 mm in 4, and > 5 cm in 1 (Table 2). Six patients were treated for centrally located tumors and 4 had peripheral lesions. Four patients received 10-fraction hypofractionated radiation with daily IGRT, and 6 received 5-fraction SBRT; the physical dose ranged from 50 to 60 Gy with the BED ranging from 75 to 115.5 (median, 100 Gy) and the equivalent dose in 2-Gy fractions (EQD2) ranging from 62.5 to 96.3 Gy (median, 83.30 Gy). Three patients had received previous treatments: 2 with previous surgery and 1 with previous conventionally fractionated RT.

Follow-up after SBRT ranged from 6 to 56 months (median, 25 months). Four patients were alive with stable disease at their last follow-up. Two patients died from disease progression in the mediastinal lymph nodes as well as in the lung (with new pulmonary nodules). They were offered further treatment but both opted for palliative treatment. The other 4 patients died from their comorbid medical conditions, but again had stable disease at their last follow-up. Median OS was 27.1 months (range, 5.5-56 months). One patient died from sepsis; interestingly, the autopsy showed her irradiated tumor was still viable after 56 months after SBRT, although follow-up CT scans showed stable disease. One patient was treated for symptomatic pneumonitis with steroid inhalers and oral prednisone. Among those factors analyzed, 5- versus 10-fraction SBRT, EQD2 > 80 Gy, and tumor size < 4 cm were associated with improved OS (Tables 4 and 5). Figure 1 shows the Kaplan–Meier curve for OS in the study population of 10 pulmonary carcinoid patients who underwent SBRT/hypofractionated radiation. Figure 2 shows Kaplan–Meier survival estimates on

Table 3 Tumor Histology and Pathology

Histology	WD Typical (n = 9 Patients)	Atypical (n = 1 Patient)
Synaptophysin		
Positive	100 (9)	0 (0)
Negative	0 (0)	0 (0)
Unknown	0 (0)	100 (1)
Chromogranin		
Positive	67 (6)	0 (0)
Negative	33 (3)	0 (0)
Unknown	0 (0)	100 (1)
CK7		
Positive	11 (1)	0 (0)
Negative	89 (8)	0 (0)
Unknown	0 (0)	100 (1)
CD56		
Positive	11 (1)	0 (0)
Negative	89 (8)	0 (0)
Unknown	0 (0)	100 (1)
TTF-1		
Positive	22 (2)	0 (0)
Negative	78 (7)	0 (0)
Unknown	0 (0)	100 (1)

Data are presented as % (n) except where otherwise noted.
Abbreviations: TTF = thyroid transcription factor; WD = well differentiated

Table 4 Overall Survival (Months)

Category	Median	Range
All Patients	27.1	5.5-56.0
BED		
BED ≤95	20.5	18.1-51.2
BED >95	33.7	5.5-56.0
EQD2		
EQD2 ≤80	65.7	62.5-80.0
EQD2 >80	83.3	83.3-96.5
Number of Fractions		
5	33.7	5.5-56.0
10-11	20.5	18.1-51.2
Location		
Peripheral	20.5	5.5-56.0
Central	33.7	18.1-51.2
CT Size		
≤2 cm	33.7	5.5-56.0
2.1-4 cm	34.65	18.1-51.2
>4 cm	20.5	20.5-20.5

Abbreviations: BED = biologically effective dose; CT = computed tomography; EQD2 = equivalent dose in 2-Gy fractions.

the basis of stage of the patients who underwent SBRT/hypofractionated radiation ($P = .697$; not significant).

Discussion

We present tumor control and survival outcomes of 10 patients treated for 12 lesions with SBRT/hypofractionated radiation with daily IGRT for pulmonary carcinoid tumors. To our knowledge, this is only the second report to address use of SBRT in this patient population.

Colaco and Decker published the first series on SBRT for 4 typical (n = 2) and atypical (n = 2) pulmonary carcinoid patients.[1] In their study, tumor size ranged from 1.5 to 6.4 cm and the tumors were prescribed a dose of 50 to 54 Gy in 3 fractions. At a median follow-up of 14.4 months, all patients' tumors were locally controlled. Two patients had relapse-free survivals of 15 and 32.4 months, respectively, whereas 1 patient died from an unrelated cause at 14.4 months from colitis and another died of distant metastatic disease 2 months after SBRT. Our series with 10 patients showed OS ranging from 5.5 months to 56 months with a median survival of 27.1 months (Figure 1). In this series, with the limitation of small patient numbers, we showed that smaller tumor size and 5-fraction dosing were associated with better survival (Table 3).

Surgery remains the standard of care for pulmonary carcinoid patients and affords surgical staging as well as excellent LC and survival.[8,13-15] Compared with standard thoracotomy and resection, endoscopic resection is a less invasive surgical alternative for patients with endoscopically accessible tumors.[16,17] Purely intraluminal location and tumor diameter < 20 mm on CT scan have been reported as independent factors predictive of successful endobronchial treatment in patients with bronchial carcinoid tumors.[18] However, endoscopic resection or debulking is not considered to be a curative treatment because pulmonary carcinoid tumors often involve the thickness of the bronchial wall. These patients are still offered adjuvant chemotherapy or conventionally fractionated radiation.

In the pre-SBRT era, conventionally fractionated radiation with or without chemotherapy was the only option for some patients. Abraham et al published a retrospective review of 18 patients using high doses of conventionally fractionated RT (50-64 Gy) and reported a median survival of 39 months from diagnosis without significant side effects.[19] Wirth et al described a series of 18 patients treated with chemotherapy alone or chemoradiation therapy; they reported a poor response rate of 22% and concluded that response of pulmonary carcinoid tumor to chemotherapy with or without RT was not clearly established.[20] In their series, the 4 patients who received RT in addition to chemotherapy survived 84 months, more than 60 months, 10 months, and 8 months, respectively. A report from Memorial Sloan Kettering Cancer Center described the role of radiation in locally unresectable or metastatic carcinoid tumors and concluded that no clear dose response could be discerned, but for nonhepatic carcinoid tumors, they recommended a dose > 45 to 50 Gy for achieving reasonable control.[21] In a study from University of California San Francisco (UCSF), 53 patients underwent surgery, 11 received chemotherapy, 2 received chemotherapy with fractionated RT, and 1 received SBRT with chemotherapy. They reported stability of 22 months after SBRT in the latter patient.[22]

Stereotactic body RT has emerged as an acceptable alternative for those non–small-cell lung cancer patients not amenable to resection. SBRT offers the advantage of irradiating the tumor very precisely with ablative doses in a short period of time, and delivers doses that are radiobiologically superior (BED > 100 Gy compared

Table 5 Patient Summary

Patient	Age/ Sex	Presenting Symptoms	TC/AC	Ki-67 (%)	Lesion Number = Size (mm), T Stage[a]	Peripheral/ Central	Dose, Gy/ Fractions, n	BED, Gy	EQD2, Gy	Local Control[b]	Disease Status[c]	Alive or Dead[d]	Survival, mo[d]	RT-Related Complications
1	77/F	C/SOB	TC	5	1 = <10, T1 2 = 11-20, T1	Central	50/5	100	83.3	Yes	SD	Dead	34	None
2	51/F	C/SOB	TC	NR	1 = 11-20, T1	Peripheral	50/5	100	83.3	Yes	SD	Dead	56	None
3	66/F	C/SOB	TC	1	1 = 41-50, T2	Central	50/5	100	83.3	Yes	SD	Alive	16	None
4	57/F	Hemoptysis	TC	2	1 = 11-20, T1	Peripheral	55/5	115.5	96.5	Yes	SD	Alive	30	Focal fibrosis
5	67/M	C/SOB	AC	NR	1 = 21-30, T1	Central	50/10	75[e]	62.5	Yes	POD	Alive	36	None
6	58/M	Incidental	TC	2	1 = 31-40, T2	Central	60/10	96	80.0	Yes	SD	Dead	51	None
7	74/M	C/SOB	TC	2	1 = >50, T3	Peripheral	55/11	82.5	68.8	Yes	POD	Dead	20	None
8	83/M	Hemoptysis	TC	2	1 = 31-40, T2	Central	50/10	75	62.5	Yes	SD	Dead	18	None
9	81/M	Incidental	TC	10	1 = <10, T1 2 = <10, T1	Peripheral	50/5	100	83.3	Yes	POD	Dead	6	Pneumonitis Grade III
10	40/F	C/SOB	TC	NR	1 = 11-20, T1	Central	50/5	100	83.3	Yes	SD	Alive	16	None

Abbreviations: AC = atypical carcinoid; BED = biologically effective dose; C = cough; CT = computed tomography; EQD2 = equivalent dose in 2-Gy fractions; F = female; M = male; PET = positron emission tomography; POD = progression of disease; RT = radiotherapy; SOB = shortness of breath; TC = typical carcinoid; XRT = radiation treatment.

[a]Tumor presented with only 1 lesion unless 2 are listed.

[b]Per latest PET/CT or CT before subject death or last available follow-up as of March 2018.

[c]Overall disease status per imaging available before subject death or last available follow-up as of March 2018.

[d]At time of follow-up in March 2018.

[e]History of previous XRT 64.8 Gy for lung cancer.

Figure 1 Kaplan–Meier Curve for Overall Survival in the Study Population of 10 Pulmonary Carcinoid Patients Who Underwent Stereotactic Body Radiotherapy/ Hypofractionated Radiation

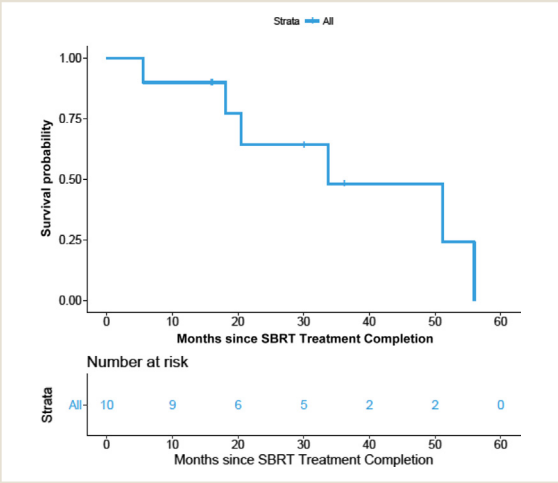
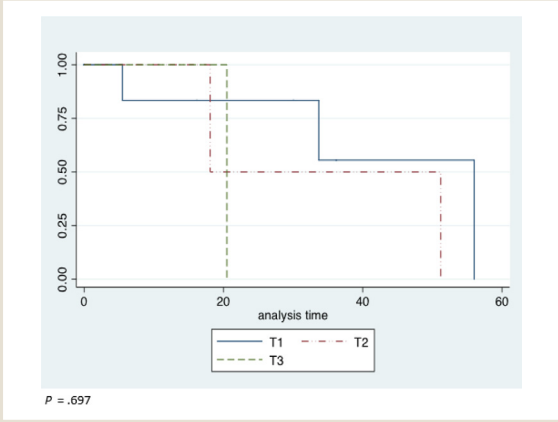


Figure 2 Kaplan–Meier Survival Estimates on the Basis of Stage of the Patients Who Underwent Stereotactic Body Radiotherapy/Hypofractionated Radiation



with BED < 100 Gy)[23,24]; SBRT yields long-term control in tumors that were thought to be radio-resistant or nonresponsive.[1] Although the numbers are very small in the series from Yale as well as in the UCSF study, it is hard to say if SBRT can render long-term control rates as opposed to conventionally fractionated RT.[1,22] In our series, we saw sustained LC with OS up to 56 months (Figure 1) especially with BED > 95 Gy, which showed a trend for better OS with a median survival of 33.7 months, as opposed to 20.5 months for BED < 95 Gy. The early stage of the tumors showed a trend in longer survival (Figure 2; $P = .697$; not significant).

Conclusion

We report the second known series of pulmonary carcinoid tumors treated with SBRT/hypofractionated radiation with daily IGRT. Although we analyzed a very small number of patients, the tumor control rate and survival are promising. Because of the relative rarity of these tumors, and the fact that most are amenable to resection, prospective study is not feasible. However, multi-institution pooled data might be feasible if more institutions analyze their outcomes in the patient population.

Clinical Practice Points

- Pulmonary carcinoid tumors are rare and might present incidentally.
- Surgery is the standard of care for early stage pulmonary carcinoid tumors but some patients might not be suitable candidates for resection because of underlying medical comorbidities or decline surgery for personal reasons.
- Standard fractionated RT has not shown much promise because pulmonary carcinoid tumors are considered relatively radiation-resistant.
- Hypofractionated RT, using SBRT, facilitates the delivery of biologically effective high radiation doses in a short treatment time. Although SBRT is well suited for delivering potentially ablative doses of radiation to lung tumors only 1 study of 4 patients with pulmonary carcinoid tumors treated with SBRT has been published to date, to our knowledge.
- We treated 10 patients with 12 lesions using 5- to 10-fraction hypofractionated SBRT regimens with excellent LC rates. Radiation dose ranged from 50 to 60 Gy with the BED ranging from 75 to 115.5 (median, 100 Gy).
- For our patients, follow-up ranged from 6 to 56 months (median, 25 months). At the time of writing this report, 4 patients are alive with stable disease at their last follow-up with CT scan showing no change in size precisely in millimeters. Two patients died from disease progression in the mediastinal lymph nodes as well as in the lung (with new pulmonary nodules). They were offered further treatment but both opted for palliative treatment. The other 4 died from other comorbidities but again had stable disease at their last follow-up, and 2 died from progression of disease. The median OS was 27.1 months (range, 5.5-56 months).
- SBRT/Hypofractionated RT appears to be promising local therapy for inoperable pulmonary carcinoid tumors with favorable outcomes and is well tolerated without significant long-term morbidity.

Acknowledgments

The authors thank Ria Syam for her statistical help and editorial assistance.

Disclosure

The authors have stated that they have no conflicts of interest.

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