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Early-Stage Primary Lung Neuroendocrine Tumors Treated With Stereotactic Body Radiation Therapy: A Multi-Institution Experience

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Abstract

Purpose: Current guidelines recommend surgery as standard of care for primary lung neuroendocrine tumor (LNET). Given that LNET is a rare clinical entity, there is a lack of literature regarding treatment of LNET with stereotactic body radiation therapy (SBRT). We hypothesized that SBRT could lead to effective locoregional tumor control and long-term outcomes.

Methods and Materials: We retrospectively reviewed 48 tumors in 46 patients from 11 institutions with a histologically confirmed diagnosis of LNET, treated with primary radiation therapy. Data were collected for patients treated nonoperatively with primary radiation therapy between 2006 and 2020. Patient records were reviewed for lesion characteristics and clinical risk factors. Kaplan-Meier analysis, log-rank tests, and Cox multivariate models were used to compare outcomes.

Results: Median age at treatment was 71 years and mean tumor size was 2 cm. Thirty-two lesions were typical carcinoid histology, 7 were atypical, and 9 were indeterminate. The most common SBRT fractionation schedule was 50 to 60 Gy in 5 daily fractions. Overall survival at 3, 6, and 9 years was 64%, 43%, and 26%, respectively. Progression-free survival at 3, 6, and 9 years was 88%, 78%, and 78%, respectively. Local control at 3, 6, and 9 years was 97%, 91%, and 91%, respectively. There was 1 regional recurrence in a paraesophageal lymph node. No grade 3 or higher toxicity was identified.

Conclusions: This is the largest series evaluating outcomes in patients with LNET treated with SBRT. This treatment is well tolerated, provides excellent locoregional control, and should be offered as an alternative to surgical resection for patients with early-stage LNET, particularly those who may not be ideal surgical candidates.

Introduction

Primary lung neuroendocrine tumor (LNET), also known as bronchial carcinoid tumor, a rare tumor of neuroendocrine origin, comprises approximately 1% to 2% of all primary thoracic malignancies.[1,2] These tumors generally follow an indolent course and fall into 2 distinct World Health Organization classifications: well-differentiated, low-grade typical carcinoid (TC) or intermediate, atypical carcinoid (AC).[1,3–5] AC tumors have been associated with smoking and worse overall prognosis.[6,7] Surgical resection is considered standard of care for early-stage LNET, with formal lobectomy and lymph node dissection to be considered for AC tumors.[7–10]

Conventionally fractionated radiation therapy (CFRT) has not traditionally been offered as treatment for LNET, owing to its relatively radioresistant nature.[11,12] Stereotactic body RT(SBRT) offers precise, ablative, localized doses of radiation, and it has been shown

to yield excellent local control (LC) with minimal toxicity in the treatment of inoperable early-stage non-small cell lung cancer (NSCLC)[13]; this treatment strategy has become an increasingly adopted alternative to surgery in this patient population over the past 15 years.[14] Recently, SBRT has even been associated with excellent LC rates in early-stage small cell lung cancer.[15]

Current guidelines recommend surgery as standard of care for early-stage LNET,[16] despite increasing utility of SBRT among practices nationally.[17] There is a paucity of data evaluating LC outcomes and associated toxicity of SBRT in the management of LNET, with only several small retrospective series recently published.[11,18,19] Through a higher deliverable biologically effective dose (BED),[20] SBRT may be a particularly effective modality in treating tumors in select patients, given their relatively low Ki-67 and the inherent biological benefit of high dose per fraction with SBRT. In this multi-institutional collaboration, we evaluated LC, toxicity, survival, and dosimetric data to further clarify the role of SBRT in this group of patients.

Methods and Materials

Patient population

After obtaining institutional review board approval, we performed a multi-institution retrospective review of 48 lesions in 46 patients from 11 separate centers in the United States. Patients included in the study had a histologically confirmed diagnosis of LNET, specified as either TC or AC, with 9 lesions classified as indeterminate carcinoid. Patients with high-grade carcinoid tumors were excluded. Patients were treated nonoperatively with primary RT between 2006 and 2020. Data were collected through a standardized format and variables were deidentified. Patient records were reviewed for lesion characteristics and clinical risk factors, including age at treatment, smoking status, T stage, N stage, primary tumor size, grade, histology, dose, fractionation, planning target volume (PTV) size, lung V20 (volume of tissue receiving 20 Gy), BED (BED $\alpha/\beta = 3$, 5, and 10), and mean lung dose (MLD). Patients with large cell and small cell neuroendocrine tumors were excluded from this analysis. Primary lung tumor site (ie, specific lobe) information was not available for 10 lesions. Patients with presumed synchronous primaries were allowed, and 2 patients with pathologically confirmed LNET and no evidence of distant metastasis had 2 lung lesions treated simultaneously.

Radiation therapy

SBRT was defined as treatment given to a minimum BED of 100 Gy ($\alpha/\beta = 5$, given low Ki-67 expression of this histology), with the goals of dose escalation and fractionation determined secondary to organ-at-risk constraints. The most common SBRT fractionation schedule was 50 to 60 Gy in 5 daily fractions at 10 to 12 Gy per fraction. BED was calculated based on prescription dose and fractionation to adjust for variability in differing regimens across institutions. Additional RT data are reported in the following sections. Toxicity was reported by each treating physician, as evaluated by the Common Terminology Criteria for Adverse Events, version 4.0.

Statistical analysis

Statistical analysis was performed using R, version 4.0.2. The primary endpoints were LC, defined as freedom from disease recurrence within the irradiated field; progression-free survival (PFS), defined as freedom from disease recurrence at any site or death; and overall survival (OS) among all patients. Survival time for each of these outcomes was calculated from SBRT completion. Actuarial rates of LC, PFS, and OS were calculated using the Kaplan-Meier method, and differences in rates based on individual variables were assessed with the log-rank test. All clinical, histopathologic, and treatment variables were added to Cox univariate analysis regression models. Pathologic, clinical, and treatment risk factors found to be predictive on univariable analysis (UVA) were included in the Cox multivariable (MVA) regression model. A 2-sided model was used for all tests, with an α (type I) error of <0.05 considered to be statistically significant.

Results

Patient and tumor characteristics

Patient and tumor characteristics for all 46 patients and 48 tumors in this study are shown in Table 1. Median follow-up was 30 months (range, 6–108 months). Median age at time of treatment was 70 years old. Most patients were either former or current smokers (29 of 46, 63%), and 54% of all patients were female. Of the 48 lesions, 32 (67%) were typical carcinoid histology, 7 (14%) were atypical, and 9 (19%) were indeterminate. Mean tumor size was 2 cm (range, 0.6–6 cm). Forty-two of 48 lesions (88%) were T1 to T2 tumors, and 1 patient had N1 disease (described in the following sections). The majority (94%) were overall stage I to II (American Joint Committee on Cancer eighth edition) disease. A single patient had presumed pulmonary metastases at presentation, with the dominant lesion treated by SBRT and the other smaller lesions stable on follow-up.

Patient outcomes

Patient outcomes are displayed in Fig. 1 and Table E1. Thirty-five patients (76.1%) were without evidence of disease on last follow-up. Seven patients experienced disease progression. There were 2 local recurrences (LR) (1 TC patient experienced LR alone, and another with indeterminate histology had concurrent local and distant recurrences), with additional details provided in Table E2. There was 1 regional recurrence (biopsy proven) in a paraesophageal lymph node in a patient with TC, and 4 other patients had distant recurrence (2 TC, 2 AC). Data on 5 patients were missing at last follow-up date, and thus only OS and not LC or PFS could be calculated.

On Kaplan-Meier analysis, LC at 3, 6, and 9 years 91%, and 91%, respectively (Fig. 1a). PFS at 3, 6, and 9 years was 88%, 78%, and 78%, respectively (Fig. 1b). OS at 3, 6, and 9 years was 64%, 43%, and 26%, respectively (Fig. 1c). Variables associated with OS, PFS, and LC are shown in Table E3. On UVA, variables associated with worse OS were T and N stage ($P = .007$ and $P = .01$, respectively; Table E4); however, these variables were not associated with OS on MVA. The only variable associated with worse PFS was T stage ($P < .001$); however, upon MVA, no variables were associated with PFS. No comparisons could

be made with respect to LC because of the low number of LRs. Full UVA and MVA results are found in Tables E4 and E5.

Outcomes by histology

For the 32 patients with TC, LC at 3, 6, and 9 years was 96%, PFS at 3, 6, and 9 years was 91%, and OS at 3, 6, and 9 years was 62%, 31%, and 15%, respectively (Table E3). For 7 patients with AC, LC at 3 and 6 years was 100%, PFS at 3 and 6 years was 67% and 44%, respectively, and OS at 3 and 6 years was 50%. Nine-year outcomes for patients with AC were not estimable because of the number of patients at that timepoint. No significant differences in outcome were noted between histologies on UVA and MVA (Tables E4 and E5).

Toxicity

Only 2 cases of SBRT-related toxicity were reported. One patient with TC with a history of right upper lobectomy for early-stage NSCLC 5 years earlier, receiving baseline supplemental oxygen, experienced a grade 2 radiation pneumonitis (PTV size 35.8 cc, V20 = 8%, MLD = 4 Gy, BED_3 = 300). A second patient with indeterminate carcinoid developed grade 2 radiation pneumonitis 6 months after SBRT (PTV size 29.1 cc, V20 = 10%, MLD = 6.2 Gy, BED_3 = 300); this patient developed a pulmonary embolism in the interim, 3 months after SBRT. Both patients received a total of 60 Gy, delivered in 5 fractions. No grade 3 or higher toxicity was identified.

RT characteristics

RT data are reported in Table 2. Median total dose and dose per fraction were 50 Gy and 10 Gy/fraction, respectively. Median PTV was 34.2 cc (range, 4.7–106 cc). All but 4 lesions were treated with ≤5 fractions, with the remaining lesions treated with ≤11 fractions (Table 3). Median BED_3, BED_5, and BED_{10} were 271, 150, and 100, respectively. Median V20 Gy and MLD were 5.6% and 4.7 Gy, respectively. One patient was found to have regional metastatic disease after resection of an infrahilar lymph node at the time of thoracotomy, which was then aborted. The patient was subsequently treated to right middle and right lower lobe lesions simultaneously, using 2 isocenters (50 Gy in 5 fractions to both, Fig. 2). A second patient without evidence of nodal or distant disease received SBRT to 2 synchronous primaries in the right lower lobe with the same regimen.

Discussion

The implementation of SBRT for early-stage, inoperable NSCLC provides an excellent alternative to CFRT, which in comparison is more toxic and offers lower rates of LC.[13,30] Because of the initial success of SBRT, this approach has been further investigated and shown to be effective in other primary pulmonary histologies, such as stage I small cell lung cancer.[15] Per current National Comprehensive Cancer Network guidelines, the standard of care for early-stage LNET remains surgery, despite recent national data showing an increase in use of SBRT in select early-stage patients.[17] Particularly in a radioresistant tumor such as LNET, the use of high-BED ablative RT is an important tool for patients who are unable to undergo surgery. There has been a limited number of small retrospective studies evaluating

SBRT in this patient population,[11,18,19] and to our knowledge, the current study is the largest and first multi-institutional series evaluating LC, toxicity, and dosimetric outcomes with SBRT for early-stage LNET. In our analysis, SBRT was associated with excellent LC and well tolerated, with minimal grade ≥ 3 toxicity.

Various surgical techniques have been explored for medically operable patients with LNET to provide maximal tumor resection while sparing normal lung parenchyma. For those with tumors in the peripheral lung, complete resection with either segmentectomy or lobectomy is preferred.[31] In patients with central airway or endobronchial tumors, an alternative sleeve resection or endoscopic approach has been used to spare lung tissue, when feasible.[9,32] A summary of the seminal surgical studies is presented in Table 3; while these studies show excellent locoregional control (LRC) and survival outcomes, we find that SBRT performs well in comparison with historical surgical experience, despite a generally less favorable patient population treated with RT.[7,9,10,21–27,29]

In a multicenter retrospective analysis of 139 patients, Ferguson et al[7] evaluated patients treated primarily with lobectomy. Although most patients in their study had early-stage disease, those with AC presented with more advanced tumors. They reported the 5-year LRC for TC and AC tumors to be 97% and 80%, respectively. Terzi et al[10] presented results of 25 patients with symptomatic central airway tumors treated with bronchoplastic resection. Although they had excellent long-term LRC (96%), recurrence occurred as late as 19 years, indicating a potential need for longer follow-up. A 2003 study from UT—MD Anderson Cancer Center reported significantly worse LRC and distant control in patients with AC, a finding that has been consistent throughout the literature.[27] For stage I patients in their study, 5-year LRC for TC and AC was 92% and 77%, respectively. Two large studies within the past decade collectively evaluated over 1000 patients treated with surgery for LNET, primarily with stage I and TC disease, reporting excellent LRC, distant control, and OS outcomes (>90%).[22,25] These results suggest that members of this subset of patients with LNET are unlikely to die of locoregional or distant progression of their disease. Data from Brazil showed that, regardless of surgical technique, there was a significant disparity between TC and AC in terms of 5-year relapse-free survival (94% vs 74%, respectively) and 5-year OS (91% vs 56%).[24] A significant proportion of LNETs will originate in the central airways and may present with symptoms of obstruction.[32,33] For this type of endobronchial disease, endoscopic resection in node-negative patients has been shown to be effective; yet this is not considered to be rigorous oncologic surgery because of frequent complete invasion of the adjacent bronchial wall.[9]

The role of RT in patients with LNET is certainly less well studied. Two early retrospective studies (N = 18 in each study) of palliative intent CFRT showed good objective and symptomatic response with acceptable toxicity.[34,35] In the postoperative setting, however, data from Memorial Sloan Kettering Cancer Center showed no clear survival benefit with the receipt of adjuvant CFRT for patients with N2 disease.[36] A more recent series by Wirth et al[37] evaluated 18 patients with primarily advanced stage LNET (8 TC, 10 AC), treated with either chemotherapy or chemoradiotherapy (CFRT dose, 46–54 Gy). They concluded that response rates of LNET to chemoradiation were poor (22%) and that alternative treatments in inoperable patients require further exploration. Of note, these

doses have a very low comparative BED and should be considered palliative in nature. A series by Okoye et al[38] included a group of patients with LNET managed definitively with either surgery, chemoradiation, or RT alone. Of the 3 patients receiving RT, 2 received CFRT concurrently with chemotherapy, while a single patient received definitive SBRT (50 Gy in 5 fractions).[38] Although the 2 patients receiving definitive chemoradiotherapy both experienced rapid disease progression, the patient undergoing SBRT experienced stable disease after 22 months of follow-up.

Within the past 7 years, there have been several small single institutional series evaluating LC outcomes in patients (included in this manuscript) with inoperable early-stage LNET treated with SBRT.[11,18,19] Most recently, an analysis of the National Cancer Database showed increasing use of SBRT (55%) among inoperable patients with cT1-2N0M0 TC treated with primary RT, particularly after 2007.[17] Although specific operability of patients was not discussed further, 63% of all patients (of whom more than half received SBRT) had a Charlson-Deyo comorbidity score of 0. Although this study showed a modest OS benefit with the use of SBRT (median OS 66 vs 58 months with CFRT), most patients with local TC will not die of their disease. LC data are, unfortunately, not provided through the National Cancer Database, and thus remains a key endpoint of interest in this patient population.

In the current study, LC was excellent with SBRT (>90% at 9 years). Outcomes for OS were significantly worse than LC and PFS, and it should be noted that a substantial proportion of patients had documented comorbidities (ie, congestive heart failure, end-stage renal disease, other metastatic cancers). Though patient preference may play a role, poor baseline health status is often the reason for selection of SBRT rather than surgery in this group of patients. Thus, considering the excellent rates of disease control, the presumption is that many patients died of unrelated causes. Lastly, although novel systemic immunotherapies have shown limited efficacy with LNET,[39] there may be a future role for combined modality treatment with SBRT. To this end, the abscopal effect remains a recurring area of study with regards to ablative RT, and a recent case example of this phenomenon following SBRT in a patient with TC has garnered interest.[40]

The present study contains several important limitations. There is inherent bias in patient selection because of its retrospective, nonrandomized nature. Given the rarity of these tumors, it is unlikely that any prospective randomized trial comparing surgery and SBRT will be attempted in this group of patients; therefore, only indirect comparison with historical surgical outcomes is possible. Multivariable results are reported, but because the data are limited by few events and small sample size, there is imbalance with respect to reported variables across institutions, making these results difficult to assess. Although caution should be applied when drawing conclusions from a limited sample size, this study provides LC outcomes for the largest group of patients with LNET treated with SBRT to date, an important endpoint for which there are limited prior data. Because of the very recent trend of using SBRT for LNET, our study has limited follow-up compared with the surgical literature discussed. Given the variability in patient comorbidity and date of death data collection among the 11 contributing institutions, a competing risk of death analysis was not able to be performed. Finally, potential differences in RT technique, fractionation,

equipment, and treatment planning systems between institutions cannot be avoided entirely in a study of this design.

Conclusion

This multi-institutional analysis provides the most current and largest available evidence that SBRT is an effective and well-tolerated treatment for early-stage LNET. Our analysis demonstrates similar rates of LC and toxicity compared with the historical surgical data. Although surgery provides excellent outcomes and remains the standard of care, SBRT should be a recommended alternative for patients who either are unable to safely undergo resection without excess morbidity or who decline surgery.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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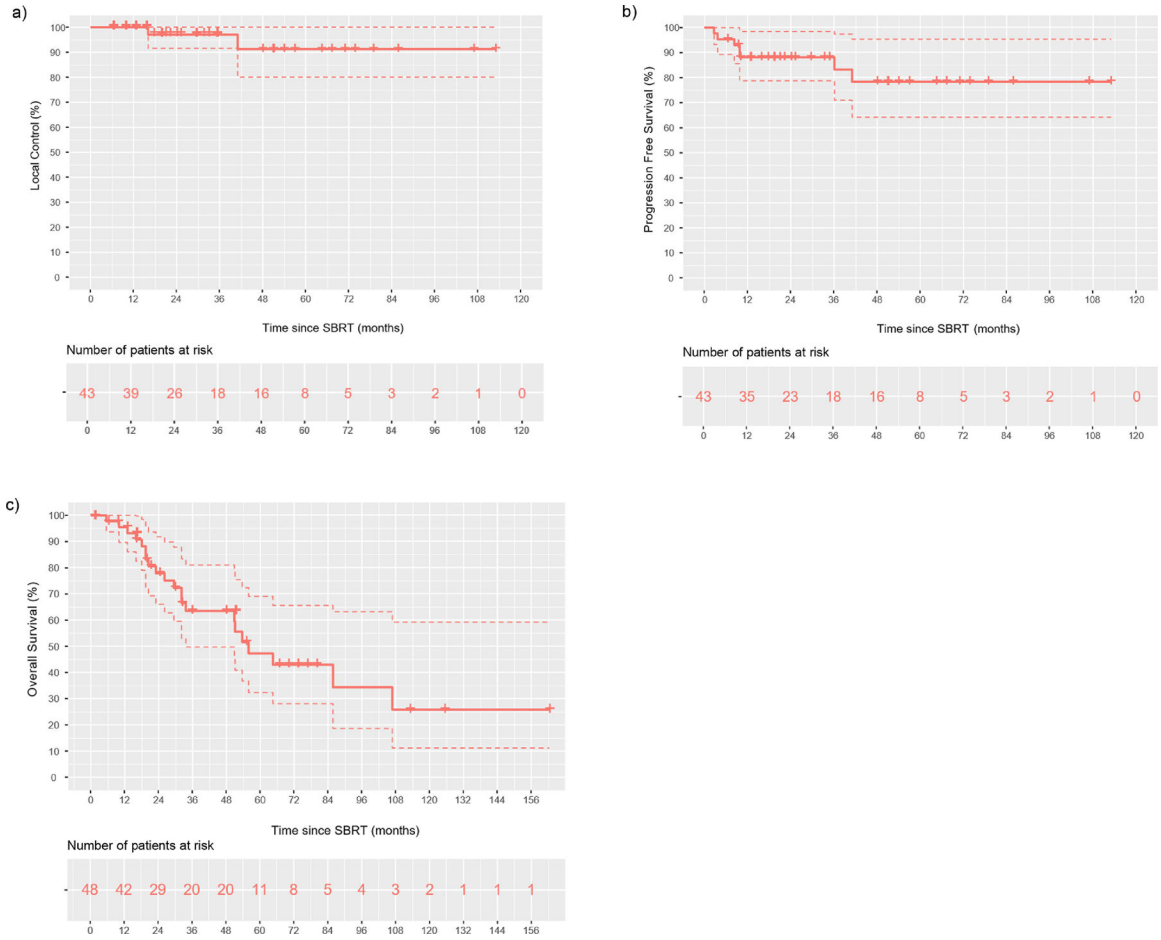

Fig. 1.

(a) Local control, (b) progression-free survival, and (c) overall survival outcomes.

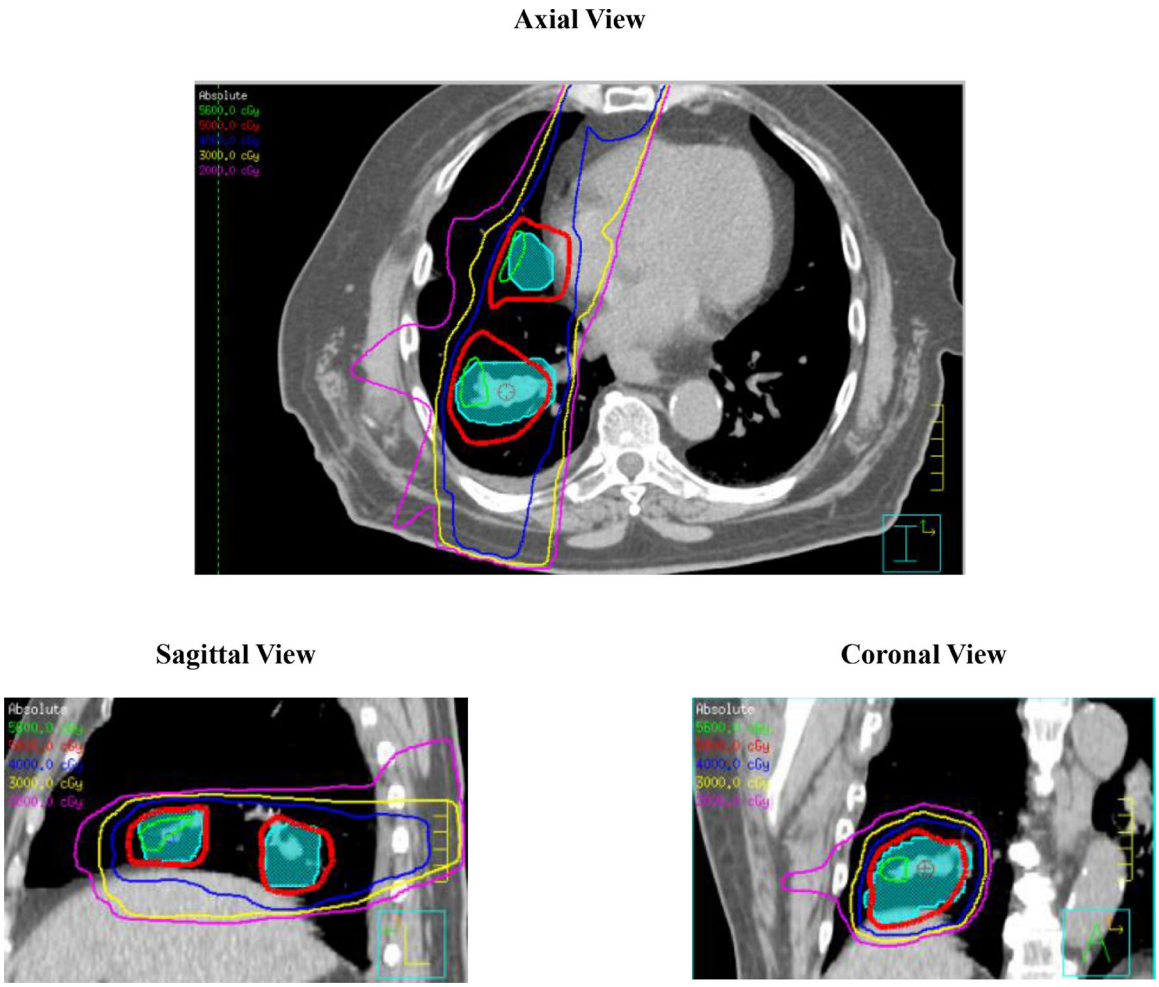

Fig. 2.

One patient was treated for a right middle and right lower lobe lesion simultaneously.

Table 1

Patient and tumor characteristics

Characteristic	No. (%)
Patients (N = 46)	
Institution	
Institution 1	11 (23.9)
Institution 2	6 (13.0)
Institution 3	1 (2.2)
Institution 4	1 (2.2)
Institution 5	10 (21.7)
Institution 6	6 (13)
Institution 7	2 (4.4)
Institution 8	2 (4.4)
Institution 9	3 (6.4)
Institution 10	2 (4.4)
Institution 11	2 (4.4)
Age at treatment (y), median [range]	70.5 [40–85]
Sex	
Male	21 (45.7)
Female	25 (54.3)
Smoker	
Never	17 (37.0)
Former	21 (45.6)
Current	8 (17.4)
Tumors (N = 48) *	
Primary site	
Left lower lobe	11 (22.9)
Right lower lobe	11 (22.9)
Left upper lobe	5 (10.4)
Right middle lobe	5 (10.4)
Right upper lobe	6 (12.5)
Not specified	10 (20.8)
Tumor size (cm), mean [range]	2 [0.6–6]
T stage	
1A	8 (16.7)
1B	16 (33.3)
1C	7 (14.6)
2A	7 (14.6)
2B	4 (8.33)
3	3 (6.25)
4	3 (6.25)
N stage	

Characteristic	No. (%)
0	46 (95.8)
1	2 (4.17)
AJCC 8 stage	
IA1	8 (16.7)
IA2	16 (33.3)
IA3	7 (14.6)
IB	9 (18.8)
IIA	2 (4.17)
IIB	3 (6.25)
IIIA	2 (4.17)
IV	1 (2.08)
Histology	
Typical carcinoid	32 (66.7)
Atypical carcinoid	7 (14.6)
Indeterminate carcinoid	9 (18.8)

Abbreviation: AJCC = American Joint Committee on Cancer.

* Two patients had synchronous lesions without evidence of distant metastatic disease, and thus both lesions were treated as separate primaries.

Table 2

Treatment characteristics

RT characteristics (N = 48)	Median [range]
Dose (Gy)	50 [40–60]
Number of fractions	5 [3–11]
Dose per fraction (Gy)	10 [5–18]
BED_3	217 [133–378]
BED_5	150 [100–248]
BED_{10}	100 [72–151]
PTV size (cc)	34.2 [4.7–106]
V20 Gy	5.6 [0.13–22.3]
Mean total lung dose (Gy)	4.7 [1.25–13.7]
RT regimens	**No. (%)**
RT dose and fractionation	
55 Gy in 11 fractions	1 (2.1)
50 Gy in 10 fractions	2 (4.2)
60 Gy in 10 fractions	1 (2.1)
40 Gy in 5 fractions	1 (2.1)
50 Gy in 5 fractions *	29 (60.4)
55 Gy in 5 fractions	1 (2.1)
60 Gy in 5 fractions	6 (12.5)
48 Gy in 4 fractions	1 (2.1)
50 Gy in 4 fractions	3 (6.2)
54 Gy in 3 fractions	3 (6.2)

Abbreviations: BED = biologically effective dose; PTV = planning target volume; RT = radiation therapy.

* Two patients were treated concurrently for synchronous primaries.

Table 3

Pertinent surgical series for primary lung neuroendocrine tumors

Study type*	N	Histology (n)	Stage (n)	Endpoint (y)	Result	Reference (first author)	Comments
Multicenter	661	TC (569) AC (92)	IA (225) IB (325) IIA (11) IIB (52) III (41) IV (7)	TC LRC (10) AC LRC (10) TC DC (10) AC DC (10) TC OS (10) AC OS (10)	99% 97% 98% 84% 92% 67%	Garcia-Yuste[21]	Patients with AC more likely to have LN involvement (23% vs 4% in TC) AC with significantly worse DC, OS
Multicenter	876	TC (876)	I (876)	OS (5)	94%	Filosso[22]	Lobectomy superior to wedge resection Patients with stage I TC only
Single-center	72	TC (57) AC (15)	N0† (72)	LRC (10)	97%	Brokx[9]	Endoscopic resection for endobronchial/unresectable lesions
Multicenter	139	TC (109) AC (26) UNK (4)	IA (94) IB (27) IIA (3) IIB (6) III (6) IV (3)	TC OS (5) AC OS (5) TC LRC (5) AC LRC (5)	90% 70% 97% 80%	Ferguson[7]	AC presented at more advanced stage, majority of patients received lobectomy
Single-center	163	TC (121) AC (42)	T1 (101) T2-T4 (62) N0 (122) N1 (32) N2 (9)	TC OS (5) AC OS (5)	99% 70%	Cardillo[23]	N2 status was strongest prognostic factor
Single-center	126	TC (110) AC (16)	T1 (51) T2 (67) T3-T4 (8) N0 (109) N1 (9) N2 (8)	TC OS (5) AC OS (5) TC RFS (5) AC RFS (5)	91% 56% 94% 74%	Machuca[24]	Surgical outcomes not affected by parenchymal-sparing surgeries such as sleeve and sublobar resection
Single-center	337	TC (291) AC (46)	IA (242) IB (35) IIA (31) IIB (4) III (20) IV (5)	TC DC (10) AC DC (10) TC LRC (10) AC LRC (10)	97% 76% 100% 91%	Lou[25]	Most recurrences not detected by surveillance imaging
Single-center	126	TC (83) AC (43)	IA (64) IB (26) IIA (13) IIB (5) III (16) IV (2)	TC OS (5) AC OS (5) TC LRC (5) AC LRC (5)	91% 69% 96% 88%	Filosso[26]	Systematic LN dissection performed; +LN and AC histology associated with poor DC
Single-center	117	TC (95) AC (22)	I (117)	TC LRC (5) AC LRC (5)	92% 77% 93% 77%	Kaplan[27]	Comparing stage I patients only, surgery vs SBRT in current series

Study type*	N	Histology (n)	Stage (n)	Endpoint (y)	Result	Reference (first author)	Comments
				TC DC (10) AC DC (10)			
Single-center	252	TC (174) AC (78)	N0† (223) N1 (19) N2 (10)	TC OS (10) AC OS (10) TC RFS (10) AC RFS (10)	93% 64% 97% 82%	Rea[28]	84% patients symptomatic on presentation, 77% central location
Single-center	95	TC (81) AC (14)	N0† (80) N1 (13) N2 (2)	OS (12) LRC (12) DC (12)	97% 96% 96%	El Jamal[29]	Early conservative resection recommended, no association between +LN and outcome

Abbreviations: AC = atypical carcinoid; DC = distant control; LN = lymph node; LRC = locoregional control; OS = overall survival; RFS = relapse-free survival; SBRT = stereotactic body radiation therapy; TC = typical carcinoid; UNK = unknown.

*All studies were retrospective reviews.

†Tumor size not specified, M0.

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