Chapter 6

Curative treatment of stage I non-small cell lung cancer in patients with severe COPD: Stereotactic radiotherapy outcomes and systematic review

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Abstract

Purpose

Patients with severe chronic obstructive pulmonary disease (COPD) have a high risk of lung cancer, and a high risk of post-surgical complications. We studied outcomes after stereotactic body radiotherapy (SBRT) in patients with severe COPD, as defined by Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria, and performed a systematic review of the literature on outcomes after SBRT or surgery in these patients.

Methods

A single-institution cohort of 173 patients with COPD GOLD III-IV and stage I NSCLC treated with SBRT was evaluated. A systematic review identified studies reporting outcomes after SBRT or surgery for stage I NSCLC in patients with GOLD III-IV or a predicted post-operative forced expiratory volume in 1 second (FEV1) of ≤40%.

Results

In the single-institution cohort, median follow-up was 21 months and median overall survival (OS) was 32 months. Actuarial 3-year local control was 89%, and 1- and 3-year OS were 79% and 47%, respectively. COPD severity correlated with OS (p=0.01). The systematic review identified four other studies (two surgical, two SBRT, n=196 patients). SBRT studies were published more recently and included older patients than surgical studies. Mean thirty-day mortality was 0% post-SBRT and 10% after surgery. Local or loco-regional control was high (≥89%) after both treatments. Post-SBRT, actuarial OS was 79-94% at 1 year and 43-70% at 3 years. Post-surgical actuarial OS was 45-86% at 1 year and 31-66% at 3 years.

Conclusion

SBRT and surgery differ in risk of 30-day mortality in patients with severe COPD. Despite the negative selection of SBRT patients, survival at 1- and 3-years is comparable between the two treatments.

Introduction

Chronic obstructive pulmonary disease (COPD) is present in 50-70% of patients with lung cancer at the time of diagnosis [1]. COPD is an independent predictor of lung cancer, even after controlling for smoking history [1-3]. Lung cancer risk increases as forced expiratory volume in 1 second (FEV1) decreases, with the risk highest in patients with an FEV1 of less than 40% of predicted [1-3]. Patients with severe COPD have a high annual mortality rate [4,5], even in the absence of malignancy. COPD itself is associated with other co-morbid conditions (including cardiovascular disease) which can in turn further reduce suitability for radical treatment [6].

Surgery has historically been the primary treatment option for patients with stage I NSCLC. Although stage I NSCLC is technically curable, the presence of severe COPD increases the risk of post-operative complications and reduces the extent of lung that can be safely resected [7,8]. As non-surgical treatment options such as conventional radiotherapy have historically achieved suboptimal outcomes [9], some have argued that the risks associated with surgery in patients with severe COPD were justified [10]. Recent surgical guidelines have even suggested lowering the predicted post-operative FEV1 (ppo-FEV1) high-risk threshold from <40% of predicted to <30% [8].

The advent of stereotactic body radiotherapy (SBRT) has provided a safe and effective alternative treatment for stage I NSCLC in patients who are unfit for surgery or decline resection [11,12]. The role of SBRT in low-risk patients who are fit to undergo surgery is currently being investigated in the phase III setting [13]. Given the higher complication rates and long-term competing mortality risks associated with severe COPD, we evaluated post-SBRT outcomes in a cohort of stage I NSCLC patients with severe COPD, as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria [14]. Since the benefits of expanding surgical access to such a population are not readily evident, we also conducted a systematic review of the published literature, to allow for a broader assessment of outcomes after surgery or SBRT in these patients.

Methods

The objectives of this study were as follows:

1. To determine local control and survival outcomes after curative-intent treatment (surgery or SBRT) for stage I NSCLC in patients with severe COPD or ventilatory impairment.
2. To determine treatment complication rates and 30-day mortality in this patient population.

VUmc Series

All patients with severe COPD who were treated with SBRT for stage I NSCLC at the VU University Medical Centre (VUmc) between inception of the SBRT program in 2003 and March 2010 were included in this study. COPD severity was defined according to the GOLD criteria [14]: 'severe' if FEV1/FVC <70% and FEV1 30-50% predicted (GOLD class III); and 'very severe' if FEV1/FVC <70% and FEV1 <30% predicted (GOLD class IV).

All patients are discussed by a multidisciplinary oncology tumor board prior to treatment and entered into a prospective database. The risk-adapted fractionation schemes and treatment planning techniques have been described in detail previously [15-17]. Most patients (n=157) were treated with fixed gantry multiple beam SBRT delivery, and the remainder (n=19) were treated with volumetric modulated arc therapy (RapidArc™, Varian Medical Systems Inc, Palo Alto, California), which was implemented in 2008. SBRT fractionation depended on tumor size and location, with a total prescribed dose of 60 Gy in 3-8 fractions (or equivalent, depending on dose calculation software) [13,15-17]. No patients received adjuvant chemotherapy.

Treatment planning for static beam plans were performed with the BrainLab software (Brainscan v. 5.2, BrainLab Inc., Feldkirchen, Germany) using 8–12 noncoplanar static beams and 6 MV photons. RapidArc plans consisted of at least one pair of 358° clockwise and counter-clockwise coplanar arcs using 6 MV photons.

Fractionation choice was dependent on tumor size and location [13,15-17]. T1 tumors surrounded by lung parenchyma were treated in 3 fractions. T2 tumors, or T1 tumors with broad contact with the chest wall, were treated in 5 fractions. Centrally

located tumors and tumors adjacent to the brachial plexus were treated in 8 fractions. The nominal prescribed doses depended on the dose calculation algorithm used. With the pencil beam algorithm used in the BrainLab software, the three fractionations were: 3 x 20 Gy, 5 x 12 Gy, or 8 x 7.5 Gy. With the AAA algorithm used for the RapidArc patients, the fractionations were 3 x 18 Gy, 5 x 11 Gy, or 8 x 7.5 Gy. SBRT doses were prescribed at the 80% isodose line. Four-dimensional (4D) CT scans (GE Medical Systems, Waukesha, USA) were used to delineate internal target volumes (ITVs). A PTV margin of 3-5 mm was added to account for potential baseline tumor shifts and setup errors. Respiratory gating was not routinely used.

Routine practice requires outpatient assessments at 3-6 monthly intervals post-SBRT, with a diagnostic scan performed at each visit. Toxicity was assessed using the Common Terminology Criteria for Adverse Events, version 3.0 [18]. Post-treatment pulmonary function was not measured routinely.

Systematic Review

Study inclusion criteria

1. Studies reporting on clinically- and/or pathologically-staged stage I NSCLC
2. All patients must have had either a pre-treatment FEV1≤50% (corresponding to GOLD class III/IV), or ppo-FEV1≤40%. Although the relationship between pre-operative and post-operative FEV1 varies by individual patient, these cutoffs appear to be similar, based on studies reporting both values [19-21].

Percent predicted FEV1 values were used since they are a more accurate indicator of pulmonary function than absolute values, and they minimize confounding effects of height, sex, and age [22,23]. In cases where means and standard deviations/standard errors of FEV1 values were reported in place of ranges, the cutoffs above had to lie at least two standard deviations above the mean in order for the study to be included. In studies reporting a subgroup of patients meeting the above criteria, only that subgroup was included in this review.

Exclusion criteria

- Studies published only as conference abstracts
- Less than 20 patients in the applicable subgroup
- Only absolute FEV1 values reported (not predicted values)
- Published prior to 1995 (due to changes in surgical, anaesthetic and radiotherapy technology)
- Outcomes for stage I patients not specified separately in the paper
- Outcomes reported after conventional radiotherapy only

Search strategy

Combinations of terms were used to search the MEDLINE and EMBASE electronic databases from 1995 until March 2010, relating to the following concepts:

- lung cancer ("lung cancer", "lung neoplasms", etc.)
- stage one ("early stage", "stage 1", "stage I", etc.)
- pulmonary function: ("forced expiratory", "FEV1", "chronic obstructive pulmonary disease", "pulmonary function", etc.),

Both text and exploded Medical Subject Heading (MeSH) terms were used. The search was conducted by a librarian and a physician. Only English-language articles were included. Studies were screened by abstract (MEDLINE n=224; EMBASE n=120), and 146 full papers were retrieved, usually because outcomes stratified by pulmonary function or stage were not specified in the abstracts. Thirty-one papers (including three other systematic reviews) were selected for detailed review and their reference lists were hand-searched.

Eight papers fulfilled all the inclusion criteria above. They were assessed by two independent data abstractors (DP and GBR), and any disagreements between the two abstractors were resolved by consensus. Three of these were from a single institution (Glenfield Hospital, UK) and included overlapping patient groups [19-21]; therefore the most recent report (published in 2010) was considered to be the definitive update and is reported herein. Data from the two earlier studies were used only if they provided further specific information not included in the latest study. One study (Cancer and Leukemia Group B [CALGB] 9335) that specifically enrolled high-risk patients only reported the median FEV1; it was excluded after obtaining more complete data on baseline lung

function by contacting the CALGB [24]. One surgical study from 1995 was excluded as it reported on a cohort of patients stage I patients with respiratory impairment who all underwent pneumonectomy, which was not felt to be reflective of current practice for treatment of stage I NSCLC [25].

Ultimately, four other studies were included in the systematic review [19,26-28]. For one SBRT study [Henderson *et al* [27]], some data were abstracted from an earlier report on the same cohort of patients [29]. No studies of surgery with intra-operative brachytherapy or surgery with additional lung volume reduction met the inclusion criteria.

Statistical Analysis

For VUmc data, Kaplan-Meier survival estimates were generated and differences compared using the log-rank test. Median follow-up was calculated using the reverse Kaplan-Meier method. For abstraction of survival data for the systematic review, 30-day mortality, median survival, and 1-, 3-, and 5-year survivals were estimated from the graphs if not provided in the text. If a large discrepancy was noted between a Kaplan-Meier curve and the associated text, the data from the graph was used. All statistical tests were two-sided with $p \leq 0.05$ indicative of statistical significance, and all statistical analyses were performed using the Statistical Package of Social Sciences (SPSS version 15.0, Chicago, USA).

Results

VUmc SBRT patients and outcomes

A total of 176 patients with COPD scored as GOLD III (n=133) or IV (n=43) with stage I NSCLC were treated between 2003 and March 2010. The median age was 70 years (range 47-86), and most patients were male (n=97; 55%). The median Charlson co-morbidity score was four (range 2-9), and 96% were considered medically inoperable. The median FEV1 was 0.94 L (range 0.36-1.99 L), corresponding to 38% of predicted (range 16-50% of predicted).

All patients underwent a pre-treatment FDG-PET scan. Many patients did not have pathological confirmation of malignancy (n=119; 68%). Although a biopsy was

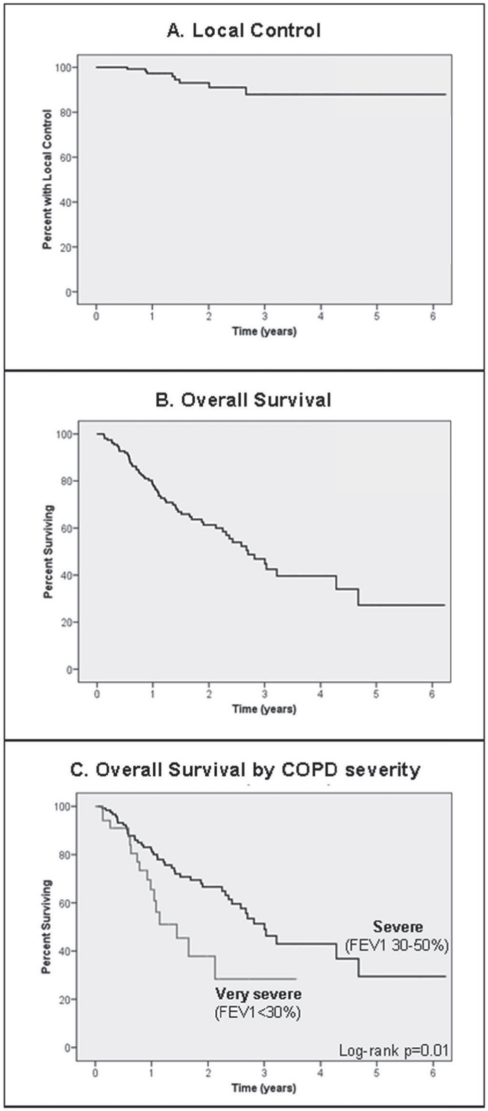
sought wherever safely possible, the risk of trans-thoracic biopsy was often considered too high by the treating physician, given the poor baseline lung function of this population. For patients without pathological confirmation of malignancy, the median probability of malignancy, based on a validated calculation algorithm that includes patient history, CT, and PET, was 96.4% [30].

Most patients had T1 disease (n=111; 63%), and 16 patients had a second primary T1 tumor treated synchronously. The median planning target volume (PTV) was 26 cc. Most patients received the 3-fraction scheme (n=78; 44%); 69 (39%) received 5 fractions; and 29 (17%) received 8 fractions.

Early side effects, occurring within 6 weeks of treatment, were common and mild, with most patients (55%) experiencing grade 1 or 2 toxicity (most commonly fatigue n=55, cough and/or dyspnea n=24, chest wall pain n=18, or nausea/decreased appetite n=10). One patient developed early grade 3 radiation pneumonitis. Late side effects (occurring >6 weeks after treatment) of grade 3 or more were uncommon: there were two cases of grade 3 radiation pneumonitis, two patients with rib fractures, and one case of hemoptysis requiring transfusion. All grade 3 toxicities ultimately resolved.

The median length of follow-up was 21 months. There were 8 local relapses (crude rate 4.5%), 12 regional relapses, 34 distant relapses, and 62 deaths (with some patients having more than one of these events). Three-year actuarial local control was 89% (Figure 1A). OS was 79% at 1 year, 47% at 3 years, and 28% at 5 years (Figure 1B). Estimates beyond 3 years are less reliable due to low patient numbers. Patients with GOLD IV COPD had worse survival than those with GOLD III COPD, with a median survival of 17 months vs. 36 months, respectively (Figure 1C, log-rank p=0.01).

Figure 1. Outcomes for 176 patients with severe COPD and stage I NSCLC treated with stereotactic radiotherapy (SBRT) between 2003 and 2010. 1A: Local control; 1B: overall survival (OS); 1C: OS stratified by COPD severity



Systematic Review

The characteristics of the four studies identified in the systematic review, along with the current study, are shown in Table 1. Two studies reported on surgery (total n=121 patients) and two on SBRT (total n=75 patients). In all four studies, stage I patients with poor FEV1 represented a subgroup of all patients included in the report.

Table 1. Characteristics of five studies reporting outcomes after curative intent surgery or stereotactic body radiotherapy for patients with poor ventilatory function. N=number of patients; VATS: video-assisted thoracoscopic surgery; RT: radiotherapy; SBRT: stereotactic body radiotherapy

First author	Institution	Year	Accrual Period	N	Treatment
Surgery					
Magdeleinat [26]	Hopital Hotel Dieu and Lannelongue Surgical Centre, Paris, France	2005	1983-2003	58	Segmentectomy or wedge (n=15) Lobectomy or greater (n=43)
Lau [19]	Glenfield Hospital, Leicester, UK	2010	1997-2009	63	Open segmentectomy or VATS procedure (n=43) Open lobectomy (n=20)
SBRT					
Henderson [27]	Indiana University, USA	2008	2002-2004	33	60 - 66 Gy/3 fractions
Stephans [28]	Cleveland Clinic, USA	2009	2004-2007	42	50 Gy/10 fractions to 60 Gy/3 fractions
Palma (current study)	VU University Medical Centre, Netherlands	2010	2003-2010	176	60 Gy/3-8 fractions

Patient and tumour characteristics are shown in Table 2. Patients in the SBRT studies were older than those in the surgical studies (weighted mean 71 vs. 66 years old). The surgical reports included patients with pathologically-staged disease, whereas SBRT studies reported on patients who were clinically staged, and included PET scans in the staging algorithm.

Table 2. Baseline patient characteristics. FEV1= baseline forced expiratory volume in 1 second (as percent predicted); ppoFEV1=predicted post-operative FEV1 (as percent predicted); NR=not reported

First author	**Age** (mean or median)	**Stage**	**FEV1** (mean or median)
Surgery			
Magdeleinat [26]	62*	Pathological stage I	40% (range 23-50%)*
Lau [19]	69*	Uncomplicated pathological stage I	ppoFEV1: 33% (range 14%-40%)* FEV1: 41% (range 18-54%)*
SBRT			
Henderson [27]	70.5*	Clinical stage I	NR (range 13-46%)
Stephans [28]	74*	Clinical stage I	NR (range 15%-50%)
Palma (current study)	70	Clinical stage I	38% (range 16%-50%)

*value not reported for subgroup of interest; the value listed applies to the whole study population

Complications and 30-day mortality

Complications and 30-day mortality are shown in Table 3. Reporting of complications for this specific subgroup of patients was limited. The surgical studies had discordant rates of ICU admission (>90% vs <10% admitted), likely reflecting different institutional policies. Median hospital stay ranged from 8-12 days after surgery.

SBRT appeared to be well tolerated with minor toxicity. The Henderson SBRT study did not report complication rates specifically for the subgroup of patients with severe COPD, but in the whole cohort of patients enrolled in the phase II trial, 8% experienced grade 3-4 toxicity, and excessive late toxicity was noted in patients who

received 60 Gy in 3 fractions to central tumours [29]. It cannot be determined from the reports if patients in this poor-ventilatory subgroup experienced those toxicities.

There was no 30-day mortality after SBRT. After surgery, the 30-day mortality ranged from 7-25%, with a weighted mean of 10%.

Table 3. Thirty-day mortality and complications associated with treatment of stage I NSCLC in patients with poor ventilatory function.

First author	30-day mortality	Complications
Surgery		
Magdeleinat [26]	8%*	> 90% admitted to ICU > 45% with complications (pneumonia, air leak, and arrhythmia most common)
Lau [19]	25% after open lobectomy* 7% for open segmentectomy or VATS procedure*	Median hospital stay 8-12 days <10% admitted to ICU
SBRT		
Henderson [27]	0%*	>69% with grade 1 or 2 toxicity of some kind**
Stephans [28]	0%*	No grade 3 or higher pneumonitis
Palma (current study)	0%	6 patients (3%) with grade 3 toxicity

*denotes values measured from Kaplan-Meier curves;
**8% grade 3-4 toxicity with some late deaths related to treatment of central tumors in larger Phase II study, but these rates not specified for subgroup with poor pulmonary function

Local Control and Survival

Loco-regional control after surgery was reported in two of the earlier surgical papers from Glenfield Hospital [20,21] that were considered subsets of Lau *et al*, and ranged from 89%-94%, although patients did not undergo routine follow-up CT scans. All SBRT studies reported local control rates of 89% or greater [27,28].

Long-term outcomes are shown in Table 4 and Figure 2. Median follow-up in the surgical studies ranged from 3.4-4.7 years, longer than the median follow-up available for SBRT patients (1.5-2.7 years). Long-term survival is attainable after SBRT and surgery. There was substantial overlap in survival outcomes between the two treatment modalities at all time periods. Very few patients were available for follow-up beyond 3 years, rendering the longest estimates less reliable. The worst survival outcomes reported after surgery were in a subgroup of patients who underwent open lobectomy (8% 5-year survival).

Figure 2. Survival outcomes for patients with stage I NSCLC with severe ventilatory dysfunction after surgery or stereotactic radiotherapy (SBRT). Values plotted are 1-year, 3-year and 5-year overall survival as extracted from Kaplan-Meier curves. Superscript numbers refer to references, "C" = current study.

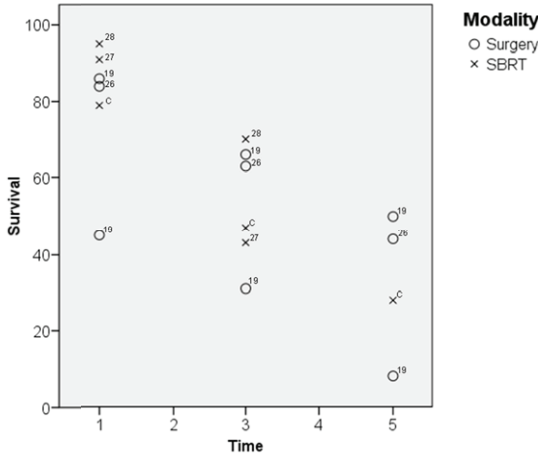


Table 4. Length of follow-up and survival outcomes after treatment of stage I NSCLC in patients with poor ventilatory function. OS: overall survival; VATS: video-assisted thoracoscopic surgery;

First author	Followup (years) (mean or median)	Median OS (years)	Percent Surviving		
			1 year	3 years	5 years
Magdeleinat [26]	3.4**	4.2	84%*	63%*	44%
Lau [19]	4.7**				
	Open segmentectomy or VATS:	5.5*	86%*	66%*	50%*
	Open lobectomy:	0.8*	45%*	31%*	8%*
SBRT					
Henderson [27]	2.2**	1.6	91%*	43%*	
Stephans [28]	1.5**	Not reached*	95%*	70%*	
Palma (current study)	1.7	2.7	79%	47%	28%

*denotes values measured from Kaplan-Meier curves;
**value is reported for whole study population (not just stage I patients with poor ventilatory function).
Empty cells denote values not reported and unavailable from Kaplan-Meier curves.

Discussion

This single-institutional study and systematic review of observational studies suggests that SBRT achieves comparable long-term survival outcomes to surgical resection for patients with stage I NSCLC in the setting of severe COPD or ventilatory dysfunction. SBRT is associated with low risks of operative mortality, rarely requires a hospital stay, and is associated with a favourable toxicity profile. However, this review indicates that published data reporting survival outcomes in patients with severe COPD and stage I NSCLC are lacking. Comparisons of outcomes across studies can be biased by differences in baseline populations, and definitive conclusions cannot be made.

However, the long-term survival of patients in this review are relatively poor, compared to the general population of patients with stage I NSCLC [31], likely because of a higher risk of death from non-lung cancer causes. In the first U.S. National Health and Nutrition Examination Survey (NHANES-I) 19% of patients with severe COPD had died within 5 years [4]. In the U.S. National Emphysema Treatment Trial comparing medical therapy with lung volume reduction for patients with severe COPD (median FEV1 27% predicted), the annual death rate was 11% [32]. This high competing risk of death from non-cancer causes can result in a lower rate of lung-cancer death: in the Lau study included in this review, only 37% of deaths were cancer-related [19]. As a result, small differences in oncologic outcomes between surgery and SBRT could take on lesser importance in determining survival.

The use of surgery or SBRT as primary treatment for stage I NSCLC has been the subject of increasing recent interest, and the question is being examined in phase III trials [13]. However, even once these are completed, the outcomes may not necessarily apply to patients with severe COPD; this will depend on the characteristics of patients enrolled. Recently, Markov modelling was used to simulate a clinical trial comparison of SBRT and surgery, with a small survival advantage predicted for surgery over SBRT of 2-3% at 5 years. This effect was highly sensitive to the predicted operative mortality rate; once operative mortality increased above 4%, SBRT appeared more favourable [33]. In this systematic review, the SBRT patients are a negatively selected group, in terms of age, lack of fitness for surgery, and reporting of outcomes for clinically-staged (rather than pathologically-staged) disease. Yet despite this negative selection, SBRT outcomes do not appear to be inferior than those after surgery.

Surgery confers two theoretical advantages over SBRT: since it is invasive, definitive pathological diagnosis and more complete nodal staging are possible. These theoretical benefits should be carefully considered. Although many SBRT patients included herein did not have pathological confirmation of disease, most often because poor lung function precluded safe biopsy, malignancy risk was estimated using clinical and imaging findings. This has been validated in several studies and achieves a low rate of benign disease at thoracotomy [30,34-36]. In a previous population-based study in North Holland, RT patients treated without pathological diagnosis had a markedly

inferior survival (hazard ratio of death of >2, compared to radiotherapy patients with a pathological diagnosis), likely reflecting death from the underlying co-morbidities that initially precluded biopsy [37]. Although the more definitive nodal staging provided by surgery could theoretically be beneficial (e.g. in removing occult disease or identifying patients for chemotherapy), these benefits are likely to be negligible in patients with severe COPD, considering the poor general condition and high risk of intercurrent death of these patients, the relatively low risk of occult nodal disease in stage I patients (approximately 15% [38]), and the small absolute benefit of adjuvant chemotherapy in those who receive it (5% at 5 years [39]). Furthermore, in patients with respiratory impairment, compliance with systematic ipsilateral lymph node sampling procedures is poor [24].

This study must be considered in the context of its limitations. All studies reported herein were observational, and as such are subject to the biases inherent in non-randomized studies. For this systematic review, a pre-specified cut-off of pulmonary function was required to ensure that all included patients had pulmonary dysfunction. However, FEV1 is only one surrogate for pulmonary dysfunction, whereas treatment decisions should be based on more comprehensive pulmonary testing and physiological assessments [7]. Not all patients with FEV1<50% predicted will have COPD, and more comprehensive scales assessing COPD severity are available [40]. However, for purposes of systematically reviewing the literature, FEV1 is commonly reported and can distinguish between the different GOLD levels of severity. This cutoff may also limit the generalizability of the study. Despite use of strict inclusion criteria in this review, the differences in patient selection, staging investigations, follow-up, extent of surgery (e.g. VATS vs. open surgery) and radiotherapy doses hamper direct comparisons between studies. Finally, data is not available on all outcomes of importance, especially baseline co-morbidities and post-treatment quality of life.

Conclusion

Limited published data is available to assess outcomes after curative treatment of stage I NSCLC in the setting of severe COPD. SBRT is a safe and effective treatment option for these patients, with outcomes that do not appear to be inferior to surgery. SBRT is not

associated with the considerable initial risks of operative mortality and prolonged hospitalization. Patients who do undergo surgery may benefit from avoiding open lobectemy, instead using less invasive approaches such as VATS or open segmentectomy. All patients with stage I NSCLC and severe COPD should be evaluated in a multidisciplinary setting and afforded an informed decision of the risks and benefits of both surgery and SBRT.

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Chapter 7

New Developments in Arc Radiation Therapy: A Review

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