Stereotactic body radiotherapy for early stage lung cancer

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Stereotactic Body Radiotherapy (SBRT) for Early Stage Lung Cancer

Outline:

1. Definitions
2. Who is eligible for SBRT?
3. What are the current recommendations for the use of SBRT for early stage lung cancer?
4. What is the evidence supporting treatment of early stage lung cancer with SBRT?
5. Is histologic confirmation of malignancy necessary in order to treat with SBRT?
6. What are the potential toxicities of SBRT?
7. What are the appropriate outcome measures?

1. Definitions

Stereotactic Body Radiotherapy (SBRT) = Stereotactic Ablative Radiotherapy (SABR)

Radiotherapy:	Use of ionizing radiation to eradicate areas of cancer
Radiosurgery:	Precision delivery of high dose radiation to target areas in the body, with the intent of destroying malignant tissue while sparing adjacent normal tissue
Stereotactic:	3-dimensional coordinate system to correlate virtual target on imaging with actual target in a patient

Radiation Therapy for Early Stage Lung Cancer

External beam, conventionally fractionated radiation therapy

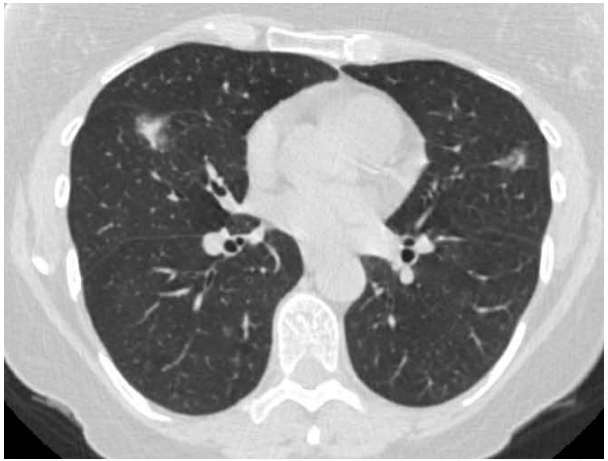
- Simple beam arrangements typically given in daily doses over 4-6 weeks
- Limitations related to defining and constraining treatment volume and radiation dose to normal tissues
- Effective, but with high rates of local and distant failure

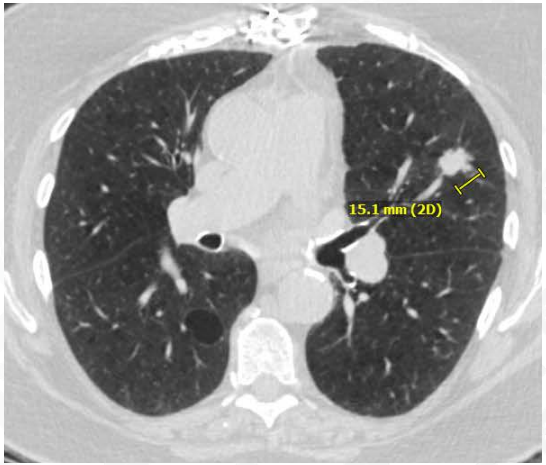
Stereotactic body radiotherapy (SBRT)

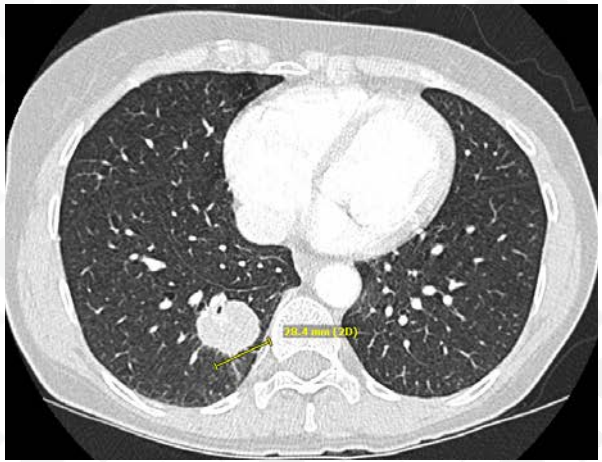
- Delivery of high (ablative) radiation doses using conformal techniques
- Requires management/accommodation for motion related to breathing
- Rapid fall off of dose beyond target minimizes toxicity to normal tissue

2. SBRT Treatment of Early Stage Lung Cancer: Who is eligible?

- SBRT is a potential treatment alternative for “early stage lung cancer”
  - T1-2, N0, M0
  - 16% of patients with NSCLC in the US present with this stage
    - likely to increase with lung cancer screening







Case

JD is a 74 year old woman with a 50 pack-year smoking history, discontinued 10 years ago. She states that she had been in excellent health with no medical problems until 6 weeks ago, when she was hospitalized with congestive heart failure, and underwent emergent 4 vessel coronary artery bypass surgery. Her recuperation from surgery has been uneventful, though she is still fatigued. Post-op echocardiogram showed LVEF 35% with global hypokinesis. In the course of her hospitalization, chest radiograph demonstrated a 1.5 cm left upper lobe nodule. She presents for evaluation of the nodule.

Case

Physical examination: Elderly woman in no distress.
BP 142/72, P 80, RR 14, afebrile.
Lungs – timpanic to percussion; distant breath sounds with prolonged expiratory phase, no rales
Cardiac – S1, S2, no murmurs
Abdominal exam – unremarkable
Extremities – no edema
Neurologic exam – no focal findings

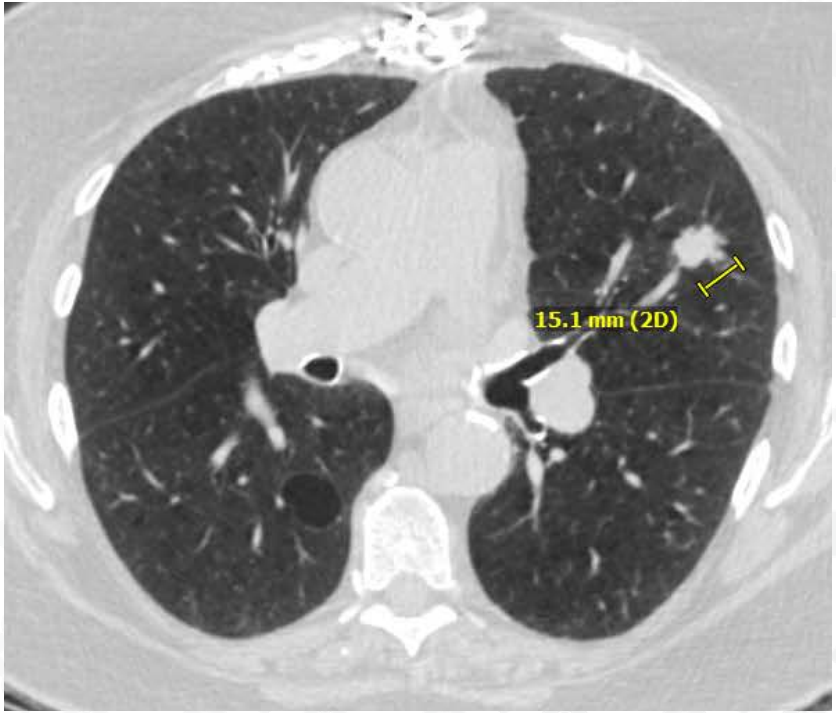
Laboratory examination: unremarkable

Case

CXR: 1.5 cm irregular nodule in the left upper lung zone

Chest CT:

- 1.5 cm spiculated, solid nodule in the lingula
- No hilar or mediastinal adenopathy
- No pleural effusion
- Evidence of emphysema

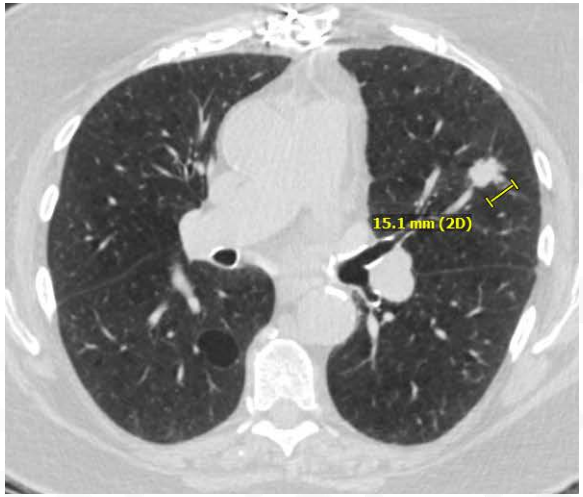


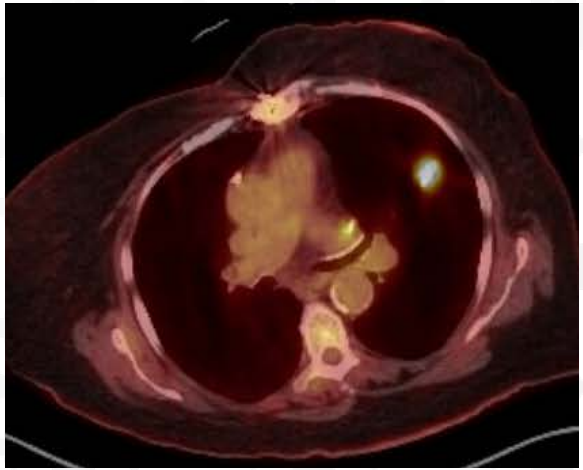
Case

A PET scan was performed, which demonstrated intense FDG uptake in the left upper lobe nodule (SUV 7.6). There was no hypermetabolism in any hilar or mediastinal lymph nodes or any distant structures.

EBUS with electromagnetic navigation:

- Left upper lobe nodule: squamous cell carcinoma
- Lymph node stations 11L, 7, 4L, 4R:
  + lymphocytes on aspiration without malignancy



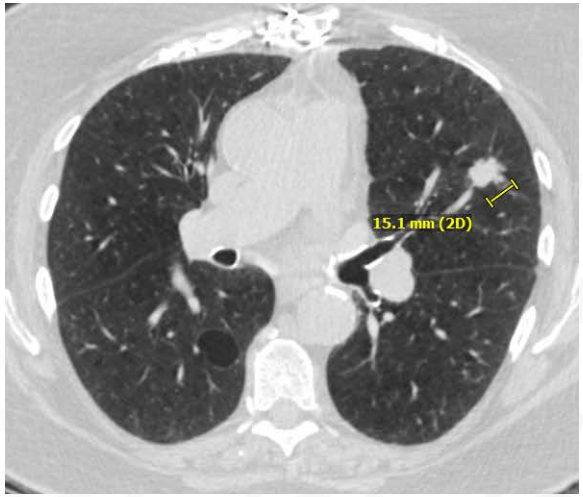


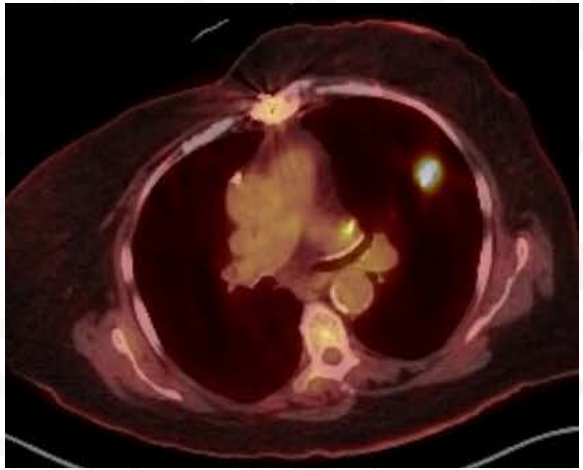
Case

Clinical stage: T1bN0M0, Stage IA2

Possible treatment approaches:

- Lobectomy
- Sublobar anatomic resection (segmentectomy)
- Stereotactic Body Radiotherapy
- (Radiofrequency Ablation)





Current recommendations for treatment of early stage lung cancer: American College of Chest Physicians (CHEST)

American College of Chest Physicians: Recommendations for Treatment of Stage I and II Non-small Cell Lung Cancer. Chest 2013; 143:278S-313S

- For patients with clinical stage I and II non-small cell lung cancer (NSCLC) and no medical contraindications to operative intervention, surgical resection is recommended (Grade IB)
- For patients with clinical stage I NSCLC who may tolerate operative intervention but not a lobar resection due to decreased pulmonary function or comorbid disease, anatomic sublobar resection is recommended over nonsurgical therapy (Grade IB)

Current recommendations for treatment of early stage lung cancer: American Society for Radiation Oncology (ASTRO)

Videtic GMM et al. Stereotactic Body Radiation Therapy for Early Stage Non-Small Cell Lung Cancer: an ASTRO Evidence-Based Guideline. Prac Radiat Oncol 2017; 7:295-301.

- For patients with "standard operative risk" (i.e., with anticipated operative mortality of < 1.5%) and Stage I NSCLC, SBRT is not recommended as an alternative to surgery outside of a clinical trial. Discussions about SBRT are appropriate, with the disclosure that long-term outcomes with SBRT > 3 years are not well established. For this population, lobectomy with systematic mediastinal lymph node evaluation remains the recommended treatment, though a sublobar resection may be considered in select clinical scenarios. *(Recommendation strength: Strong: Quality of evidence: High)*

3. What are the current recommendations for the use of SBRT for early stage lung cancer?

American College of Chest Physicians: Recommendations for Treatment of Stage I and II Non-small Cell Lung Cancer. Chest 2013; 143:278S-313S

- For patients with a clinical stage I NSCLC who cannot tolerate a lobectomy or segmentectomy, stereotactic body radiation therapy (SBRT) and surgical wedge resection are suggested over no therapy (Grade 2C).

Videtic GMM et al. Stereotactic Body Radiation Therapy for Early Stage Non-Small Cell Lung Cancer: an ASTRO Evidence-Based Guideline. Prac Radiat Oncol 2017; 7:295-301.

- For patients with "high operative risk" (i.e., those who cannot tolerate lobectomy, but are candidates for sublobar resection) stage I NSCLC, discussions about SBRT as a potential alternative to surgery are encouraged. Patients should be informed that while SBRT may have decreased risks from treatment in the short term, the longer-term outcomes >3 years are not well-established. *(Recommendation strength: Conditional [risk/benefit balance even]; Quality of evidence: Moderate)*

Treatment of Stage I NSCLC: Summary of Guideline Recommendations

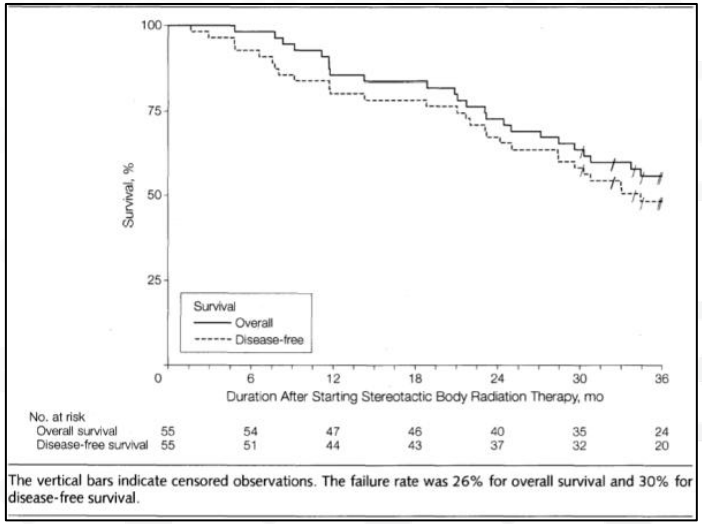
- Surgery has the best oncologic outcome for Stage I NSCLC.
  - Lobectomy is the treatment of choice in medically fit patients who can tolerate lobectomy
  - Exceptions:
    - Patients who are poor candidates for lobectomy because of medical limitations should be considered for sublobar resection or SBRT
    - Patients with predominantly ground glass opacities < 2 cm may have equivalent outcome with sublobar resection

4. Evidence supporting SBRT for treatment of early stage lung cancer

Timmerman R et al. JAMA 2010;303:1070-1076.

RTOG 0236. (Phase II) 55 patients with early NSCLC ≤ 5 cm, unable to undergo surgical resection because of medical comorbidities.

- Rate of grade 3-4 pneumonitis 16%
- 3 year follow up
  - Rate of control at primary site 97.6%
  - Rate of local-regional control 87.2%
  - Rate of disseminated recurrence 22.1%
    - T1: 14.7%
    - T2: 47.0%
  - 26/55 (47%) died
    - 10/55 (18%) died from lung cancer



The vertical bars indicate censored observations. The failure rate was 26% for overall survival and 30% for disease-free survival.

4. Evidence supporting SBRT for treatment of early stage lung cancer

Videtic GMM et al. Prac Radiat Oncol 2017; 7:295-301.

SBRT vs surgery in operable patients declining surgery

- Overall survival rates 76-86% at 3 years

Table 1: Series reporting results for SBRT for operable patients

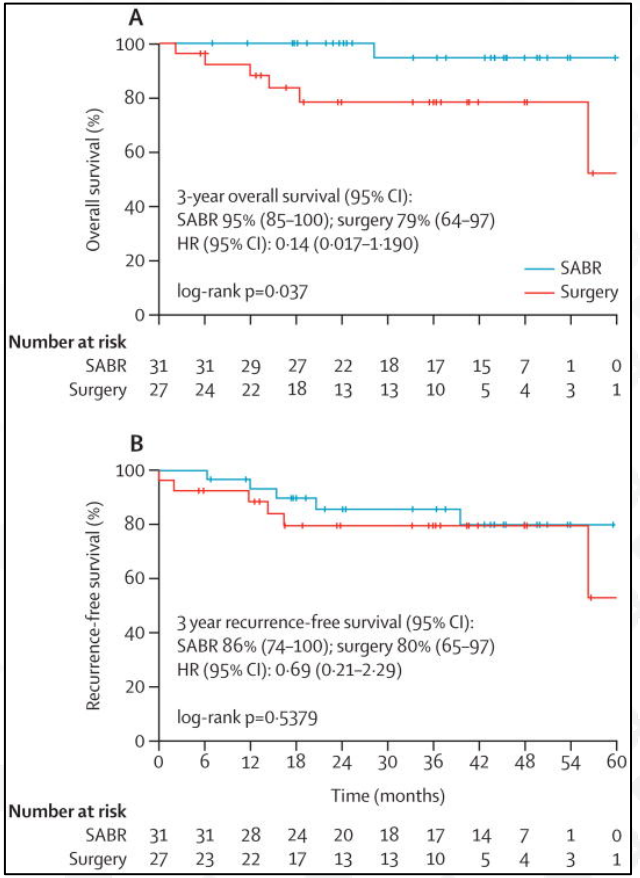
Author	N	Dose	Median F/U (mos)	OS
Uematsu, 2001[51]	29	Most commonly 50-60 Gy in 5-10 fx	36	86% (3-year)
Onishi, 2011[54]	87	45-72.5 Gy in 3-10 fx	55	72% (IA), 63.2% (IB) (5-year)
Lagerwaard, 2012[177]	177	60 Gy in 3-8 fx	31.5	84.7% (3-year)
Timmerman, 2013[53]	26	54 Gy in 3 fx	25.4	84.4% (2-year)
Chang, 2015[55]	31	50-60 Gy in 3-5 fx	40.2	95% (3-year)
Nagata, 2015[56]	64	48 Gy in 4 fx	67	76.5% (3-year)
Shibamoto, 2015[57]	60	44-52 Gy in 4 fx	52.5	74% (5-year)
Komiyama, 2015[58]	661	32-79 Gy in 4-15 fx	35	79% (3-year)

AE, adverse event; F/U, follow-up; N/R, not reported; OS, overall survival; SBRT, stereotactic body radiation therapy

4. Evidence supporting SBRT for treatment of early stage lung cancer

Chang JY et al. Lancet Oncol 2015; 16:630-637

- Several RCTs tried to compare SBRT and surgical resection; all closed because of poor accrual.
- STARS and ROSEL trial data combined
- Eligibility: T1-2aN0M0, operable NSCLC. SBRT vs lobectomy with mediastinal node dissection.
- Results: 58 patients (31 SBRT, 27 lobectomy)
  - Median f/u 40.2 mo (SBRT), 35.4 months (surgery)
  - 6 deaths in the surgery group died vs 1 in SABR
- Conclusions
  - SBRT better tolerated and with better survival
  - SBRT and lobectomy equally effective
  - Lower survival after surgery may be related to comorbidities related to decrease of lung function
  - Limitation: small sample size



4. Evidence supporting SBRT for treatment of early stage lung cancer

Conclusions:

- SBRT is well tolerated with acceptable rate of pneumonitis
- Single arm, nonrandomized studies and 1 pooled randomized study suggest 3-year survival is at least equivalent to surgery
- 3 year local control is excellent
- Failure of therapy tends to be with distance recurrence

- In patients unable medically to tolerate lobectomy or sublobar resection, SBRT is a reasonable alternative
- In patients highly averse to surgery, SBRT is a reasonable alternative, with the clear understanding that there is no evidence that long term outcomes are equivalent to surgery

4. Evidence supporting SBRT for treatment of early stage lung cancer

Ongoing RCTs

- SABR-TOOTH – SBRT vs surgery in higher risk surgical patients with peripheral Stage 1 NSCLC (UK)
- RTOG 3502 – SBRT vs lobectomy in patients with operable Stage I NSCLC (USA)
- STABLE-MATES – SBRT vs sublobar resection in high risk patients with Stage I NSCLC (USA)
- VALOR – SBRT vs surgery (lobectomy or anatomic resection) in operable stage I NSCLC (USA – Veterans Affairs)

Case

PFT:

Spirometry

P

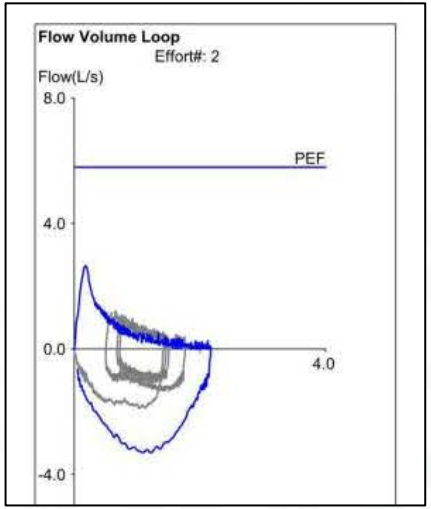
	PRED	L.L.N.	PRE	PRE % PRED
FVC	2.94	> 2.30	2.18	74
FEV1	2.26	> 1.72	0.94	41
VCmax	2.94	> 2.30	2.18	74
FEV1/FVC	78	> 68	43	55
FEV1/VCmax	78	> 68	43	55
Peak Flow	5.79	> 4.21	2.65	46
FEF25-75%	2.12	> 0.98	0.28	13
FEF50/FIF50	85	68 - 102	8	10
TET			11.10	
MVV	83.96	83.96		

Helium Dilution Lung Volumes

	PRED	L.L.N.	Pre	% PRED
TLC	4.75	> 3.54	4.69	99
FRC	2.56	1.73 - 3.38	2.91	114
RV	1.81	1.24 - 2.39	2.54	140
RV/TLC	38	38	54	141
VC	2.94	> 2.30	2.16	73

Diffusing Capacity

	PRED	L.L.N.	PRE	% PRED
Dsb	21.35	14.28 - 28.43	10.69	50
DsbHb	21.35	14.28 - 28.43	10.04	47
VAsb	4.63	4.63	3.87	84
D/VAsb	4.61	4.61	2.76	60
D/VAsbHb	4.61	4.61	2.59	56



74 year old woman with recent CABG, LVEF 35%, and severe obstruction to airflow with diffusion abnormality. Chest CT: 1.5 cm spiculated, solid nodule in the lingula, documented to be squamous cell carcinoma. Clinical stage T1bN0M0, Stage IA2

Case:

Question 1

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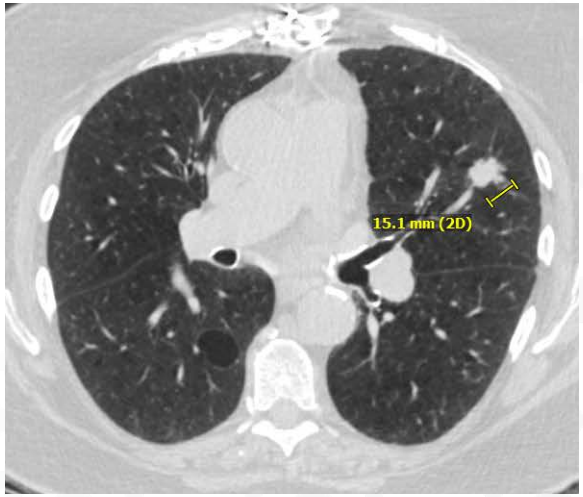
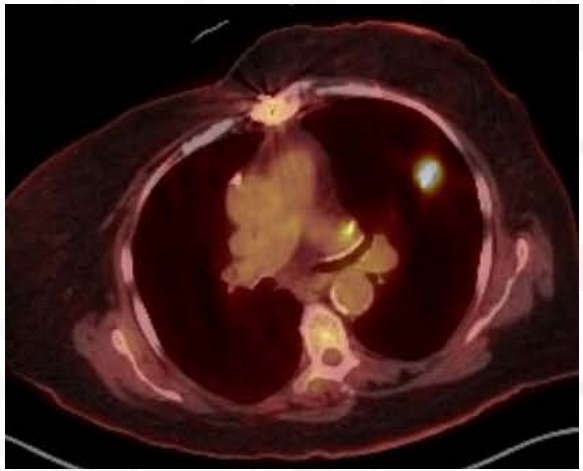
What would you recommend to this patient?

A. Left upper lobectomy
B. Lingular resection (segmentectomy)
C. Stereotactic Body Radiotherapy





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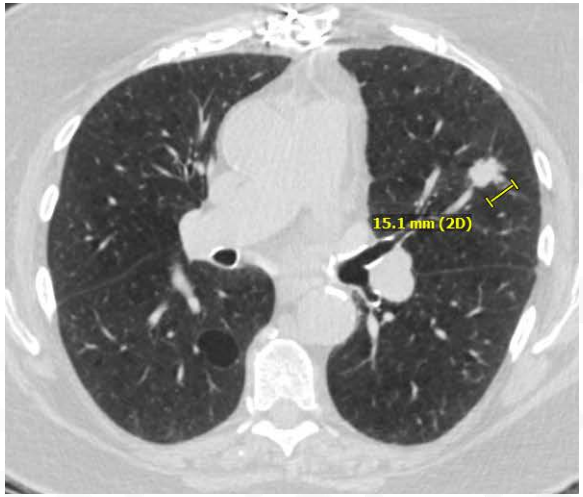

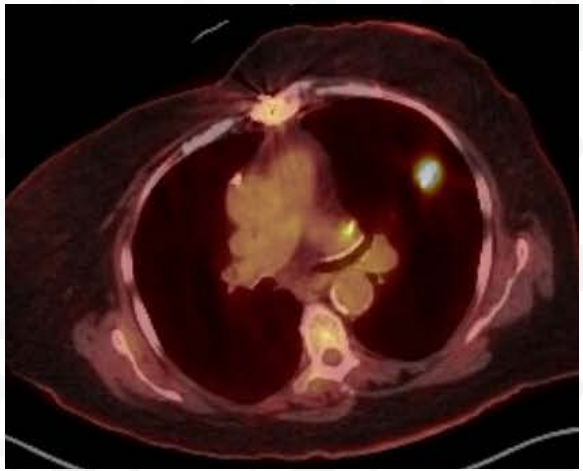

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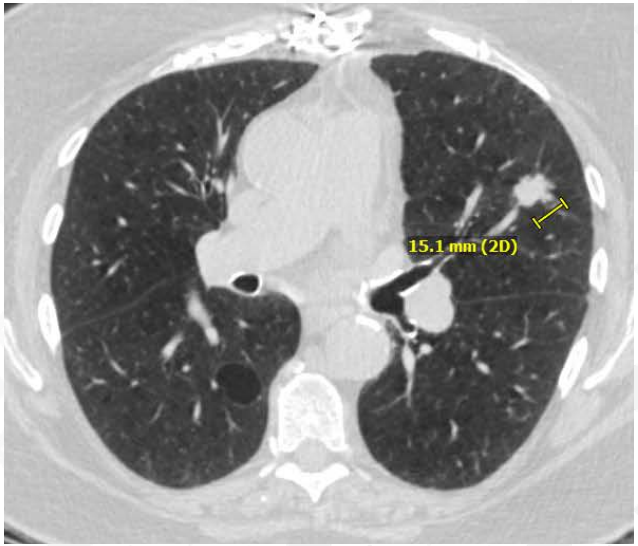
5. Is histologic confirmation of malignancy necessary in order to treat with SBRT?

74 yo woman, former 50 pack-year smoker, with severe COPD, found incidentally to have a 15 mm, solid, spiculated nodule in the left upper lobe.

Question 2:

- What if we did not have biopsy confirmation of cancer? What is the likelihood this nodule is lung cancer?
  - A. 15%
  - B. 16-25%
  - C. 16 – 50%
  - D. >50%



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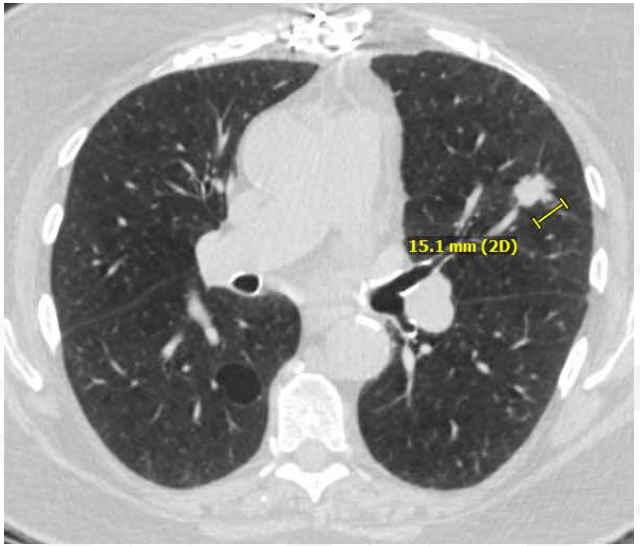

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Mayo Clinic lung nodule risk model: *Swenson SJ et al. Arch Intern Med 1997; 157:849*

Solitary Pulmonary Nodule Malignancy Risk (Mayo Clinic model) Share

Input:

Age: 74 yr

Smoker: Current or former (1) / Never smoker (0)

Cancer: Extrathoracic cancer more than 5 years prior (1) / None (0)

Nodule Diameter: 15 mm

Spiculation: Yes (1) / No (0)

Upper Lobe: Yes (1) / No (0)

Results:

X 0.59

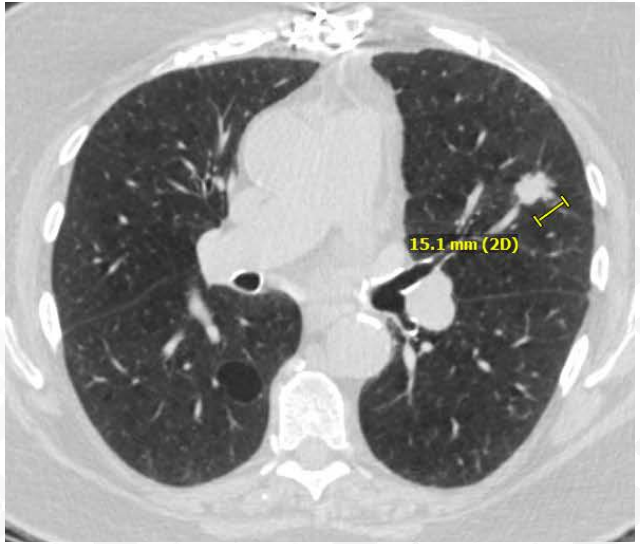
Malig Probability 64.41 %

Decimal Precision: 2

Formula | Notes | References

$X = (0.0391 * Age) + (0.7917 * Smoker) + (1.3388 * Cancer) + (0.1274 * NoduleDiameter) + (1.0407 * Spiculation) + (0.7838 * UpperLobe) - 6.8272$

$MaligProbability = 100 * e^{(X)} / (1 + e^{(X)})$



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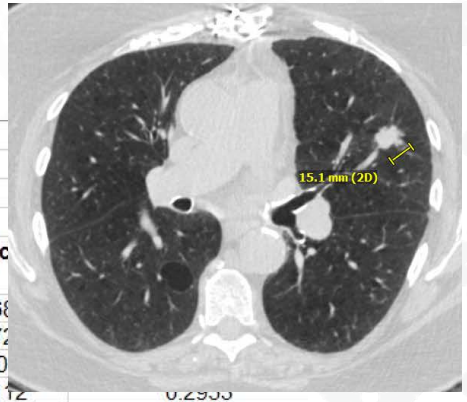
Brock University model: *McWilliams A et al. NEJM 2013: 369:10*



Probability calculator estimating a pulmonary nodule being lung cancer.* Version Tammemagi V1-2SEP13

Model: Full with spiculation.

Instructions: In column B enter the values for the variable listed in column A. Ignore columns C through F.

A **Variables**	B **Enter Values**	C **Transformation**	D **Transfomed value**	E **Beta coeffic**	
Age (years)	74	-62	12	0.02866	
Sex (Male=0, Female=1)	1			0.60107	
Family history of lung cancer (No=0, Yes=1)	0			0.29610	
Emphysema (No=0, Yes=1)	1			0.29531	
Nodule size (in millimeters)	15.0		-0.7646	-5.385484	4.1180
Nodule type (choose only one from this category)					
Groundglass/nonsolid (No=0, Yes=1)	0			-0.1276173	0.0000
Semisolid/part-solid (No=0, Yes=1)	0			0.3769578	0.0000
Solid [referent group](No=0, Yes=1)	1			0	0.0000
Upper lobe location (No=0, Yes=1)	1			0.6581383	0.6581
Spiculation (No=0, Yes=1)	1			0.7729335	0.7729
Nodule count (number of nodules detected on screen)	1	-4	-3	-0.0824156	0.2472
Model constant (do not change)					-6.78917
				xb =	0.247525
			Probability that nodule is lung cancer ** =		**0.562**

* Reference: McWilliams A, Tammemagi M, Mayo J

5. Is histologic confirmation of malignancy necessary in order to treat with SBRT?

- Most clinical trials have required confirmation of malignancy
  - Concern that inclusion of benign nodules will bias results favorably (ie. improved survival because the nodule wasn't actually cancer)
  - We don't want to radiate tuberculosis!
- Patients medically unfit for surgery may be poor candidates for any biopsy
  - Risks of biopsy: pneumothorax, hemoptysis, respiratory decompensation
- Presumption of lung cancer should be based on:
  - Patient-specific risks: smoking history, COPD, history of prior lung cancer
  - Convincing evidence of malignancy: size, growth over time; spiculation/lack of calcification; FDG avidity, location
  - Consideration of regional environmental factors
  - Tumor board multidisciplinary discussion

5. Is histologic confirmation of malignancy necessary in order to treat with SBRT?

Videtic GMM et al. Stereotactic Body Radiation Therapy for Early Stage Non-Small Cell Lung Cancer: an ASTRO Evidence-Based Guideline. Prac Radiat Oncol 2017; 7:295-301.

Statement KQ2D: Whenever possible, obtain a biopsy prior to treatment with SBRT to confirm a histologic diagnosis of a malignant lung nodule.
(Recommendation: Strong; Quality of Evidence: High)

Statement KQ2E: SBRT can be delivered in patients who refuse a biopsy, have undergone non-diagnostic biopsy, or who are thought to be at prohibitive risk of biopsy. Prior to SBRT in patients lacking tissue confirmation of malignancy, patients are recommended to be discussed in a multidisciplinary manner with a consensus that the lesion is radiographically and clinically consistent with a malignant lung lesion based on tumor, patient, and environmental factors.
(Recommendation: Strong; Quality of evidence: Moderate)

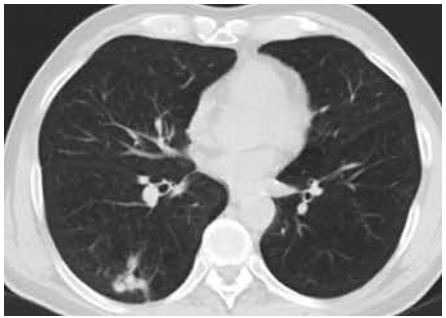
5. Is histologic confirmation of malignancy necessary in order to treat with SBRT?

How much evaluation should be done to prove that the cancer is truly Stage I?
What about the hilar and mediastinal lymph nodes?

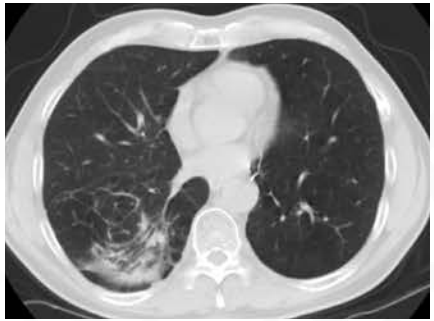
- Surgery will always yield a diagnosis. Surgery should always give information about the hilar and mediastinal lymph nodes, for accurate pathologic staging.
- Should we always do invasive mediastinal staging for Stage 1 NSCLC to be treated with SBRT?
  - *Gould MK et al. Ann Intern Med 2003;139:879:* When both CT and PET are negative and pretest probability of mediastinal lymph node metastasis is 35%, post-test probability of mediastinal metastasis is approximately 9%
  - *Silvestri G et al. Chest 2013;143:211S-250S.* Recommendation 4.4.8.1. For patients with a peripheral clinical stage IA tumor (negative nodal involvement by CT and PET), it is suggested that invasive preoperative evaluation of the mediastinal nodes is not required (Grade 2B) .

6. What are the potential toxicities of SBRT?

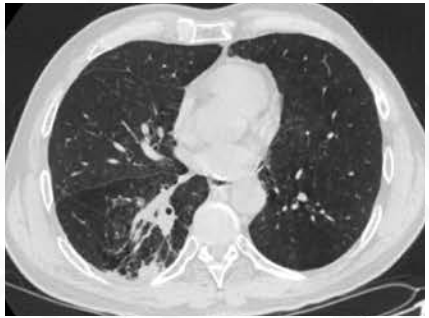
- Radiation injury and scarring is the normal response
- Area of SBRT will remain FDG+ for months – years
- Once scarred, a focal increase in a discrete area of the radiated site should trigger concern for recurrence (though local recurrence is unusual)



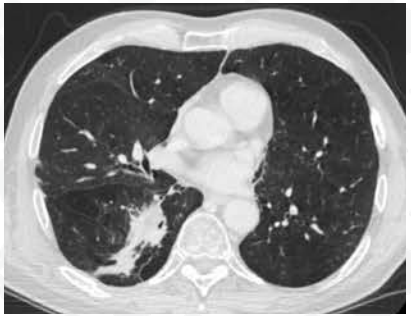
August 2017 pre-SBRT



March 2018



September 2018



March 2019

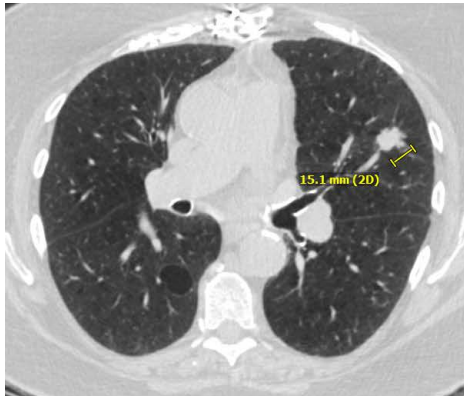
6. What are the potential toxicities of SBRT?

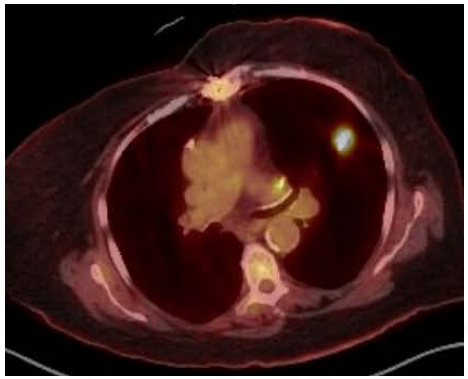
- Pulmonary parenchymal damage
  - RTOG 0236: grade 3-4 pulmonary complications occurred in 16% of patients, more commonly PFT changes than symptoms
  - Injury to adjacent lung – typically limited
  - Patients with interstitial lung disease may be at higher risk of radiation-induced injury
- Central tumors (within 2 cm of major tracheobronchial tree) associated with higher toxicity
  - Airway obstruction, hemorrhage
  - Esophageal or pericardial inflammation/injury
- Damage to structures of the chest wall (10-15% of peripheral tumors)
  - Neuropathic pain, rib fractures, skin ulcers, brachial plexopathy

7. What are the appropriate outcomes measures?

- Patients who undergo SBRT by definition are not good surgical candidates because of underlying medical limitations (poor pulmonary function, medical comorbidities, age).
  - Life expectancy often limited by factors other than the cancer
  - Survival as the primary outcome may reflect other factors
- Potential outcomes measures
  - Survival
  - Disease control at the primary site
  - Local-regional recurrence
  - Distant recurrence
  - Toxicities
  - Quality of life

Pre-treatment

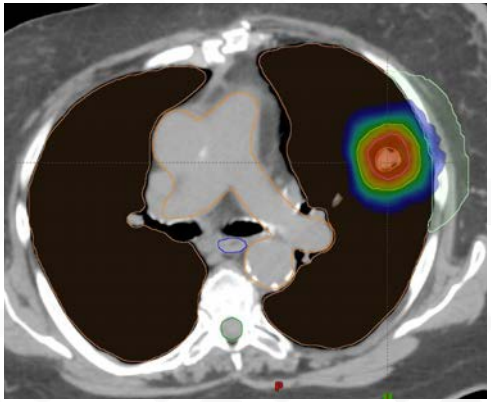


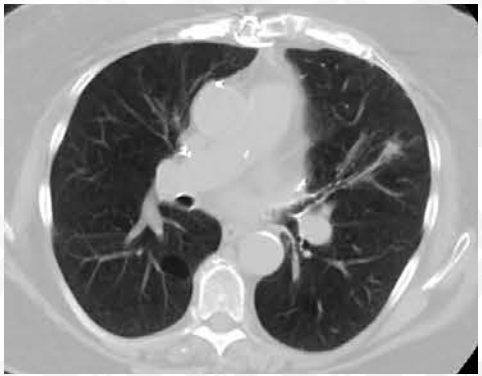


Case:

74 year old woman with recent CABG, LVEF 35%, and severe COPD with diffusion abnormality. Chest CT: 1.5 cm squamous cell carcinoma in the lingula. Clinical stage T1bN0M0, Stage IA2. Based on her severe COPD and recent cardiac issues with low LVEF, the recommendation of the tumor board was to treat the cancer with SBRT, which was also the patient's preference. She tolerated treatment without any complications and is doing well.

3 months post-treatment





Current recommendations for the use of SBRT for early stage lung cancer

American College of Chest Physicians: Recommendations for Treatment of Stage I and II Non-small Cell Lung Cancer. Chest 2013; 143:278S-313S

- For patients with a clinical stage I NSCLC who cannot tolerate a lobectomy or segmentectomy, stereotactic body radiation therapy (SBRT) and surgical wedge resection are suggested over no therapy (Grade 2C).

Videtic GMM et al. Stereotactic Body Radiation Therapy for Early Stage Non-Small Cell Lung Cancer: an ASTRO Evidence-Based Guideline. Prac Radiat Oncol 2017; 7:295-301.

- For patients with "high operative risk" (i.e., those who cannot tolerate lobectomy, but are candidates for sublobar resection) stage I NSCLC, discussions about SBRT as a potential alternative to surgery are encouraged. Patients should be informed that while SBRT may have decreased risks from treatment in the short term, the longer-term outcomes >3 years are not well-established. *(Recommendation strength: Conditional [risk/benefit balance even]; Quality of evidence: Moderate)*

Question 3.

Which of the following tumors would be not be suitable for treatment with SBRT?

A. T2a (3.2 cm) N0M0 peripheral right lower lobe adenocarcinoma
B. T1a (0.9 cm) N1M0 peripheral left lower lobe squamous cell carcinoma
C. T1b (1.3 cm) N0M0 right upper lobe large cell carcinoma abutting the mediastinum
D. T2b (5.0 cm) N0M0 peripheral left upper lobe squamous cell carcinoma

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Stereotactic Body Radiotherapy for Early Stage Lung Cancer

Summary

- For patients with early stage NSCLC (Stage I,II (N0) and medically fit for surgery, lobectomy is the treatment of choice
- For patients medically unfit or unwilling to undergo surgical resection for early stage NSCLC, SBRT is a reasonable alternative
- 3-year outcomes with SBRT appear comparable to sublobar resection; 5-year outcomes with SBRT are not well defined.
- Whenever possible, a diagnosis of lung cancer should be defined before SBRT is given. In patients who are unable or unwilling to undergo biopsy, a decision about whether or not to give SBRT without a diagnosis should be based on the probability of lung cancer and consideration of potential SBRT-related toxicities.