

Early Stage Lung Cancer:

Recent advances from screening to treatment

Alexander Geng MD

Medical Director

San Francisco CyberKnife Radiosurgery Center

St Francis Memorial Hospital

- ▶ Topics
 - ▶ Stage I Non-Small Cell Lung Cancer
 - ▶ Lung cancer screening
 - ▶ Stereotactic Ablative Radiotherapy vs. Surgery
 - ▶ Molecular targeted therapy
- ▶ Topics not covered
 - ▶ Locally advanced and metastatic lung cancer (Stage III/IV)
 - ▶ Small cell lung cancer

INTRODUCTION

- ▶ National data:
 - ▶ 230,000 cases a year in the US
 - ▶ 160,000 deaths annually
 - ▶ Mortality greater than breast, colon and prostate cancer combined
 - ▶ Median Age 70
 - ▶ 1/13 for men and 1/16 for women lifetime risk
- ▶ Historical Outcome
 - ▶ **Stage I-II** 5 year OS **15.9%** (Goldstraw J Thora Onc 2007)

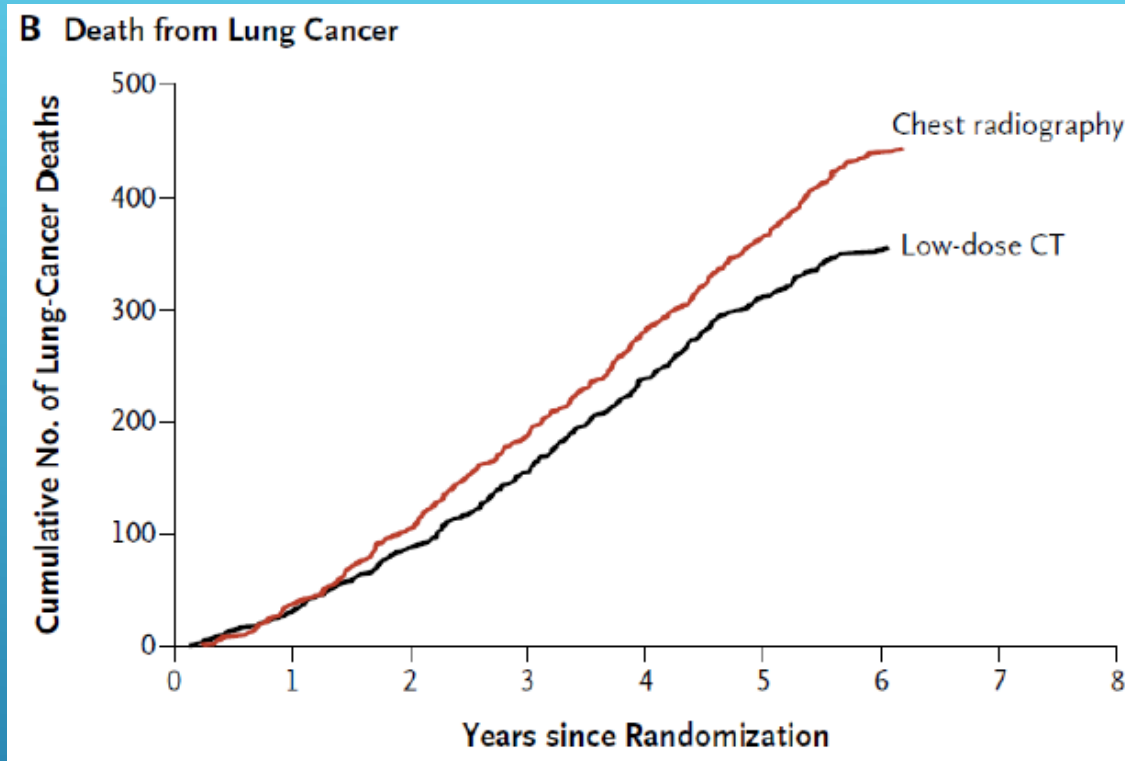
PREVALENCE AND RELEVANCE

- ▶ Histology:
 - ▶ Adenocarcinoma on the rise 50%
 - ▶ Squamous cell cancer declining 35%
 - ▶ Large cell 15%
- ▶ Risk factors:
 - ▶ Tobacco: 20x risk in current vs. 9x risk in former smokers
 - ▶ Radon
 - ▶ Asbestos
 - ▶ Organics and metals, usually occupational
- ▶ Stage on presentation
 - ▶ Historically 1/3 presents with metastatic disease
 - ▶ 40-50% with Stage II and III disease
 - ▶ Stage I is most curable but also disproportionately small

LUNG CANCER SCREENING

- ▶ Chest X-Ray screening:
 - ▶ 6 RCT trials failed to show a survival benefit
- ▶ CT screening
 - ▶ National Lung Cancer Screening Trial (NEJM 2011): **prospective RCT**
 - ▶ Annual low dose CT vs. CXR for 3 years in high risk patients (53,000)
 - ▶ 55-79 years of age
 - ▶ 30 pack year or more
 - ▶ If former smoker, quit time within 15 years
 - ▶ Relative risk of Lung Cancer Death decreased by 20%
 - ▶ Relative risk of all cause mortality decrease of 6.7%
- ▶ **The USPSTF issued a recommendation for CT screening in high risk populations**
- ▶ 7 RCT trials going in Europe: Only Nelson trial is large enough to show a mortality benefit

LUNG CANCER SCREENING: CONTROVERSIES



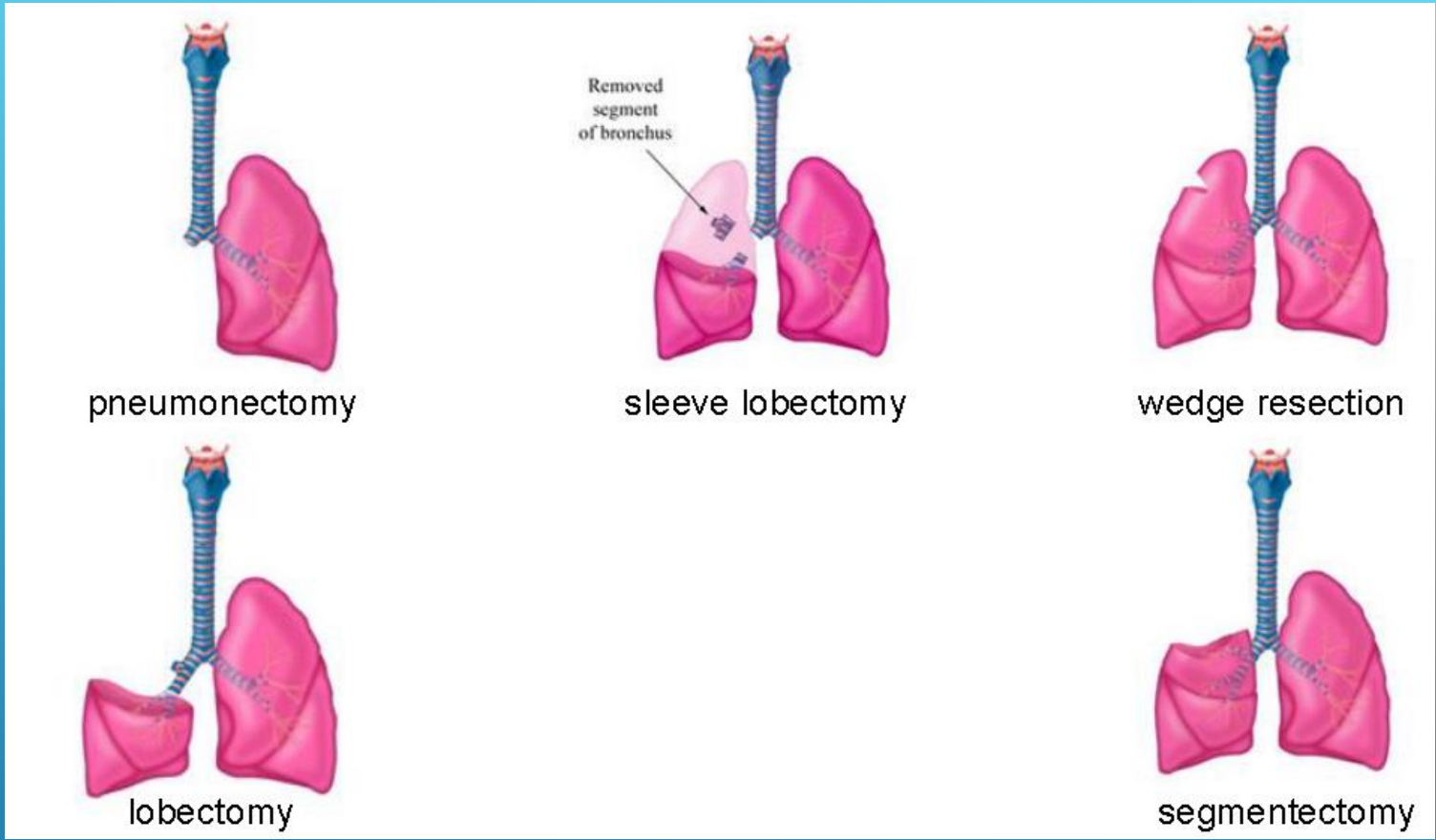
SCREENING: RESULTS FROM NLCST

- ▶ Expected rise of lung cancer presentation in Stage I and II with screening
- ▶ Smoking is on the decline in general in the bay area.
 - ▶ Significant percentage of current and former smokers in an older population
- ▶ In addition, adenoCA, least correlated with smoking is on the rise
- ▶ Our hospital is capable of low dose screening CT
- ▶ Screening program is in place

SCREENING AT ST FRANCIS

- ▶ Historical Gold Standard: **Lobectomy (94% local control/LC)**
 - ▶ **5yr OS 70-80%** (Martini J Thora Cardiovasc 1999)
 - ▶ **Medically fit and younger** population
 - ▶ **5-25% upstaged** with mediastinal LND and excluded
 - ▶ Alternative: wedge resection and pneumonectomy
 - ▶ Wedge LC is 82%
- ▶ Can **elderly and medically inoperable** patients be observed?
 - ▶ Median survival ~1 year
 - ▶ Cancer specific death quite high
 - ▶ Stereotactic Ablative Radiotherapy (SABR)'s use originates here

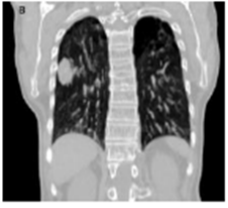
STAGE I NSCLC - TREATMENT



SURGICAL TECHNIQUES

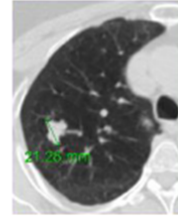
- ▶ SABR is an advanced technique of radiotherapy
 - ▶ Ablative dose of x-ray to tumors in 1-5 treatments
 - ▶ Conventional RT 30-35 treatments of small doses of x-ray
 - ▶ High precision and accuracy of less than 1mm
 - ▶ Conventional RT's margin of error is up to 5 to 10 times bigger
 - ▶ CyberKnife is one of the platforms for Lung SABR
 - ▶ Outpatient non-invasive treatment for 1-1.5 hours a day for a few days
 - ▶ Pain free; no local or general anesthesia
 - ▶ Normal breathing throughout treatment delivery tracked by the robot
- ▶ SABR originally emerged as a treatment for
 - ▶ Medically inoperable/elderly patients
 - ▶ Patients who refuse surgery

STAGE I LUNG CANCER: WHAT IS STEREOTACTIC ABLATIVE RADIO THERAPY (SABR)?



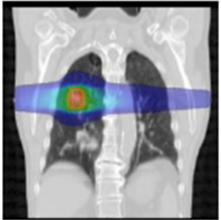
Accounting for Motion

- 4D Planning



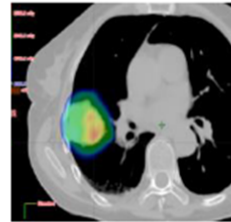
Small tumour volumes

- Small margins



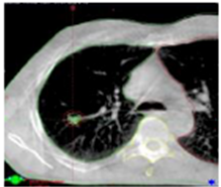
Many Beam Directions

- 7-11 Beams / Arc Therapy



Steep dose gradients

- Inhomogeneous target dose



Accurate Targeting

- CBCT pre-RT



High dose per fraction

- Short total treatment duration

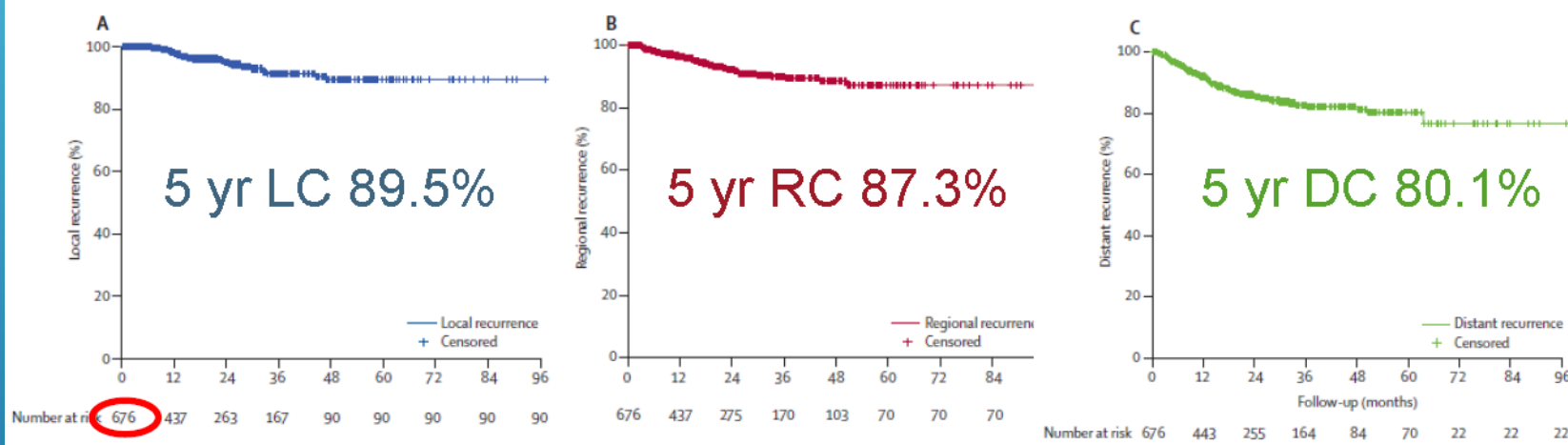
SABR CHARACTERISTICS

- ▶ RTOG 0236: a phase II prospective multicenter trial of SABR for early stage lung cancer
 - ▶ 3 yr LC of 97%, 5yr LC of 93%: same as surgery
 - ▶ 5yr OS 40%: much lower than surgery? And Why?
 - ▶ Age, pulmonary function, comorbidity: non-cancer deaths dominate
 - ▶ 5-25% upstaging at surgery vs. 0% with SABR
 - ▶ Propensity score matched analysis shows equivalent OS as surgery
 - ▶ 5yr distant metastatic rate 15-25%: same as surgery
 - ▶ No severe late toxicity or side effects

STAGE I LUNG CANCER: OUTCOME OF SABR

➤ Patterns of disease recurrence after stereotactic ablative radiotherapy for early stage non-small-cell lung cancer: a retrospective analysis

Sashendra Senthil, Frank J Lagerwaard, Cornelis J A Haasbeek, Ben J Slotman, Suresh Senan



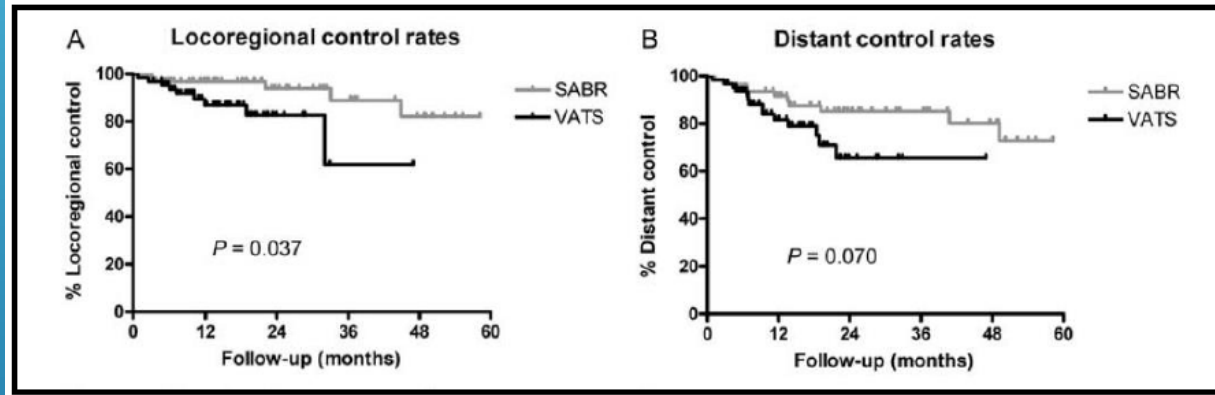
SABR FOR STAGE I LUNG CANCER

- ▶ SABR Outcome is equivalent to surgery as seen in medically inoperable
- ▶ What is SABR's outcome with operable patients
 - ▶ More than 4 prospective trials
 - ▶ Most closed early due to difficulty in patient accrual
 - ▶ Pooled analysis again shows excellent outcome

STAGE I LUNG CANCER: SABR VS. SURGERY

Stage I-II non-small-cell lung cancer treated using either stereotactic ablative radiotherapy (SABR) or lobectomy by video-assisted thoracoscopic surgery (VATS): outcomes of a propensity score-matched analysis

N. E. Versteegen^{1*}, J. W. A. Oosterhuis², D. A. Palma³, G. Rodrigues³, F. J. Lagerwaard¹, A. van der Elst⁴, R. Mollema⁵, W. F. van Tets⁶, A. Warner³, J. J. A. Joosten⁷, M. I. Amir⁸, C. J. A. Haasbeek¹, E. F. Smit⁹, B. J. Slotman¹ & S. Senan¹



SABR VS. SURGERY: LOCOREGIONAL CONTROL

SEER-Medicare: SABR vs. other techniques

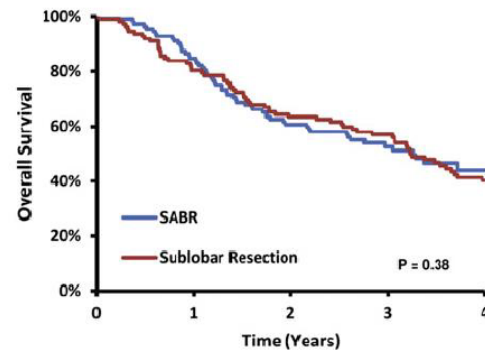
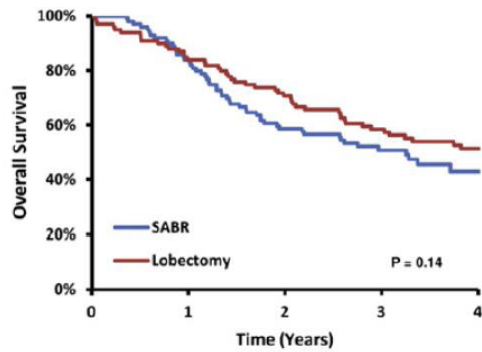


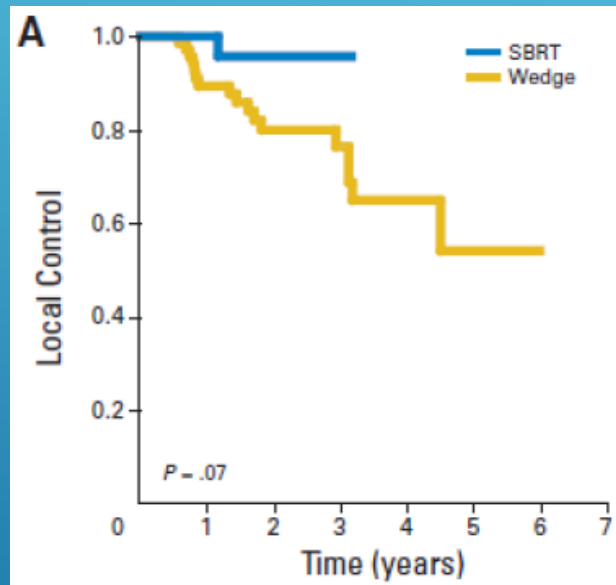
Table 4 Proportional hazards models for propensity-matched pairs of SABR cases and non-SABR controls

Comparison	Overall survival			Lung cancer-specific survival		
	HR	95% CI	$P > \chi^2$	HR	95% CI	$P > \chi^2$
Lobectomy vs SABR*	0.71	(0.45-1.12)	.14	1.00	(0.40-2.52)	>.99
Sublobar resection vs SABR	0.82	(0.53-1.27)	.38	2.14	(0.87-5.26)	.10
Conventional XRT vs SABR	1.97	(1.31-2.96)	.001	1.56	(0.67-3.59)	.30
Adj for age and grade	1.96	(1.28-3.00)	.002	1.59	(0.67-3.80)	.30
Observation vs SABR	2.10	(1.37-3.08)	<.001	3.88	(1.78-8.43)	<.001
Adj for tumor size	2.03	(1.34-3.07)	<.001	3.90	(1.76-8.61)	<.001

Abbreviations: adj = adjustment; CI = confidence interval; HR = hazard ratio; SABR = stereotactic ablative radiation; XRT = radiation therapy.
 * SABR is the referent group for all comparisons.

SABR VS. SURGERY: SURVIVAL OUTCOME BY PROPENSITY SCORE

- ▶ SABR has been shown to be equivalent to a lobectomy
- ▶ Wedge resection is inferior to lobectomy
- ▶ Similarly, data show wedge resection is inferior to SABR

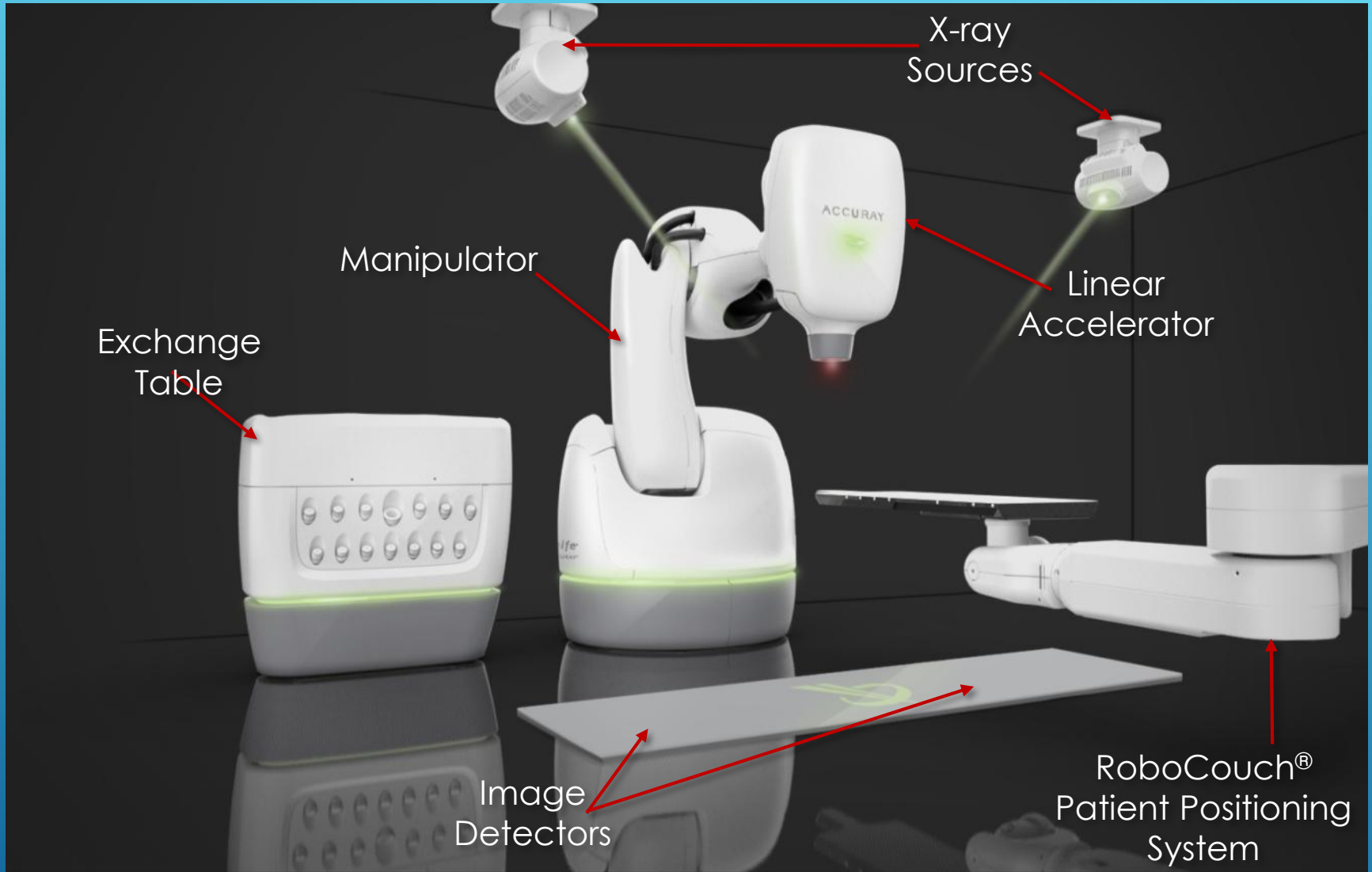


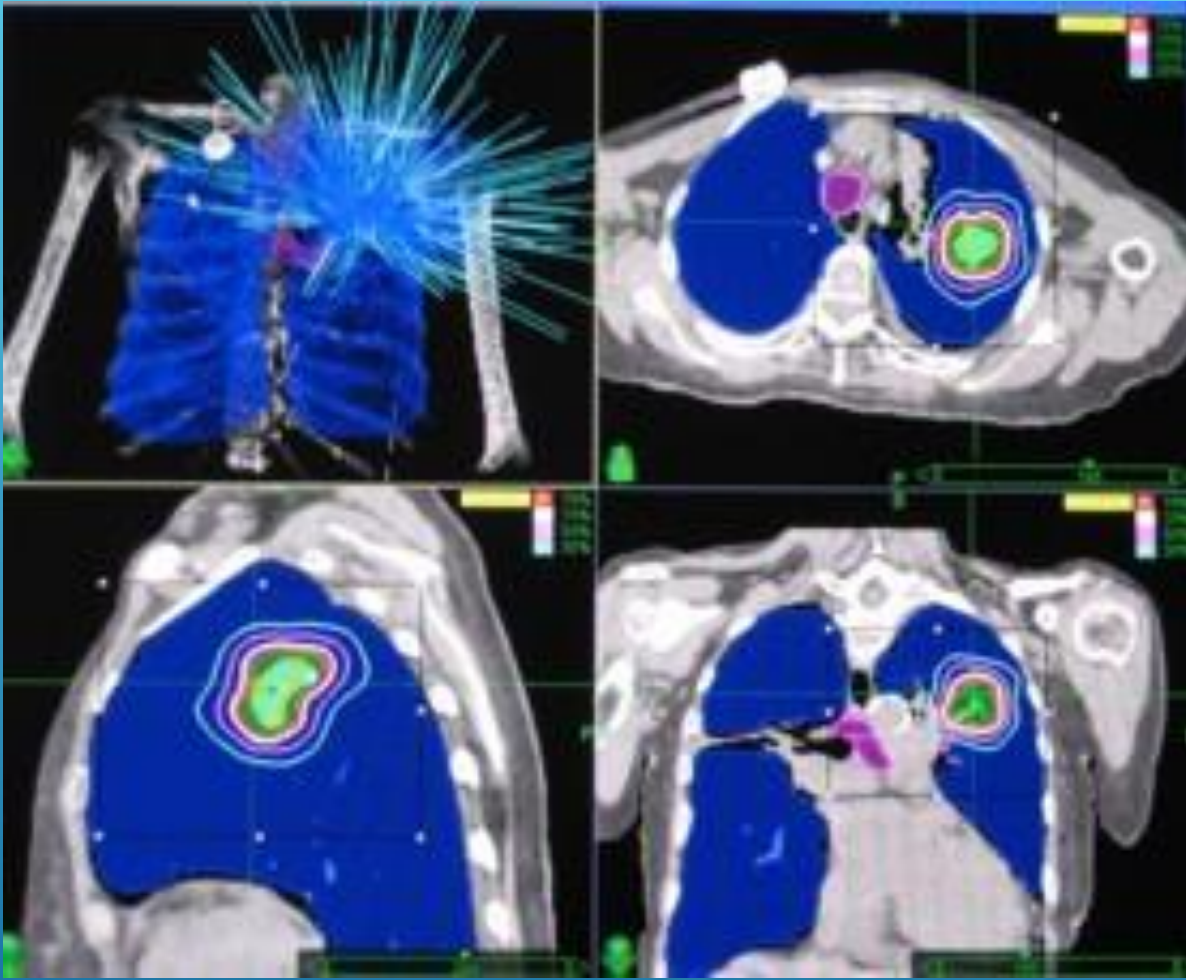
SABR VS. WEDGE RESECTION





CYBERKNIFE SABR OPERATION





CYBERKNIFE SABR TREATMENT PLAN

- ▶ Non-small cell lung cancer genotypes
 - ▶ EGFR mutation: 15% in US, 62% in Asian populations
 - ▶ TKI's: erlotinib, gefitinib and afatinib
 - ▶ ALK: 4% in US, higher in younger and non-smoking populations
 - ▶ TKI's: crizotinib and ceritinib
 - ▶ These 2 mutations and their treatment led to survival increase while reducing toxicity associated with cytotoxic chemotherapy

ADVANCES IN TARGETED AGENTS



- ▶ Other genotypes:
 - ▶ RAS oncogene family: 20-40% in US
 - ▶ mTOR inhibitors, MEK inhibitors under investigation
 - ▶ ROS1 translocation
 - ▶ HER2 (EGFR family protein kinase)
 - ▶ BRAF mutation
 - ▶ MET TKR
 - ▶ RET translocation
 - ▶ PTEN, AKT mutations
 - ▶ Others...

ADVANCES IN TARGETED AGENTS



- ▶ A dichotomy of advances in lung cancer management
 - ▶ SABR pushes the boundary in early stage lung cancer
 - ▶ Targeted agents, advanced or metastatic lung cancer
- ▶ Oligometastatic state is where these 2 modalities overlap
 - ▶ Phase I/II reports and retrospective studies illustrate efficacy of combining targeted agents with SABR
 - ▶ Results of long disease free interval and long term survival
 - ▶ Active area of investigation
- ▶ Stage IV is no longer a death sentence by default

TARGETED AGENTS AND SABR: A NEW HOPE FOR METASTATIC PATIENTS

▶ Questions?

THANK YOU FOR YOUR ATTENTION

A decorative graphic consisting of several parallel white lines of varying lengths, slanted upwards from left to right, located in the bottom right corner of the slide.