# OLIGOMETASTATIC & EARLY-STAGE LUNG CANCER - UPCOMING TRENDS AND OPPORTUNITIES

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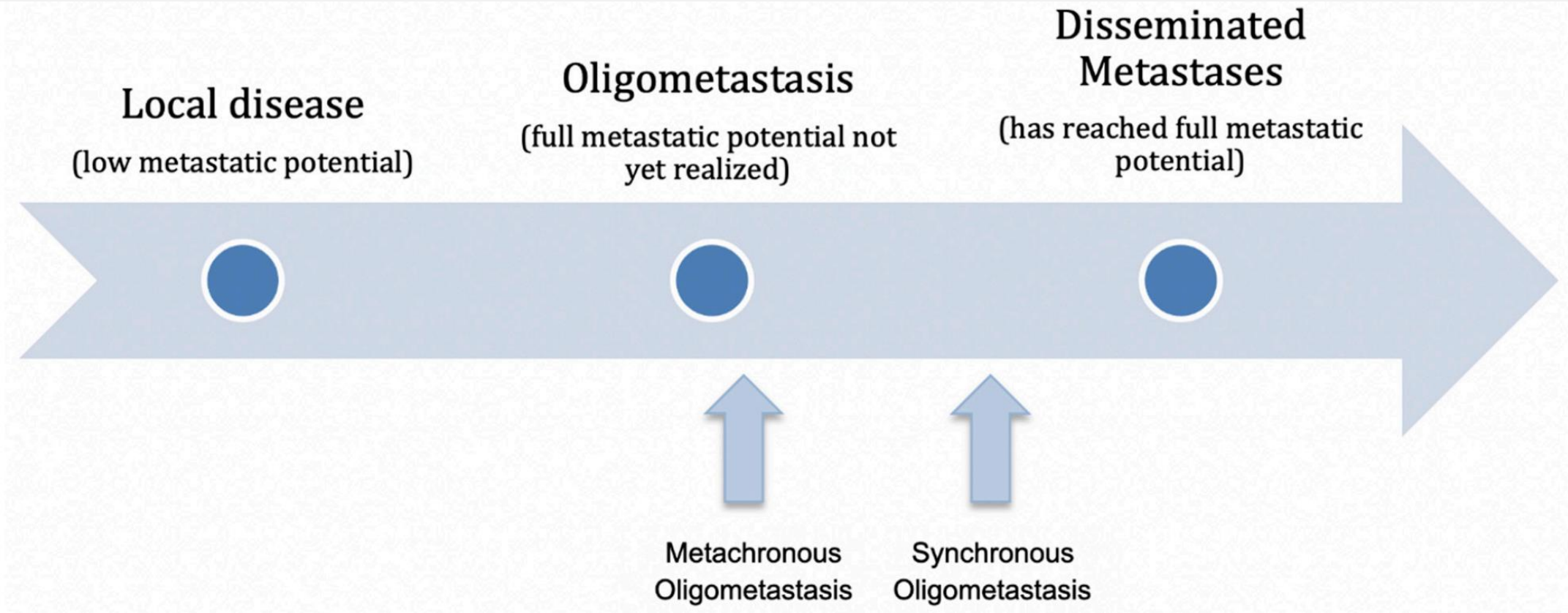
# Oligometastatic paradigm

Alternate version to Halstedian & Systemic disease (Fisher and others) hypotheses




Hellman, et al JCO 1995

# WHY IMPORTANT ?

- Imaging with high sensitivity during staging
- Frequent imaging post treatment

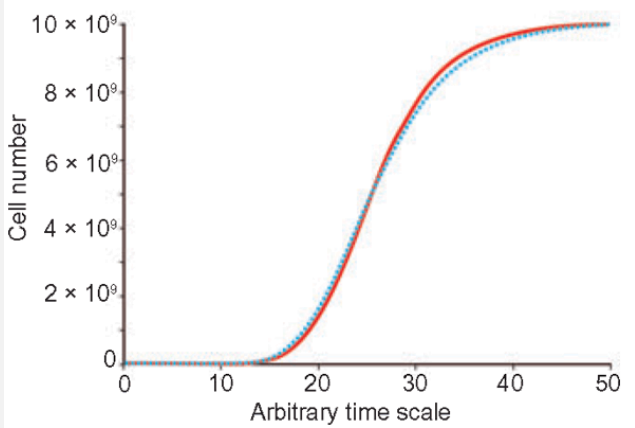
- 20% of NSCLC pts on FDG PET scan show occult oligometastasis
- Improvement of systemic control with targeted therapies/immunotherapy
- Results across cancers show improved outcomes with aggressive local therapies

# WHY LOCAL THERAPY FOR OLIGOMETASTATIC DISEASE

Local control- Important when results in measurable benefit in overall survival.

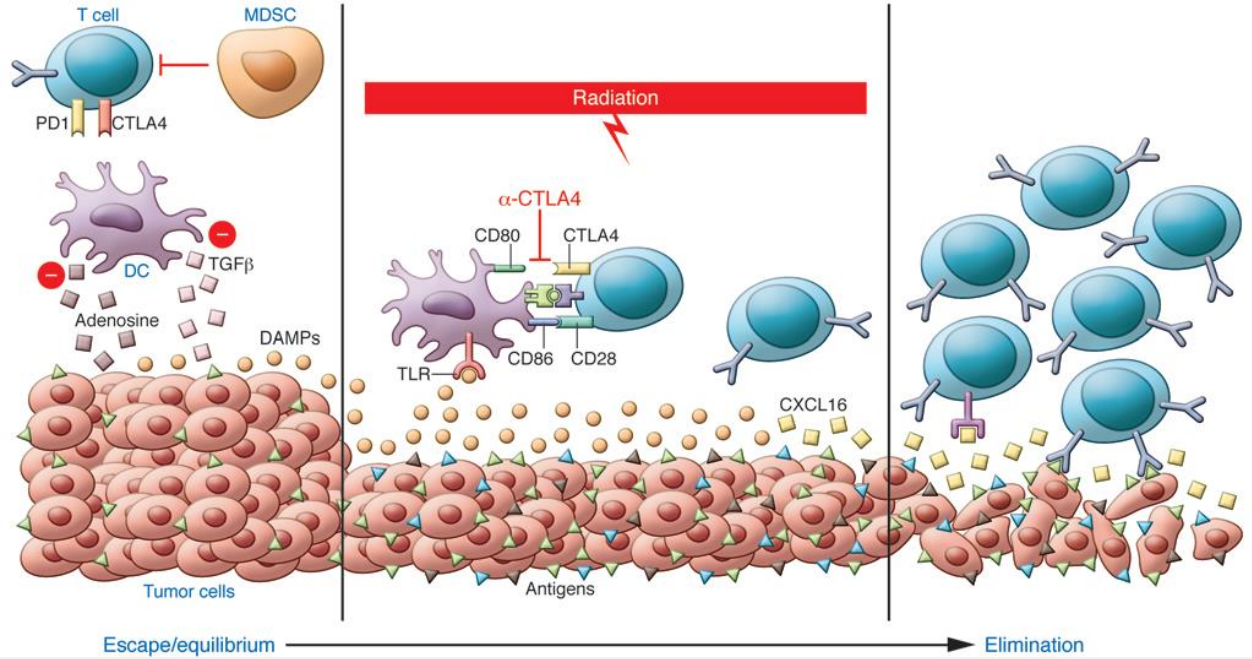
## Modification of the Norton-Simon Hypothesis

- To reduce the patient's total burden of disease in such a way that the remaining cancer within the patient's body enters into a state of relatively higher growth fraction and is thus more susceptible to systemic therapy.
- To prevent or delay as long as possible the condition of lethal tumor burden that is fatal to the patient




Most importantly emergence of more effective systemic therapy- increased local therapy benefits

# WHY LOCAL THERAPY-ERA OF IMMUNOTHERAPY



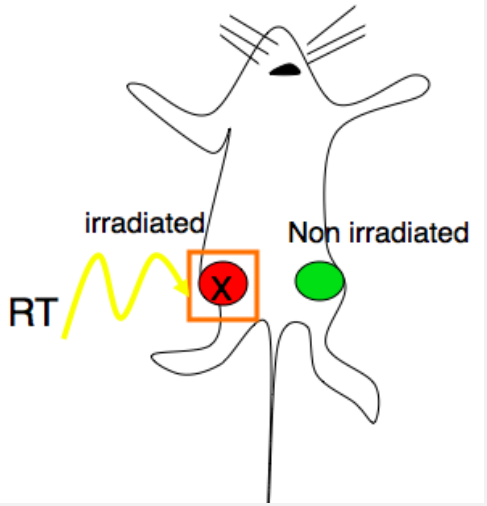

- RT can increase antigenic expression, release pro-inflammatory cytokines that recruit immune cells, promote antigen cross-presentation, and induce tumor expression of death receptors.
- Anti-CTLA4–targeted immunotherapy can enhance the adaptive immune component by promoting antigen cross-presentation and T cell activation

At baseline, both the tumor immune microenvironment and the poor antigenicity of the tumor - escape immune recognition.

Synergistic Combination may shift the tumor immune system balance towards elimination

# Local radiotherapy and granulocyte-macrophage colony-stimulating factor to generate abscopal responses in patients with metastatic solid tumours: a proof-of-principle trial

*Encouse B Golden, Arpit Chhabra, Abraham Chachoua, Sylvia Adams, Martin Donach, Maria Fenton-Kerimian, Kent Friedman, Fabio Ponzo, James S Babb, Judith Goldberg, Sandra Demaria, Silvia C Formenti*




A proof-of-principle trial: Local radiotherapy and GM-CSF—an immunotherapy—to generate abscopal responses in patients with metastatic solid tumors.

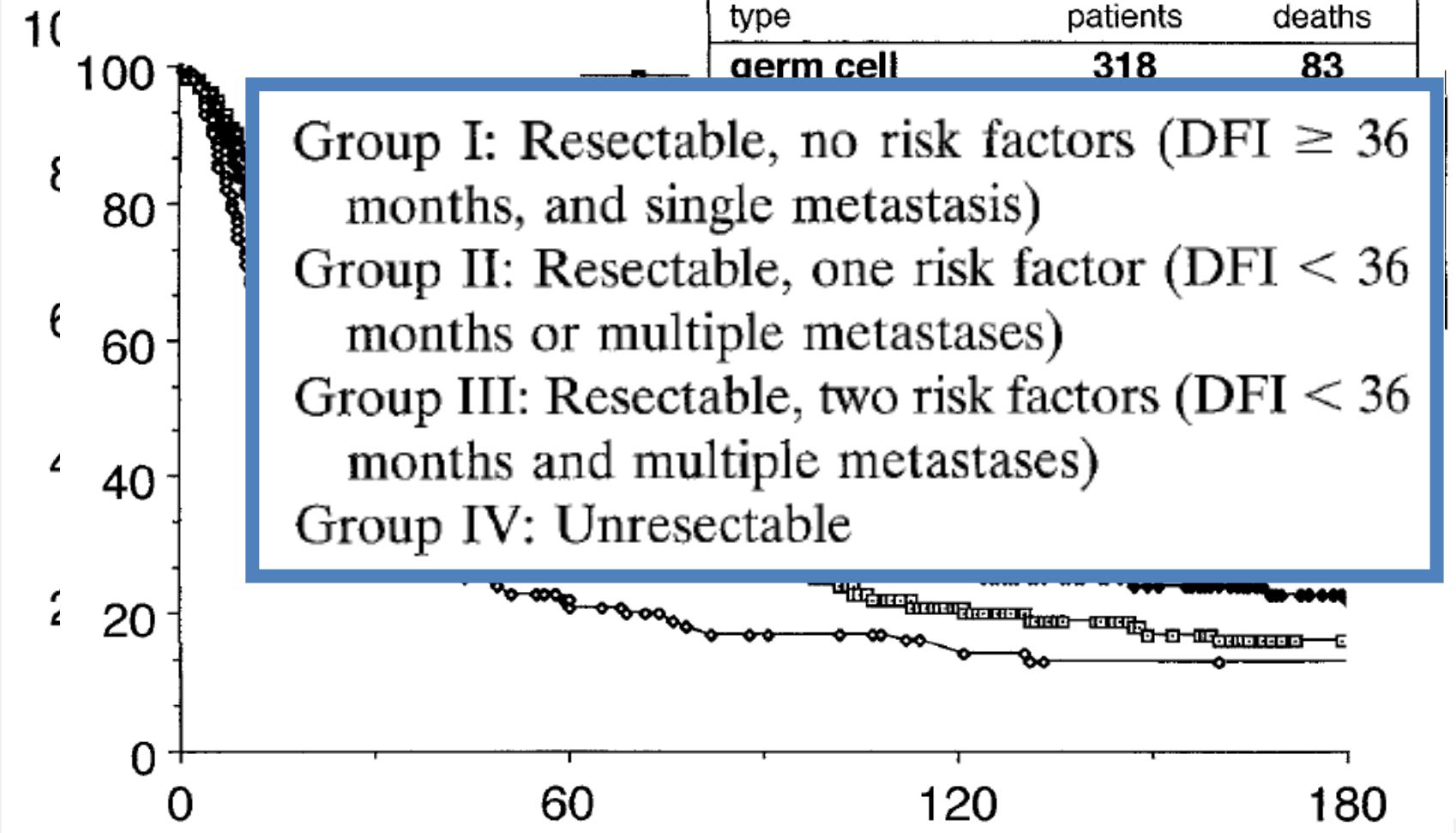
- 26.8% abscopal responses
- Median overall survival: 20.98 months versus 8.33 months (responders vs. non responders).

**Interpretation** The combination of radiotherapy with granulocyte-macrophage colony-stimulating factor produced objective abscopal responses in some patients with metastatic solid tumours. This finding represents a promising approach to establish an in-situ anti-tumour vaccine. Further research is warranted in this area.

# LONG-TERM RESULTS OF LUNG METASTASECTOMY: PROGNOSTIC ANALYSES BASED ON 5206 CASES

The International Registry of Lung

| type | patients | deaths |
|---|---|---|
| germ cell | 318 | 83 |




Group I: Resectable, no risk factors (DFI ≥ 36 months, and single metastasis)
Group II: Resectable, one risk factor (DFI < 36 months or multiple metastases)
Group III: Resectable, two risk factors (DFI < 36 months and multiple metastases)
Group IV: Unresectable

Pastorino, et al JTCVS 1997

# WHY SBRT

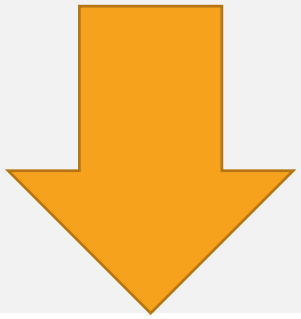
- High doses to small, well-defined targets in extreme hypofractionated scheme with a very high biological effectiveness
- Not feasible to administer such BED in conventional fractionation.
- Apart from the usual radiobiology, the effect on vasculature adds to its biological equivalence not captured by LQ model.
- Enhanced effect on immuno-modulatory effect and abscopal effects.

- A large body of evidence now for Lung, Brain and Liver.

TABLE I. Comparison of typical characteristics of 3D/IMRT radiotherapy and SBRT.

| Characteristic | 3D/IMRT | SBRT |
|---|---|---|
| Dose/fraction | 1.8–3 Gy | 6–30 Gy |
| No. of fractions | 10–30 | 1–5 |
| Target definition | CTV/PTV (gross disease+clinical extension): Tumor may not have a sharp boundary. | GTV/CTV/ITV/PTV (well-defined tumors: GTV=CTV) |
| Margin | Centimeters | Millimeters |
| Physics/dosimetry monitoring | Indirect | Direct |
| Required setup accuracy | TG40, TG142 | TG40, TG142 |
| Primary imaging modalities used for treatment planning | CT | Multimodality: CT/MR/PET-CT |
| Redundancy in geometric verification | No | Yes |
| Maintenance of high spatial targeting accuracy for the entire treatment | Moderately enforced (moderate patient position control and monitoring) | Strictly enforced (sufficient immobilization and high frequency position monitoring through integrated image guidance) |
| Need for respiratory motion management | Moderate—Must be at least considered | Highest |
| Staff training | Highest | Highest+special SBRT training |
| Technology implementation | Highest | Highest |
| Radiobiological understanding | Moderately well understood | Poorly understood |
| Interaction with systemic therapies | Yes | Yes |

SBRT:AAPM Task Group 101, Med Phys 2010



# Stereotactic body radiation therapy: The report of AAPM Task Group 101

Med Phys 2010

# ESTRO-ACROP Guideline

Equipment
Staff training, credentialing
Patient selection
Treatment planning
Dose & fractionation
Image guidance
Quality assurance
Follow-up and imaging assessment

Overview of all mandatory and recommended work-flow and equipment of SBRT for early stage NSCLC (>50% agreement).

| SBRT workflow or equipment items | MANDATORY (minimum) requirements | Recommended for best practice |
|---|---|---|
| Equipment | C-arm linear accelerator with volumetric in-room image guidance<br>Respiration correlated 4D-CT | Dedicated C-arm stereotactic linear accelerator (more advanced IGRT, more precise accuracy)<br>High-resolution MLC <10 mm |
| Staff teaching, training and credentialing | Written departmental protocols<br>Multi-disciplinary project team for SBRT implementation and application<br>Structured follow-up for clinical outcome assessment | Participation in dedicated SBRT teaching course (e.g. ESTRO)<br>Participation in Vendor-organized dedicated SBRT training<br>Hands-on training at SBRT-experienced center<br>Supervision of first SBRT treatments by SBRT-experienced colleague |
| Patient selection for SBRT | Discussion in interdisciplinary tumor board<br>Minimum ECOG 3<br>Minimum life expectancy of 1 year | Biopsy confirmation of malignancy |
| Treatment planning | 3D conformal treatment planning<br>Type B algorithms<br>Respiration correlated 4D-CT imaging<br>ITV based motion management strategy | Dynamic IMRT planning (VMAT)<br>Use of a fixed dose inhomogeneity in PTV |
| Dose and fractionation | Risk adapted fractionation schemes for peripheral and central tumors, and for tumors with broad chest wall contact | |
| Inter- and intra-fraction image guidance | Daily pre-treatment volumetric image-guidance | Daily pre-treatment 4D volumetric image-guidance (in-room 4D-CT, 4D-CBCT) |
| Follow-up | Follow-up according to published guidelines<br>FDG-PET imaging in case of suspected local recurrence | Routine biopsy confirmation of imaging-defined local failure only in patients who are likely to undergo salvage therapy |
| Quality assurance | Intensified quality assurance (mechanical accuracy of 1.25 mm and a dosimetric accuracy of 3% in a lung phantom inside the treatment field)<br>Small field dosimetry detectors for commissioning<br>End-to-end testing in a lung phantom<br>Quality assurance of in-room image-guidance systems and of the 4D-CT scanner<br>Weekly checks of the mechanical accuracy of the delivery system<br>Daily quality checks of the alignment of the IGRT system with the MV treatment beam | End-to-end testing in a moving 4D lung phantom |

M Guckenberger, et al Radiotherapy Oncol 2017

# LQ holds for SBRT

International Journal of Radiation Oncology biology • physics

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Critical Review

## The Tumor Radiobiology of SRS and SBRT: Are More Than the 5 Rs Involved?

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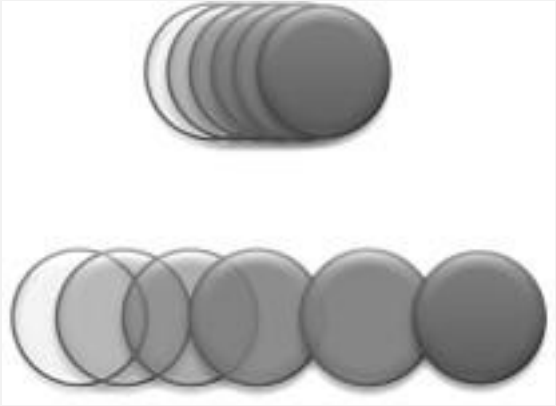
$$\mathrm{BED} = nd\left[1 + \frac{\mathrm{d}}{(\alpha/\beta}\right]$$

# DEFINITIONS OF OLIGOMETASTATIC SPECTRUM

Continuously evolving



Primarily imaging driven and does not incorporate molecular info

# Definitions

**Table 1.** Comparison of Recent Definitions for Oligometastatic Non-Small Cell Lung Cancer in Clinical Trials, National Treatment Guidelines, and Consensus Definitions. Modern definitions for oligometastatic non-small cell lung cancer have varied widely.

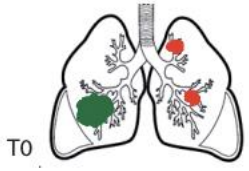
| Author | Year | Study Type | Maximum Number of Metastases | Maximum Number of Organ Sites | Maximum Lesions in Each Organ | Intrathoracic N+ as Metastasis | Pulmonary Lesion as Metastasis | Includes Intracranial Lesions | No Disease Progression after First Line Therapy | Notes |
|---|---|---|---|---|---|---|---|---|---|---|
| Ashworth [5] | 2014 | Meta-analysis | 5 | NS | NS | NS | Yes | Yes | NS | |
| Gomez [2,3] | 2016, 2019 | RCT phase II | 3 | NS | NS | Yes | NS | Yes | Yes | |
| Iyengar [27] | 2018 | RCT phase II | 5 | NS | 3 in lung or liver | NS | Yes | Exclude uncontrolled intracranial | Yes | |
| Palma [12,13] | 2019, 2020 | RCT phase II | 5 | NS | 3 | NS | NS | Exclude if only site of disease | Yes | Not lung cancer-specific |
| Dingemans [36] (EORTC-LCG) | 2019 | Consensus working group | 5 | 3 | NS | No | Yes | Yes | NS | |
| TNM stage M1a [31] | 2017 | Staging Guidelines | 1 | 1 | 1 | No | Contralateral | Yes | NA | |
| NCCN [34] | 2021 | Treatment Guidelines | 3-5 | NS | NS | No | Treat as second primary | Yes | NS | |
| ESMO [35] | 2018 | Treatment Guidelines | 3 | NS | NS | NS | Treat as second primary | Yes | NS | |

Abbreviations. NS, not specified; RCT, randomized controlled trial; EORTC-LCG, The European Organization of Research and Treatment of Cancer—Lung Cancer Group; NCCN, National Comprehensive Cancer Network; ESMO, European Society for Medical Oncology.

Blumenthaler, et al Cancers 2021

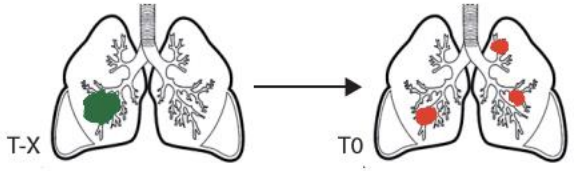
## A De-novo oligometastatic disease

### Synchronous oligometastatic disease



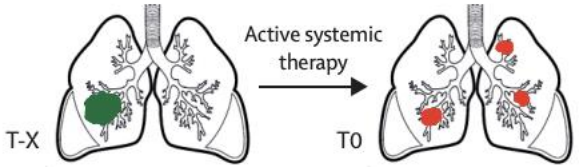

- T0: first time diagnosis of primary cancer (green) and oligometastases (red) within 6 months

### Metachronous oligorecurrence




- T-X: diagnosis and treatment of primary cancer (green) in a non-metastatic state
- Systemic therapy-free interval
- T0: First time diagnosis of new oligometastases (red) >6 months after diagnosis of cancer

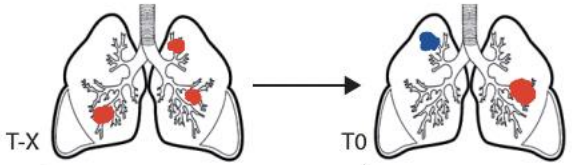
### Metachronous oligoprogression




- T-X: diagnosis and treatment of primary cancer (green) in a non-metastatic state
- Under treatment with active systemic therapy
- T0: first time diagnosis of new oligometastases (red) >6 months after diagnosis of cancer

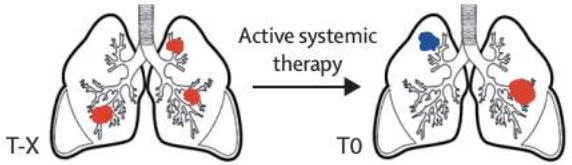
## B Repeat oligometastatic disease

### Repeat oligorecurrence



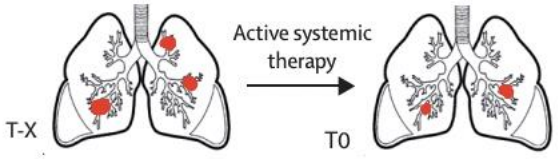

- T-X: diagnosis of oligometastases followed by local treatment or systemic treatment or both
- Systemic therapy-free interval
- T0: diagnosis of new (blue) and growing or regrowing (red) oligometastases

### Repeat oligoprogression




- T-X: diagnosis of oligometastases followed by local treatment or systemic treatment or both
- Under treatment with active systemic therapy
- T0: diagnosis of new (blue) and growing or regrowing (red) oligometastases

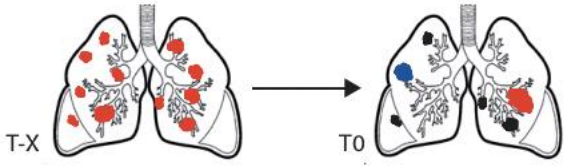
### Repeat oligopersistence




- T-X: diagnosis of oligometastases followed by local treatment or systemic treatment or both
- Under treatment with active systemic therapy
- T0: diagnosis of persistent non-progressive (red) oligometastases

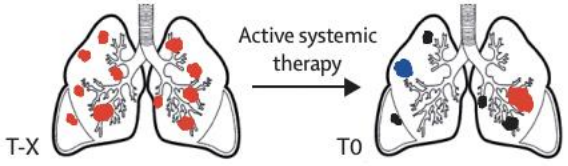
## C Induced oligometastatic disease

### Induced oligorecurrence



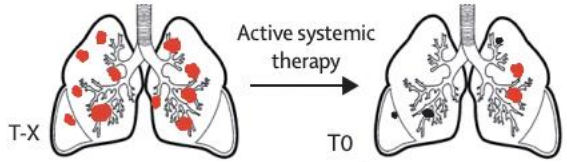

- T-X: diagnosis of polymetastatic metastatic disease followed by systemic treatment with or without local treatment
- Systemic therapy-free interval
- T0: diagnosis of new (blue) and growing or regrowing (red) oligometastases, possible residual non-progressive metastases (black)

### Induced oligoprogression




- T-X: diagnosis of polymetastatic metastatic disease followed by systemic treatment with or without local treatment
- Under treatment with active systemic therapy
- T0: diagnosis of new (blue) and growing or regrowing (red) oligometastases, possible residual non-progressive metastases (black)

### Induced oligopersistence




- T-X: diagnosis of polymetastatic metastatic disease followed by systemic treatment with or without local treatment
- Under treatment with active systemic therapy
- T0: diagnosis of persistent non-progressive oligometastases (red), where response is worse compared with other residual metastases (black)

M Guckenberger, et al Lancet Oncol 2020

# PROSPECTIVE STUDIES

**Table 1** Outcomes from completed prospective for patients with oligometastatic and oligoprogressive NSCLC

| Study | Design | Local treatment arms | Patients | RT dose | Treatment site | Systemic therapy | Primary endpoint | Outcome | Toxicity (G3+ |
|---|---|---|---|---|---|---|---|---|---|
| De Ruysscher 2012 | Prospective single arm, phase II | Radiation or surgery | 44 | Brain: 21 Gy/1; 24 Gy/3 pt undergoing resection received WBRT (30 Gy/10); lung: 54 Gy/3; other non-stereotactic regimens included (EQD2 >60 Gy) | 1–4 sites, extra/intracranial disease; 97.5% had 1–2 lesions treated | 92.3% received platinum-based CHT | OS at 2 and 3 years | mFU 27.7 m; mPFS 12.1 m; mOS 16.7 m; 2-yr OS 23.3%; 3-yr OS 17.5% | Acute esophagitis 15%; cough 2.6% |
| Collen 2014 | Prospective single arm, phase II | SBRT | 26 | SAbR: 50 Gy/10 | 1–5 metabolically active sites; extra/intracranial disease. 46% >1 lesion treated; 46% >1 organ involved | 65.4% received platinum-based induction CHT | CMR rate | mFU 16.4 m; mPFS 12.2 m; mOS 23 m; 1-yr PFS 45%; 1-year OS 67%; CMR 30%; OMR 60% | Acute cough 8%; late none |
| Iyengar 2014 | Prospective single arm, phase II | SBRT | 24 | SAbR: 19–20 Gy/1, 27–33 Gy/3, 35–40 Gy/5 | <7 sites, extracranial disease (<4 in liver and lung each); 62.5% >3 lesions treated | 100% concurrent erlotinib (50–150 mg/day) | 6-m PFS | mFU 11.6 m; mPFS 14.7 m; mOS 20.4 m | Grade 3 24%***; grade 4 4%**; grade 5 13%* |
| Iyengar 2018 | Prospective, randomized, phase II | SAbR+ maintenance CHT *vs.* maintenance CHT alone | 29 (closed early after interim analysis showed benefit | SAbR: 18–24 Gy/1, 24.6–33 Gy/3, 30–37.5 Gy/5. Hypofractionated: 45 Gy/15 | Primary disease plus up to 5 extracranial sites with no more than 3 sites in the liver or lung | Maintenance therapy: docetaxel, bevacizumab, gemcitabine, pemetrexed, erolitinib | PFS | mFU 9.6 m; mPFS 9.7 *vs.* 3.5 m SS favoring local therapy arm. mOS not reached in local therapy arm *vs.* 17 m in maintenance arm | Similar grade 3+ toxicity profiles between the two arms. 2 grade 3 AE and 1 grade 4 AE in maintenance arm; 4 grade 3 AE in local therapy arm**** |
| Theelan 2018 | Prospective randomized phase II | Pembrolizumab after SAbR to a single tumor site *vs.* pembrolizumab alone | 76 | SAbR: 24 Gy/3 | Only extracranial lesions treated with SAbR; >1 metastatic lesion with size <5 cm | Pembrolizumab (200 mg/kg every 3 weeks) | ORR | mFU 23.6 m; 12-week ORR 36% *vs.* 18 NS favoring SAbR arm; mPFS 6.6 m *vs.* 1.9 m favoring SAbR arm; mOS 15.9 m *vs.* 7.9 m favoring SAbR arm | 35 grade 3+ toxicities in the experimental arm and 37 grade 3+ in the control arm; no difference between the arms |

**Table 1** (*continued*)

| Study | Design | Local treatment arms | Patients | RT dose | Treatment site | Systemic therapy | Primary endpoint | Outcome | Toxicity (G3+) |
|---|---|---|---|---|---|---|---|---|---|
| Palma 2019 | Prospective, multicenter randomized, phase II | Standard palliative treatment *vs.* standard of care and SAbR to all sites of metastatic disease | 18 patients with NSCLC | SAbR regimens permitted 30–60 Gy/3–5 depending on location; SRS regimens permitted 16–24 Gy/1 | <6 sites of metastases (intracranial and extracranial); 75% had 1–2 metastases | Not specified however the two groups did not differ in receipt of systemic therapy | OS | mFU 26 m; mPFS 12 *vs.* 6 m in favor of SAbR arm; mOS 41 *vs.* 28 m in favor of SAbR arm | 5% grade 5 rate in treatment arm *vs.* 0% in the control arm |
| Gomez 2016, 2019 | Prospective multicenter randomized, phase II | Radiation, chemoradiation, or resection +/– maintenance treatment *vs.* maintenance treatment alone | 49 (closed early after interim analysis showed benefit) | Regimen per primary radiation oncologist-hypofractionated RT and concurrent CRT was allowed | ≤3 metastatic lesions; 35% of entire cohort had 2–3 nonregional metastases after initial systemic therapy | Could receive: platinum doublet CHT, TKI targeting EGFR mutation, crizotinib | PFS | mFU 38.8 m; mPFS 14.2 *vs.* 4.4 m SS favoring local therapy arm; mOS 42.2 m *vs.* 17 m favoring local therapy arm | Grade 3: esophagitis (n=2), pneumothorax (n=1), anemia (n=1) |

**Table 2** Summary of ongoing prospective trials evaluating patients with oligoprogressive or oligometastatic NSCLC

| Study | Disease | Design | Estimated accrual | Treatment | Lesion number | Location | Primary endpoint | Secondary endpoint |
|---|---|---|---|---|---|---|---|---|
| NRG-LU-002 (NCT03137771) | Oligometastatic NSCLC | Randomized multicenter phase II/III | 378 | MST *vs.* local consolidative therapy + plus MST** | 1–3 | Extracranial | PFS, OS | Time to in-field failure, duration of maintenance chemotherapy, time to new lesion |
| SARON (NCT02417662) | Oligometastatic NSCLC | Randomized multicenter phase III | 340 | SACT *vs.* SACT + conventional RT or SAbR | 1–5; max of 3 organs | Intracranial and extracranial | OS | PFS, toxicity, LC, QoL |
| SABR COMET 10 (NCT03721341) | Oligometastatic NSCLC | Randomized multicenter phase III | 159 | SC *vs.* SC + SAbR | 4–10 | Intracranial and extracranial | OS | QoL, toxicity, PFS, time to new metastasis |
| OMEGA (NCT03827577) | Oligometastatic NSCLC | Randomized phase III | 195 | Local ablative therapy *vs.* conventional treatment | 1–3; if brain involvement then <2 sites <3 cm | Intracranl and extracranial | OS | N/A* |

*, not specified on clinicaltrials.gov; **, MST can include immunotherapy. RT, radiation; OS, overall survival; PFS, progression-free survival; LC, local control; SACT, systemic anti-cancer therapy; SAbR, stereotactic ablative radiotherapy; MST, maintenance systemic therapy; QoL, quality of life; SC, standard of care; TKI, tyrosine kinase inhibitor.

Mutation negative

| Study | Year | Trial Type | Number of Patients | Control Treatment | Intervention Treatment | Primary Endpoint | Reported Outcomes | Notes |
|---|---|---|---|---|---|---|---|---|
| Northstar [39,42] | 2018 [a] | RCT Phase II | 143 [c] | Osimertinib alone | Osimertinib + surgery and/or radiation | PFS | Ongoing | EGFR-mutated cancers |

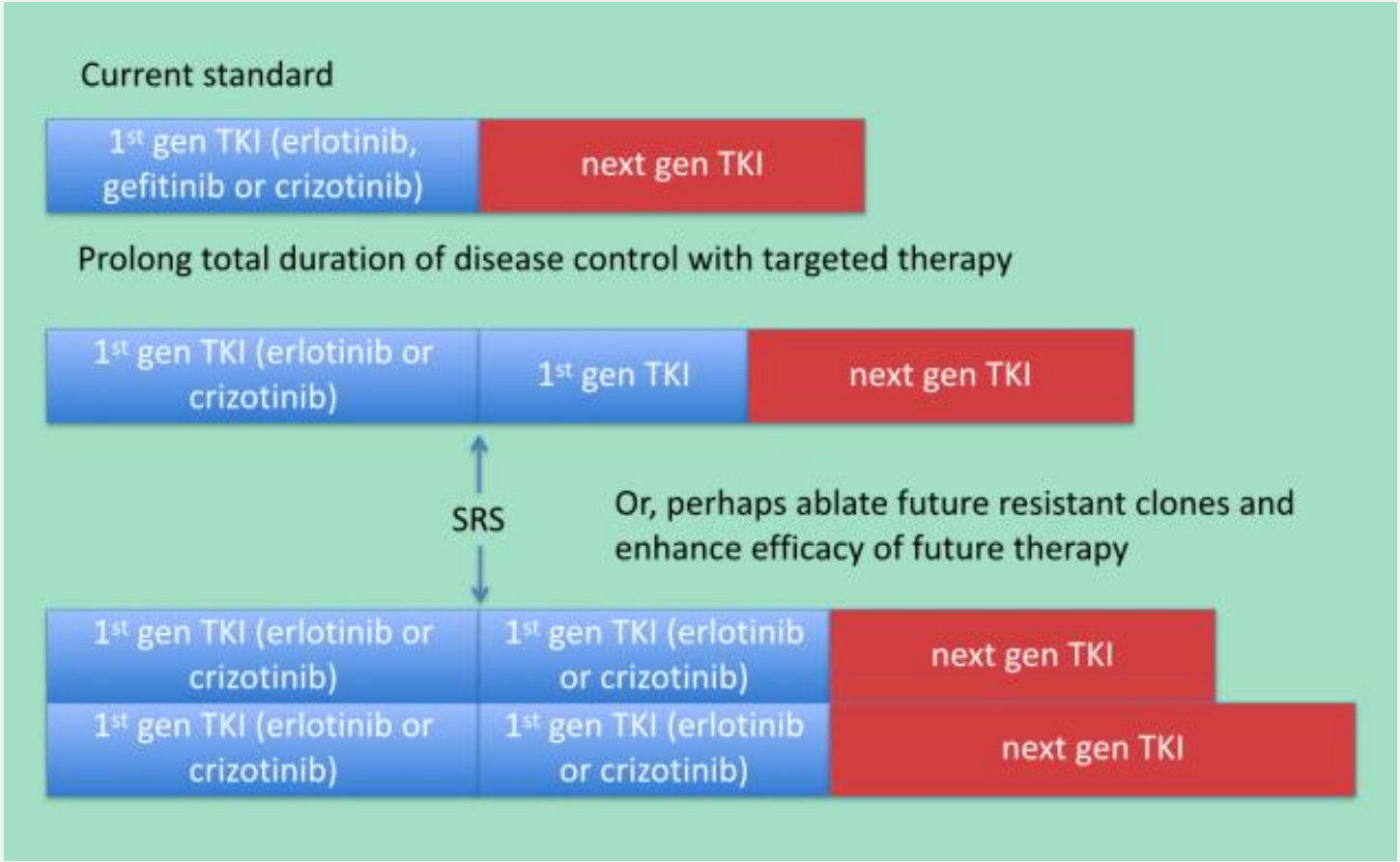
# Immunotherapy and SABR for Oligometastases

**Table 1** (*continued*)

| Study | Design | Local treatment arms | Patients | RT dose | Treatment site | Systemic therapy | Primary endpoint | Outcome | Toxicity (G3+) |
|---|---|---|---|---|---|---|---|---|---|
| Bauml 2019 | Prospective single arm, phase II | Pembrolizumab after SAbR, surgical resection, chemoradiation, or radiofrequency ablation | 45 | Unspecified radiation regimens | 1-4 sites; Intracranial and extracranial lesions were treated; 30 patients were treated with SAbR; 93% had 1–2 metastases | Median of 11 cycles of pembrolizumab (200 mg every 3 weeks) | PFS | mFU 25 m; mPFS 19.1 m; mOS 41.6 m | 5 pneumonitis (one grade 4), 2 grade 3 colitis, and 2 adrenal insufficiency (one grade 3) |

| Study | Year | Trial Type | Number of Patients | Control Treatment | Intervention Treatment | Primary Endpoint | Reported Outcomes | Notes |
|---|---|---|---|---|---|---|---|---|
| Lonestar [41] | 2017 [a] | RCT Phase III | 360 [c] | Nivolumab and Ipili-mumab | Nivolumab and ipilimumab + surgery and/or radiation | OS | Ongoing | |

# OLIGO-PROGRESSIVE NSCLC



# Phase II Trial of Stereotactic Body Radiation Therapy Combined With Erlotinib for Patients With Limited but Progressive Metastatic Non–Small-Cell Lung Cancer

**Table 1.** Baseline Characteristics of Patients Treated on Protocol

| Characeristic | No. | % |
|---|---|---|
| Sex | | |
| Female | 11 | 46 |
| Male | 13 | 54 |
| Age, years | | |
| Median | 66.9 | |
| Standard deviation | 7.6 | |
| Range | 56-86 | |
| Previously treated brain metastases | | |
| No | 22 | 92 |
| Yes | 2 | 8 |
| Follow-up, months | | |
| Mean | 16.8 | |
| Standard deviation | 14.5 | |
| Range | 3.4-60.3 | |
| Study site | | |
| University of Colorado | 6 | 25 |
| UT Southwestern Medical Center | 18 | 75 |
| Survival, last follow-up | | |
| Alive | 11 | 46 |
| Dead | 13 | 54 |
| No. of previous systemic therapy regimens | | |
| 1 | 15 | 63 |
| 2 | 7 | 29 |
| 3 | 2 | 8 |
| Race | | |
| White, Hispanic | 23 | 96 |
| African American | 1 | 4 |

**Table 2.** SBRT Treatment Patterns

| Treatment Pattern | No. | % |
|---|---|---|
| SBRT sites treated per patient | | |
| 1 | 8 | 33 |
| 2 | 8 | 33 |
| 3 | 5 | 21 |
| 4 | 2 | 9 |
| 5 | 1 | 4 |
| SBRT courses to specific sites | | |
| 18 | Lungs (35% of 52 sites treated) | |
| 13 | Mediastinum/hilum (25) | |
| 7 | Adrenals (13) | |
| 6 | Bone/spine/chest wall (13) | |
| 4 | Liver/paracaval (8) | |
| 3 | Nonmediastinal lymph nodes (5) | |
| 1 | Kidney (1) | |
| Lesions treated with specific SBRT fractionation schemas | | |
| 21 | 3 fx to 27-33 Gy (40) | |
| 21 | 5 fx to 35-40 Gy (40) | |
| 10 | 1 fx to 19-20 Gy (20) | |

Abbreviations: fx, fractions; SBRT, stereotactic body radiation therapy.

**Table 4.** Patterns of Failure

| Pattern | No. Out of 21 Patients | % | No. Out of 47 Total Evaluable Lesions Treated With SBRT | % |
|---|---|---|---|---|
| Sites of failure by patient | | | | |
| Within SBRT-treated area (in-field failure) | 3 | 14 | 3 | 6 |
| Outside of SBRT-treated area (OFF) | 10* | 48 | N/A | N/A |
| No failures | 10 | 48 | N/A | N/A |

| OFF Sites | No. of Failures | Percentage of Total OFFs | Percentage of 10 Patients With OFFs |
|---|---|---|---|
| Thorax | 6 | 43 | 60 |
| Liver | 3 | 21 | 30 |
| Brain | 2 | 14 | 20 |
| Pancreas | 1 | 7 | 10 |
| Lymph node | 1 | 7 | 10 |
| Spine | 1 | 7 | 10 |

Median PFS- 14.7 mo
Median OS- 20.4 mo

Iyengar P, et al JCO 2014

**Table 2** Summary of ongoing prospective trials evaluating patients with oligoprogressive or oligometastatic NSCLC

| Study | Disease | Design | Estimated accrual | Treatment | Lesion number | Location | Primary endpoint | Secondary endpoint |
|---|---|---|---|---|---|---|---|---|
| STOP (NCT02756793) | Oligoprogressive NSCLC | Randomized phase II | 54 | SC *vs.* SC + SAbR | 1–5; 1–3 progressing lesions; max of 3 lesions in single organ | Intracranial and extracranial | PFS | OS, QoL, toxicity, LC, total time on chemotherapy, patterns of failure |
| HALT (NCT03256981) | Oligoprogressive NSCLC | Randomized multicenter phase II/III | 110 (phase II) | TKI *vs.* TKI + SAbR | 1–3 progressive lesions | Extracranial | PFS | Time to next systemic therapy, OS, patterns of failure, toxicities, QoL |

# DOSE IN OLIGOMETASTATIC SETTING

18-24Gy/1#
24-33Gy/3#,
35-40Gy/5#,
45-50Gy/15#

- Aim is not to give additional toxicity, minimal disruption to QOL
- Easy integration of SBRT with systemic chemotherapy
- Minimal interruption to systemic therapy

Constraints- Chart for comprehensive constraints

I also use **RadOncCalc** app on my phone

# CONCLUSION- SBRT OLIGOMETASTATIC DISEASE

- Oligometastatic disease- increasingly being recognized
- Definition is evolving- Upto 5 sites apart from the primary with <3 in one site, seem to be acceptable as of now.
- Evidence from phase II and phase III trials show promising role of SBRT in improving PFS and OS
- SBRT in combination with immunotherapy- strong biological rationale, phase II trials promising, phase III trials underway
- Oligoprogression- definite biological rationale, phase II trials extremely promising, phase III trials underway.
- Dose to ensure easy integration with systemic therapy, and minimal toxicity

# SBRT IN EARLY LUNG CANCER: WHAT'S NEW

Long term Outcomes

Most guidelines recommend it for inoperable early-stage lung cancers

Status for central tumors

Comparison with other options for operable lung cancers

Ongoing research

Imaging assessment

Dose dependence/My preference for dose

Mediastinum, Systemic therapy with SBRT- Omissions due to lack of time

# LEVEL-1 EVIDENCE SBRT VS. CONV RT FOR INOPERABLE EARLY NSCLC

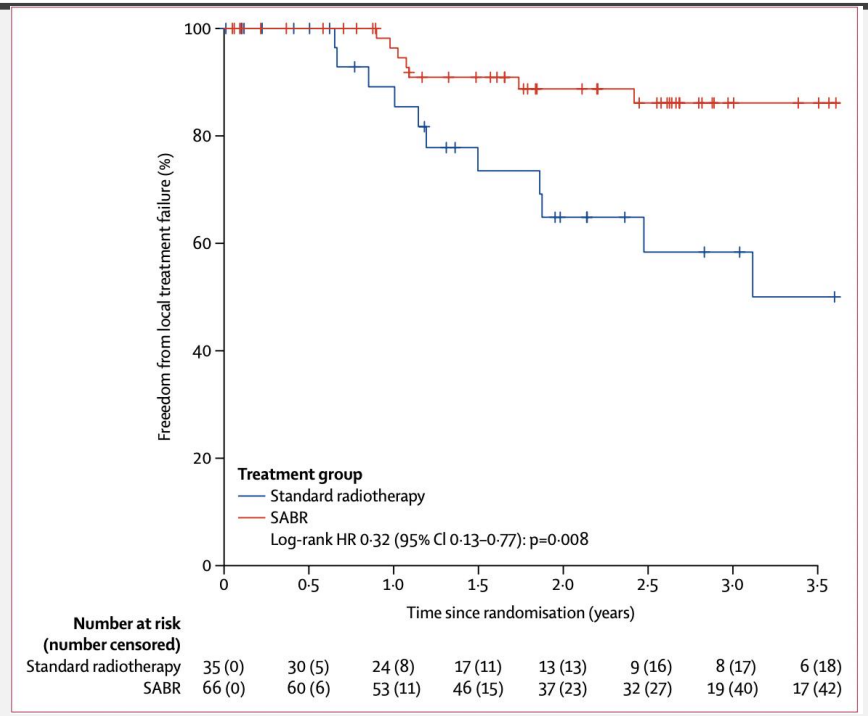
CHISEL Study

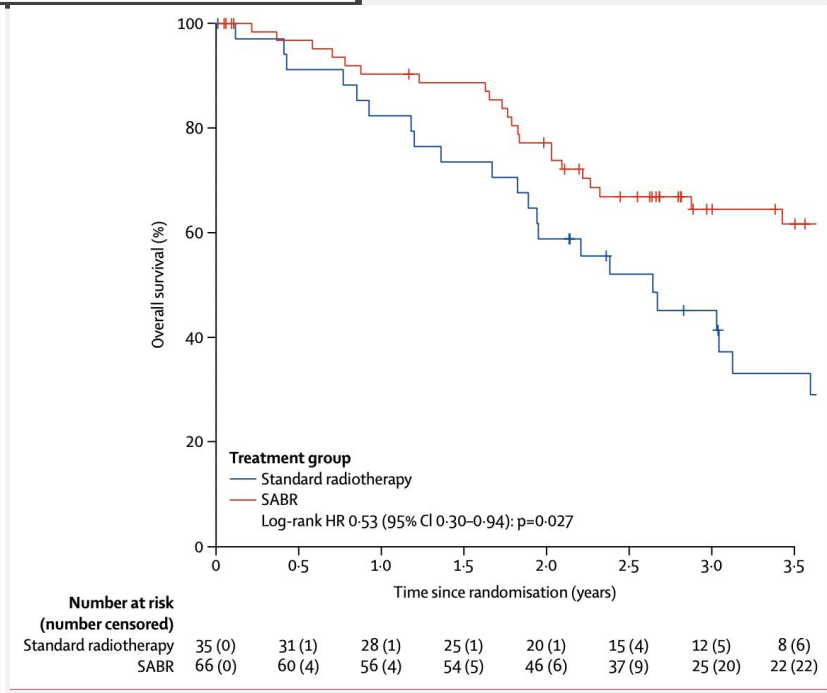
- PET staged T1-T2aN0M0,
- ECOG PS-0,1
- Inoperable or refused surgery
- Peripheral,
- Atleast 2cm away from chest-wall

54Gy/3#, 48Gy/4#

66Gy/33#, 50Gy/20#

101 patients, 2:1 Randomization




ESTRO-ACROP Recommendation- : minimum PS of ECOG 3 and a minimal estimated life expectancy of one year for SBRT patient selection

D Ball, et al Lancet Oncol 2019
M Guckenberger, et al Radiotherapy Oncol 2017

# LONG TERM OUTCOMES (5 YRS)

**Table 1** Published experience with SABR in operable patients with early NSCLC

| Study | Year | Study design | Dose/fraction | Size (n) | Age, median [range] (years) | 3-y results | | 4-y results | | | 5-y results | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | OS, % | PFS, % | OS, % | PFS, % | LC, % | OS, % | PFS, % | CSS, % | LC, % |
| Uematsu *et al.* (12)† | 2001 | Retrospective | 50–60 Gy/5–10# | 29 | 71 [54–86] | 86 | – | – | – | – | – | – | – | – |
| Chang *et al.* (STARS/ ROSEL) (9) | 2015 | Prospective | 54 Gy/3#; 50 Gy/4#; 60 Gy/5# | 31 | 67.1 [43–82] | 95 | 96 | – | – | – | – | – | – | – |
| Komiyama *et al.* (16) | 2015 | Retrospective | 32–70 Gy/4–15# | 661 | 75 | – | – | 79 | – | – | – | – | – | – |
| Timmerman *et al.* (RTOG 0618) (2) | 2013, 2018 | Prospective | 54 Gy/3# | 26 | 72.5 [54–88] | – | – | 57 | 56 | 96 | – | – | – | – |
| Lagerwaard *et al.* (11) | 2012 | Retrospective | 60 Gy/3#; 60 Gy/5#; 60 Gy/8# | 177 | 76 [50–91] | 84.7 | 81 | – | – | – | 51.3 | – | – | – |
| Onishi *et al.* (13) | 2011 | Retrospective | 45–72.5 Gy/3–10# | 87 | 74 | – | – | – | – | – | 69.5 | – | 76.1 | 86.7 |
| Shibamoto *et al.* (15)† | 2015 | Prospective | 44 Gy/4#; 48 Gy/4#; 52 Gy/4# | 60 | 77 [29–89]‡ | – | – | – | – | – | 66 | – | 74 | 88 |
| Nagata *et al.* (JCOG 0403) (8,17) | 2015, 2018 | Prospective | 48 Gy/4# | 64 (3 y); 40 (5 y) | 79§ | 76.5 | 54.5 | – | – | – | 54 | – | – | 85.4¶ |
| Eriguchi *et al.* (10) | 2017 | Retrospective | 40 Gy/5#; 50 Gy/5#; 60 Gy/5# | 88 | 79 [55–88] | 86 | – | – | – | – | 69 | – | 88 | 93 |
| Schonewolf *et al.* (14)† | 2018 | Retrospective | BED ≥100 $Gy_{10}$ | 34 | 73 [55–92] | – | – | – | – | – | 45.3 | 82.4 | 91 | 96.7 |

CP Daniels, et al TCLR 2019

# SBRT WITHOUT A BIOPSY

## ESMO Guidelines [Vansteenkiste J, Ann Oncol 2014]

A pre-treatment pathological diagnosis strongly recommended, unless a multidisciplinary tumour board (MDT) is of the opinion that the risk-benefit ratio of the procedure is unacceptable

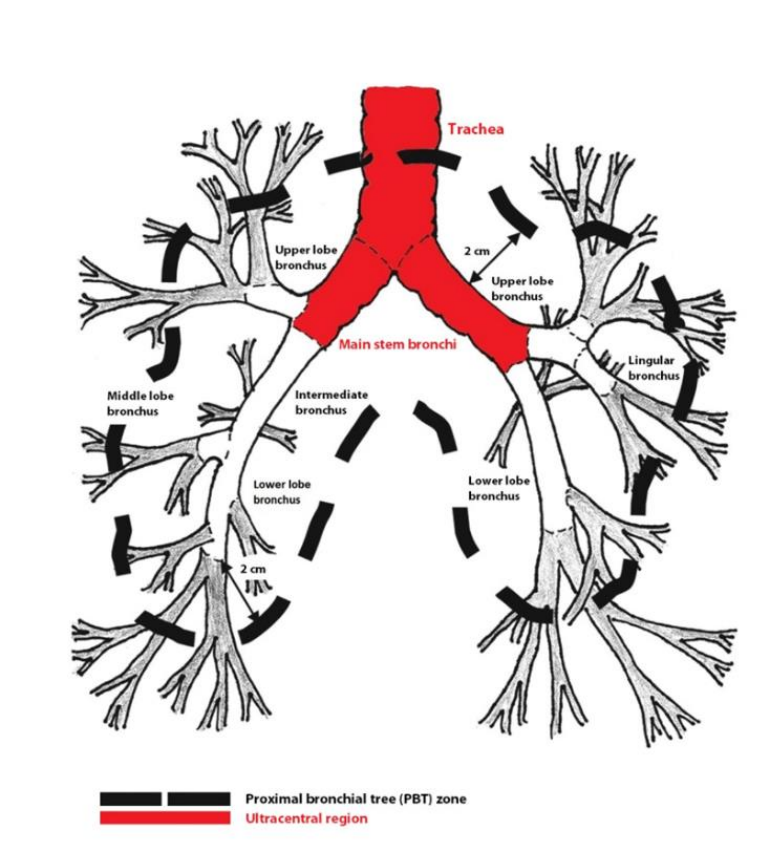
## ASTRO Guidelines [Videtic GMM, PRO 2017]

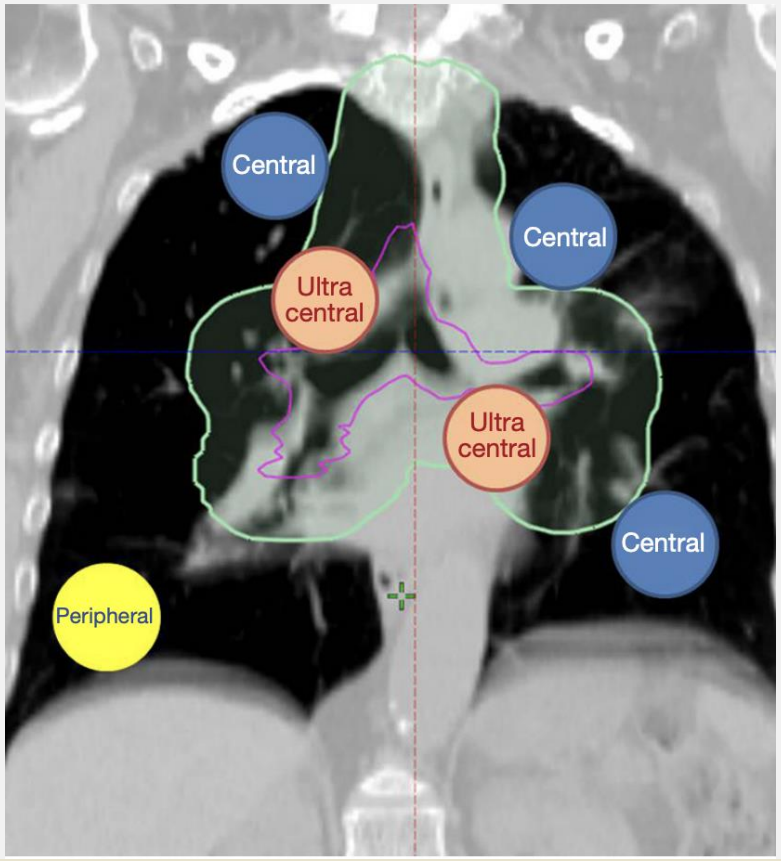
SABR can be delivered in patients who refuse a biopsy, have a non-diagnostic biopsy, or who are thought to be at prohibitive risk of biopsy. Patients are recommended to be discussed in a multidisciplinary manner with a consensus that the lesion is radiographically and clinically consistent with a malignant lesion based on tumor, patient, and **environmental factors**

## Asian clinical practice consensus [Bai C, Chest 2016]

Incidence of tuberculosis in Asia favors (i) a lesser reliance on PET scanning, and (ii) greater use of non-surgical biopsy over surgical diagnosis or surveillance

# CENTRAL TUMORS




Nomenclature of central and ultra central is less important than the actual tolerance and predicted doses to the proximal bronchial tree, vasculature, esophagus, heart etc.

**No Fly Zone** Timmerman, et al (JCO 2006); 46% severe toxicities vs. 17% in peripheral tumors

**Fly careful zone** Senthi S, et al (Radiother Oncol 2013): If BED3 <210Gy- Risk of grade 5 tox <1%

| Study | Definition of Ultra-central | Dose/Fractionation | 2-yr Local Control | Toxicity |
|---|---|---|---|---|
| HILUS Phase II, 2021 (n=65) | ≤ 1 cm from PBT | 56 Gy/8 fx (100%)<br>150% hotspot | 83% | Grade 3+: 34%<br>Grade 5: 15% |
| Breen, 2021 (n=110) | GTV abutting PBT, trachea; PTV overlap PBT, trachea; GTV ≤ 1 cm from PBT | 50 Gy/5 fx (57%)<br>60 Gy/8 fx (15%)<br>48 Gy/4 fx (13%) | 84% | Grade 5 (4%) |
| RTOG 0813, 2019 (n=120) | ≤ 2cm from PBT | 50-60 Gy/5 fx | 87.9-89.4% | 7.2% DLTs |
| Raman, 2018 (n=26) | PTV overlapping PBT, trachea, esophagus, pulmonary vein/artery | 60 Gy/8 fx (77%)<br>50 Gy/10 fx (12%) | 100% | Grade 2-3: 7.9%<br>Grade 4-5: 0% |
| Tekatli, 2016 (n=47) | PTV overlapping trachea or main bronchi | 60 Gy/12 fx<br><br>140% hotspot | 78% | Grade 3+: 38%<br>Grade 5: 13% |
| Li, 2014 (n=82) | Dose constraints for 50 Gy in 4 fx not met | 70 Gy/10 fx (100%) | 96.2% | Grade 3: 3.6%<br>Grade 5: 1.2% |

Tekatli H, et al. J Thorac Oncol. 2016 Jul;11(7):1081-9.
Lindberg K, et al.. J Thorac Oncol. 2021 April 3. Epub.
Li et al. Radiother Oncol. 2014 Aug;112(2):256-261

Breen WG, et al. Radiother Oncol. 2021 Mar 10;158:246-252.
Bezjak A, et al. J Clin Oncol. 2019 May 20;37(15):1316-1325.
Raman S, et al. Clin Lung Cancer 2018 Sep;19(5):e803-e810

**Table 2 Recommended Dose Constraints**

| Organ | Metric | Fraction | | |
|---|---|---|---|---|
| | | 5/6 | 8/10 | 15 |
| Spinal canal | Max | 30 Gy | 32 Gy | 39.5 Gy |
| Spinal canal PRV (3 mm) | Max | 32 Gy | 34 Gy | 42 Gy |
| Esophagus | Max | 40 Gy | 45 Gy | 50.5 Gy |
| | 5 cc | 35 Gy | 40 Gy | 48 Gy |
| Brachial plexus | Max | 32 Gy | 39 Gy | 50 Gy |
| Heart | Max | 62 Gy | 64 Gy | 66 Gy |
| | 10 cc | 50 Gy | 60 Gy | 62 Gy |
| Trachea | Max | 62 Gy | 64 Gy | 66 Gy |
| | 10 cc | 50 Gy | 60 Gy | 62 Gy |
| Proximal bronchus | Max | 62 Gy | 64 Gy | 66 Gy |
| | 10 cc | 50 Gy | 60 Gy | 62 Gy |
| Non-GTV lung | Mean | < 12 Gy | < 12 Gy | < 14 Gy |
| Aorta and major vessels | Max | 62 Gy | 64 Gy | 64 Gy |
| | 10 cc | 50 Gy | 60 Gy | 60 Gy |
| Stomach and intestines | Max | 40 Gy | 45 Gy | 50 Gy |
| | 10 cc | 35 Gy | 40 Gy | 48 Gy |

Abbreviations: GTV = gross tumor volume; PRV = planning organ-at-risk volume.

Caution if:

MSB involved, Endobronchial invasion present

Delivering excessive hotspots

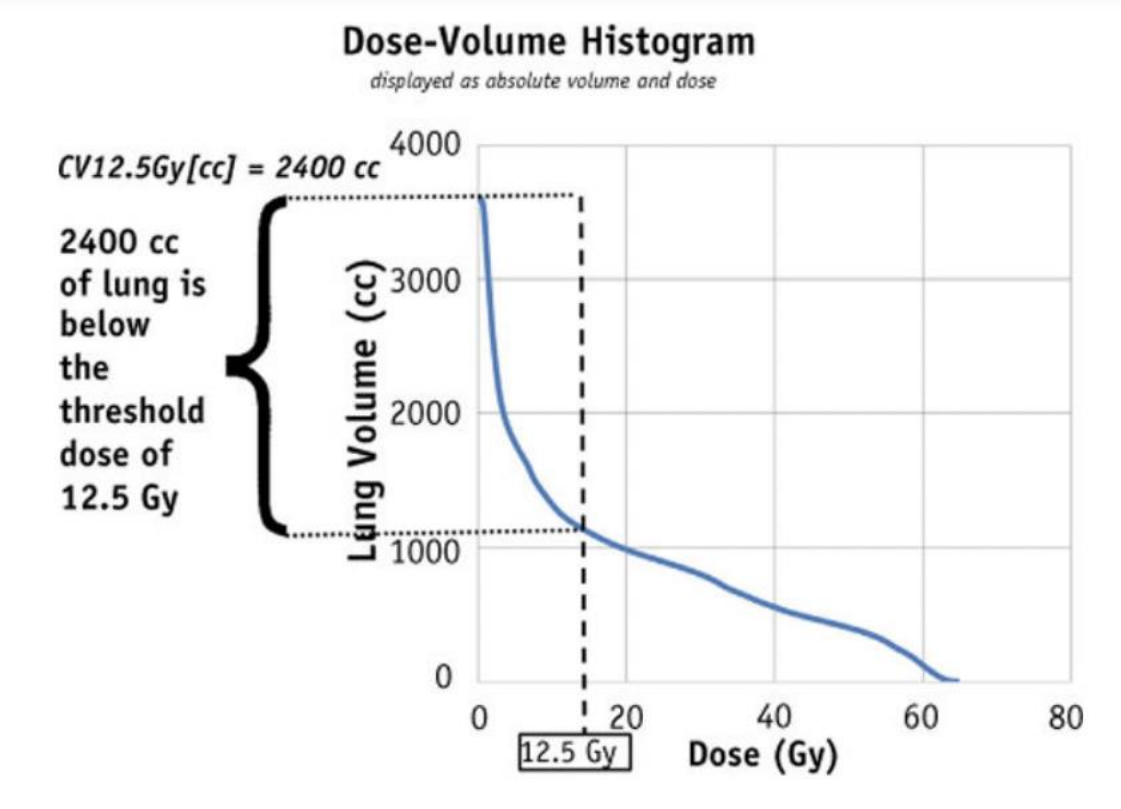
Pt on Anti-coagulants, Bev

M Guilani, et al Lung Cancer 2018

# LUNG CONSTRAINT?

Critical Volume 12.5Gy-
Volume receiving 12.5Gy or less

Constraint for 5#- 1500cc/1.5L



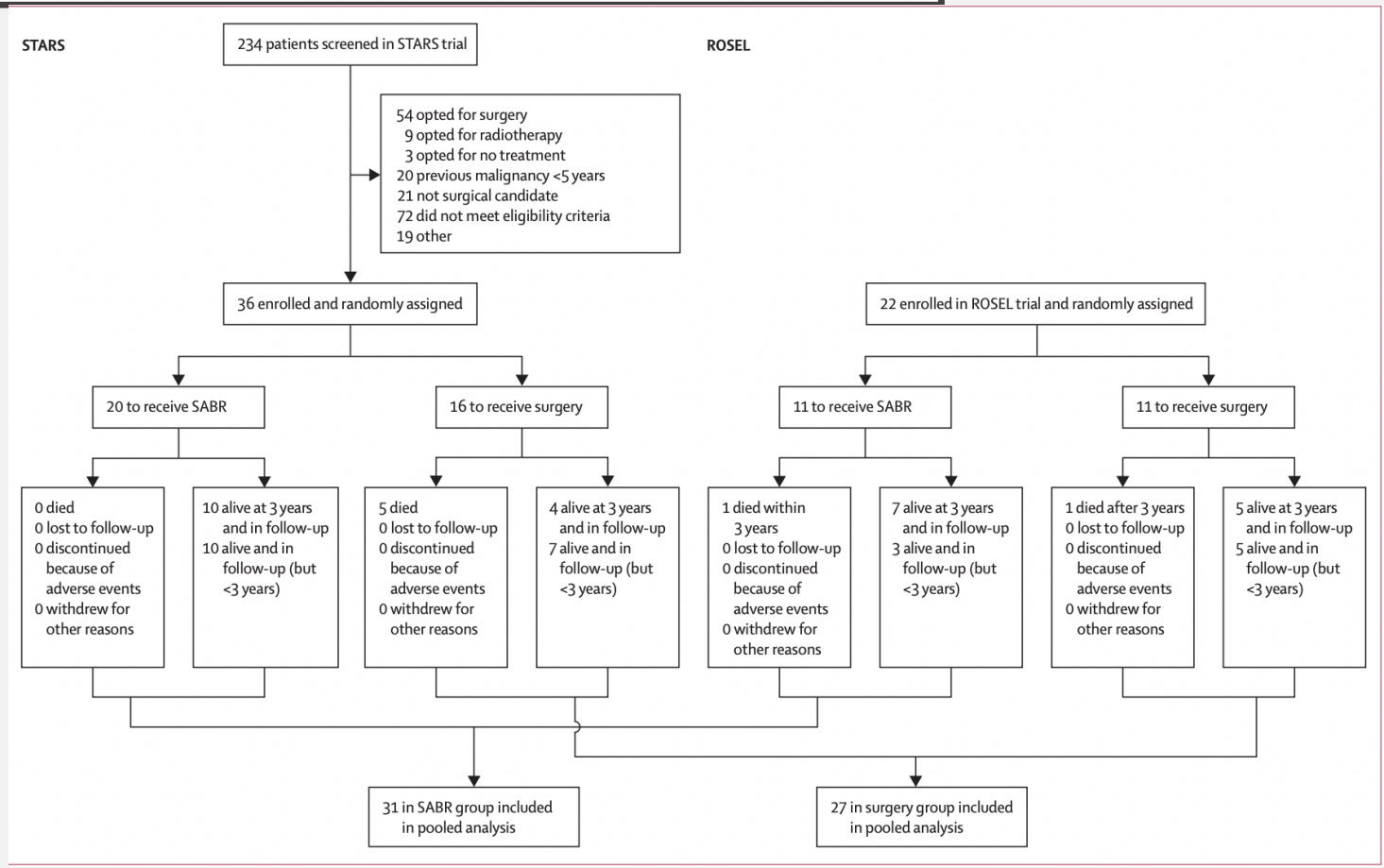

Ritter, et al IJROBP 2017

# SBRT –OPERABLE EARLY STAGE NSCLC

- Prospective, & retrospective studies, have shown efficacy and safety of SABR in operable stage I NSCLC.
- Indirect comparison show similar OS but confounded because of selection bias.

- 3 phase 3 RCTs comparing the two treatments have failed to complete accrual.

Despite limitations, this pooled analysis is the only available randomised evidence comparing SABR with surgery in patients who are fit for surgery.




Joe Chang, Lancet Oncol 2015

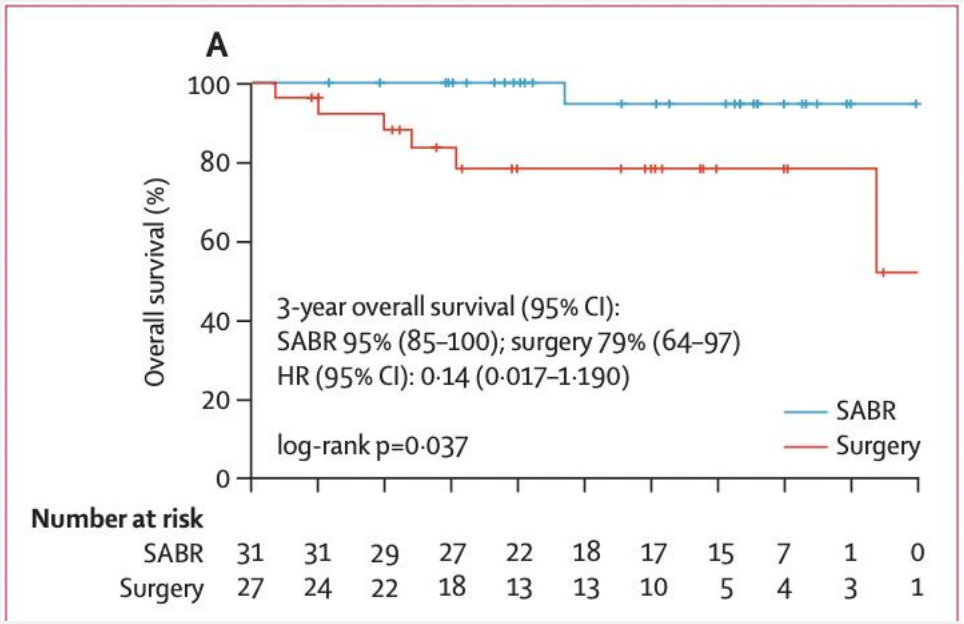
# SBRT –OPERABLE EARLY STAGE NSCLC

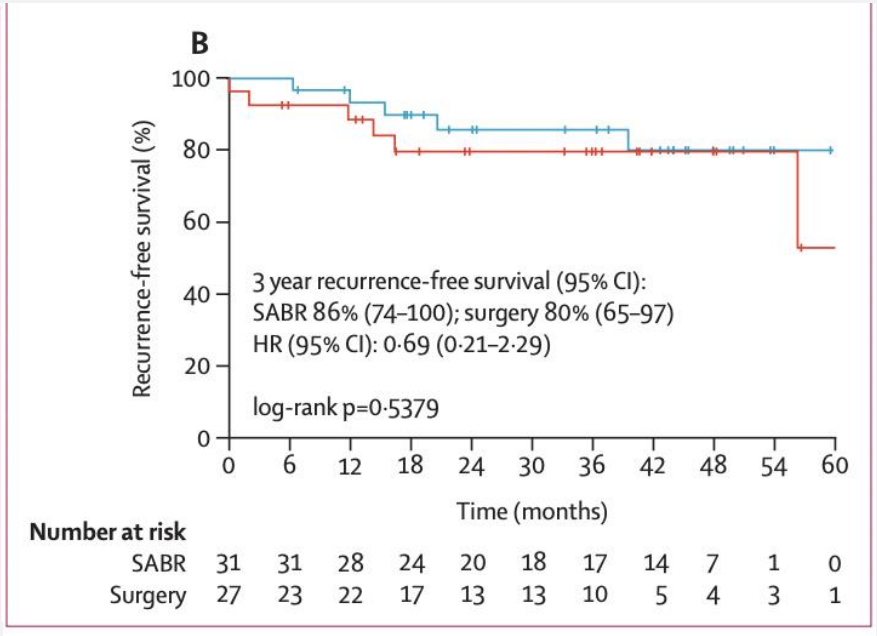
Great majority-Peripheral

Protocol defined <4cm

Median- 2,-2.5cm

Stringent QA, etc.




Joe Chang, Lancet Oncol 2015

# Stereotactic ablative radiotherapy for operable stage I non-small-cell lung cancer (revised STARS): long-term results of a single-arm, prospective trial with prespecified comparison to surgery

| | |
|---|---|
| Zubrod performance status | |
| 0 | 55 (69%) |
| 1 | 25 (31%) |
| Histology | |
| Squamous cell carcinoma | 13 (16%) |
| Adenocarcinoma | 63 (79%) |
| NSCLC, not otherwise specified | 4 (5%) |
| Tumour stage | |
| T1aN0M0 | 52 (65%) |
| T1bN0M0 | 28 (35%) |
| Tumour size, cm | 1·83 (0·56) |
| Tumour site | |
| Left lower lobe | 10 (13%) |
| Left upper lobe | 18 (22%) |
| Right lower lobe | 11 (14%) |
| Right middle lobe | 3 (4%) |
| Right upper lobe | 38 (47%) |
| Tumour location | |
| Central | 26 (33%) |
| Peripheral | 54 (67%) |
| Baseline smoking status | |
| Current | 16 (20%) |
| Former | 50 (63%) |
| Never | 14 (18%) |
| Baseline $FEV_1$, % predicted | 85·8% (19·1) |
| Baseline FVC, % predicted | 94·4% (16·5) |
| Baseline DLCO, % predicted | 81·4% (16·9) |

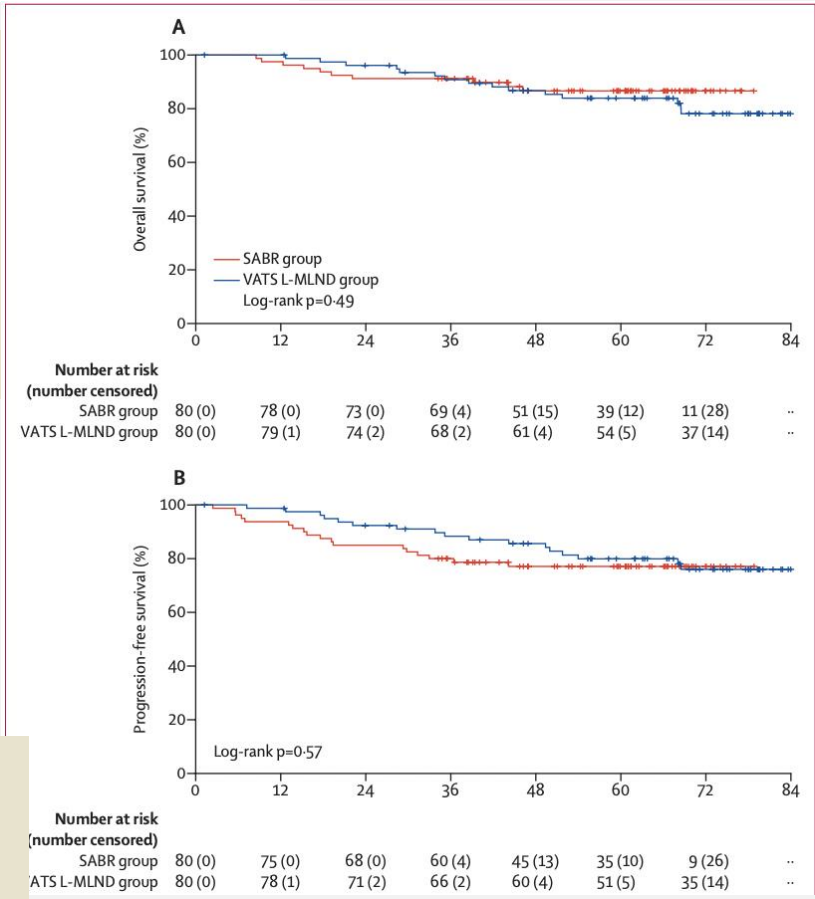
<3cm Lung lesions treated with SBRT
54Gy/3#, 50Gy/4#,
Histology confirmed
Primary Endpoint: 3-yr OS
Compared to prespecified prospective cohort
Pre-specified non-inferiority thresholds

No difference in 3-year survival- 91%

5yr OS with Surgery- 84%

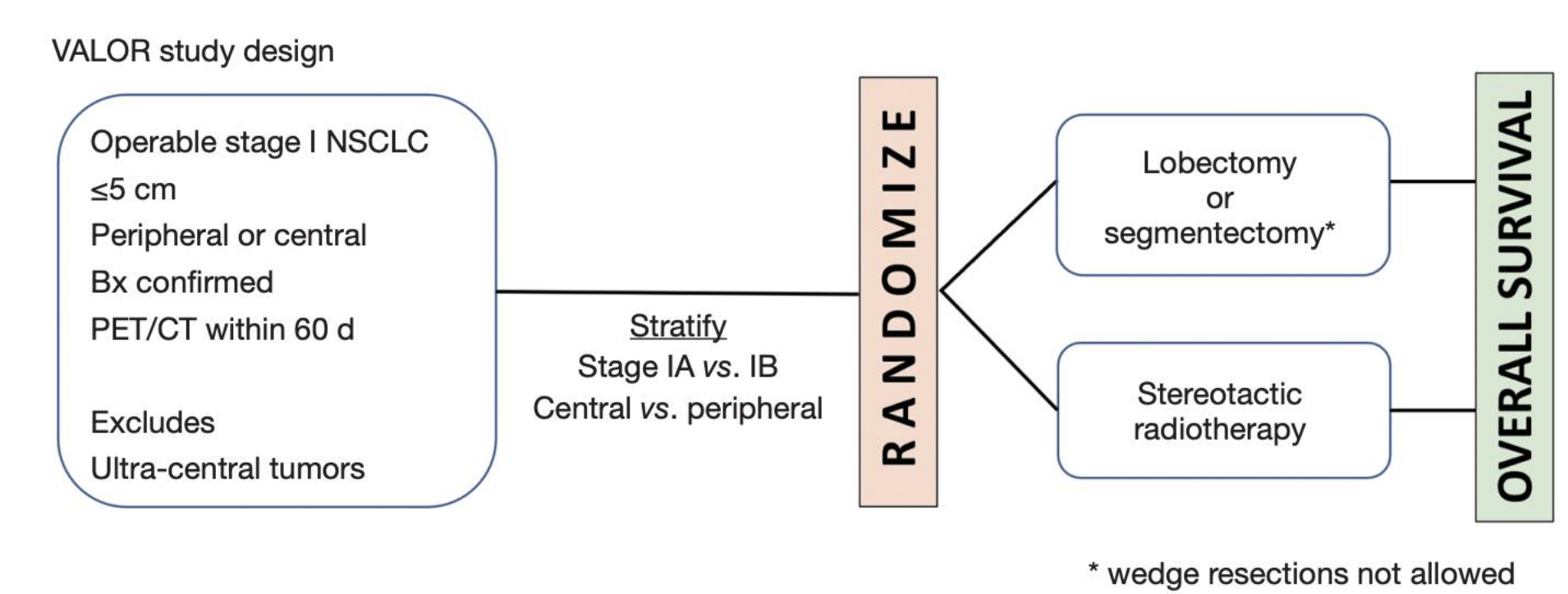
5yr OS with SBRT- 87%

- Long-term survival after SABR is non-inferior to Surgery for operable stage IA NSCLC.
- SABR remains promising but multidisciplinary management is strongly recommended




Joe Chang, et al Lancet Oncol 2021

# ONGOING RESEARCH




STABLE-MATES- cT <4cm, SBRT vs SLR vs. Choice, 3 yr OS Primary endpoint,

POSTLIV- cT <3cm, SBRT vs. SLR, 2yr Local Control Primary endpoint

# IMAGING POST SBRT

**Table 2: Early and Late CT Patterns after Lung SBRT**

| |
|---|
| Early: up to 6 months |
| Diffuse consolidation pattern |
| Diffuse ground-glass pattern |
| Patchy ground-glass pattern |
| Patchy consolidation and ground-glass pattern |
| No change |
| Late: after 6 months |
| Modified conventional pattern |
| Scarlike pattern |
| Masslike pattern |
| No change |

Febbo, et al RadioGraphics 2018

| Recurrences | Local | Regional | Distant |
|---|---|---|---|
| **VU Univ Med Center**<br><br>676 patients; median Follow-up 33 months | 10.5% | 12.7% | 20% |
| | | | |
| **MD Anderson Hospital**<br><br>912 patients; median Follow-up 59 months | 11% | 12% | 21% |

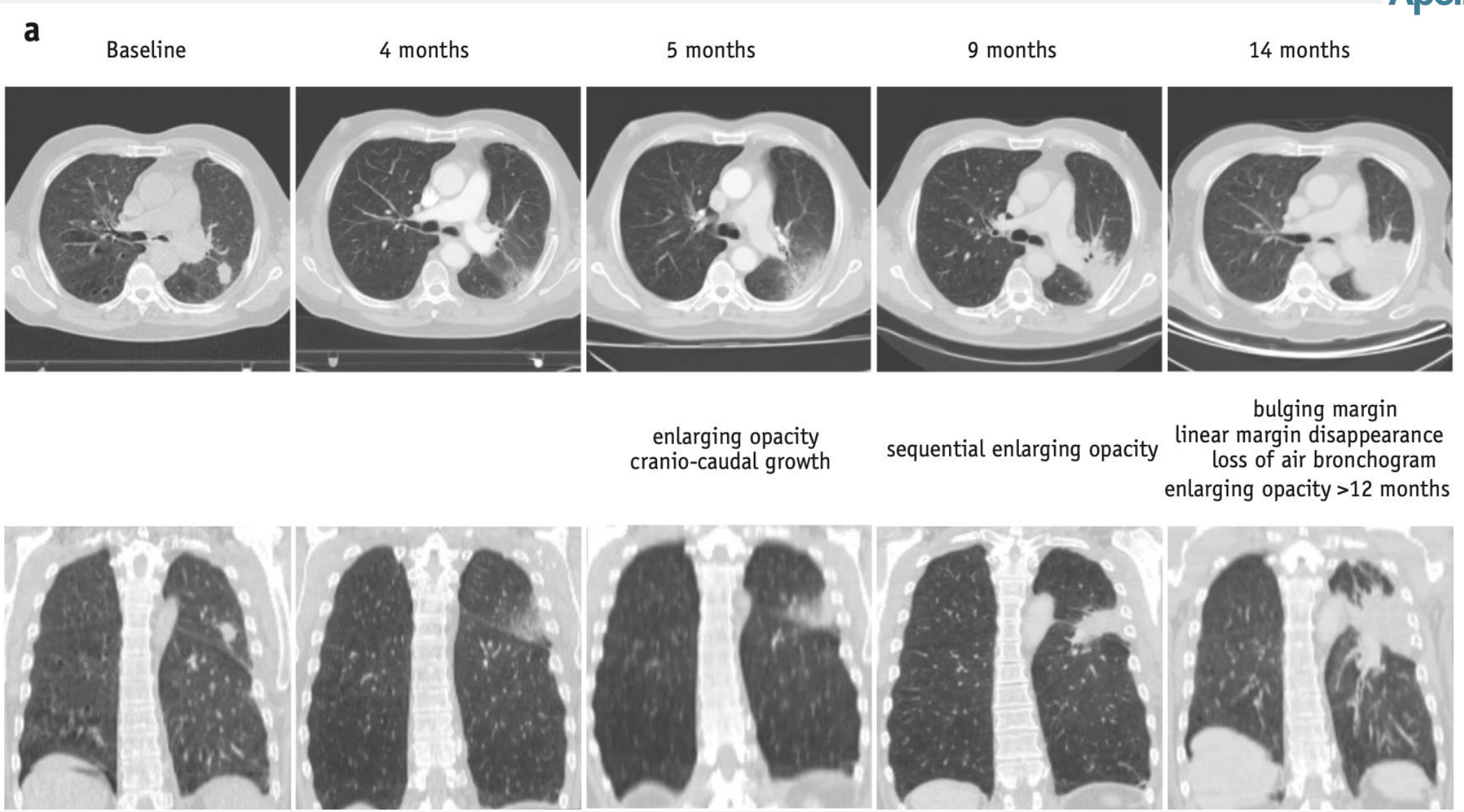
Senthi S, et al Lancet Oncol 2012
Brooks E, et al IJROBP 2017

# Bulging Margins, Cranio-caudal growth- Most Important ones to note

| High-risk feature | Sensitivity (%) | | Specificity (%) | |
|---|---|---|---|---|
| | Huang et al[40] | Peulen et al[49] | Huang et al[40] | Peulen et al[49] |
| Enlarging opacity at primary site | 92 | 100 | 67 | 31 |
| Sequential enlargement | 67 | 62 | 100 | 77 |
| Enlargement after 12 months | 100 | 92 | 83 | 50 |
| Bulging margin | 83 | 85 | 83 | 100 |
| Linear margin disappearance | 42 | 85 | 100 | 100 |
| Loss air bronchogram | 67 | 15 | 96 | 100 |
| Craniocaudal growth of ≥5 mm and ≥20% | 92 | 100 | 83 | 50 |

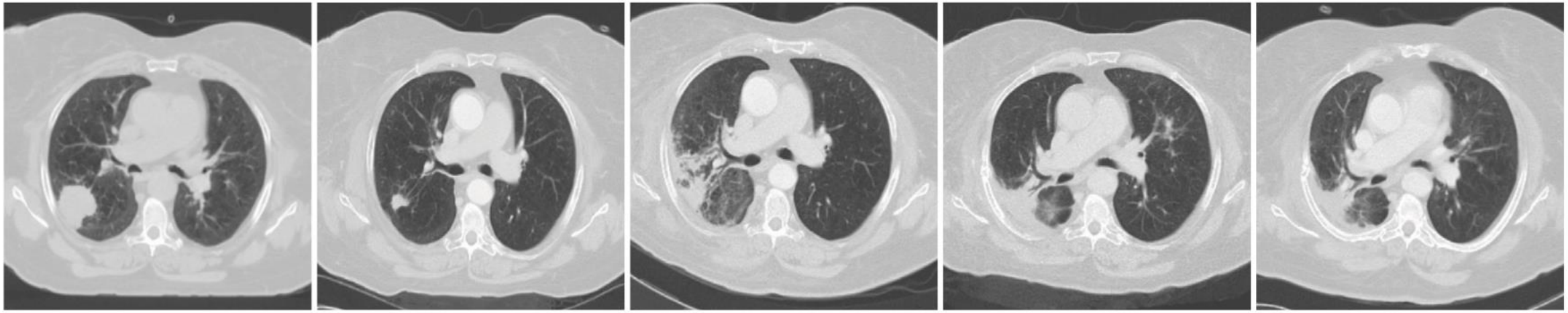
Heike Peulen, et al IJROBP 2016

SA Mattonen, et al BJR 2016


a
Baseline
4 months
5 months
9 months
14 months
enlarging opacity
cranio-caudal growth
sequential enlarging opacity
bulging margin
linear margin disappearance
loss of air bronchogram
enlarging opacity >12 months

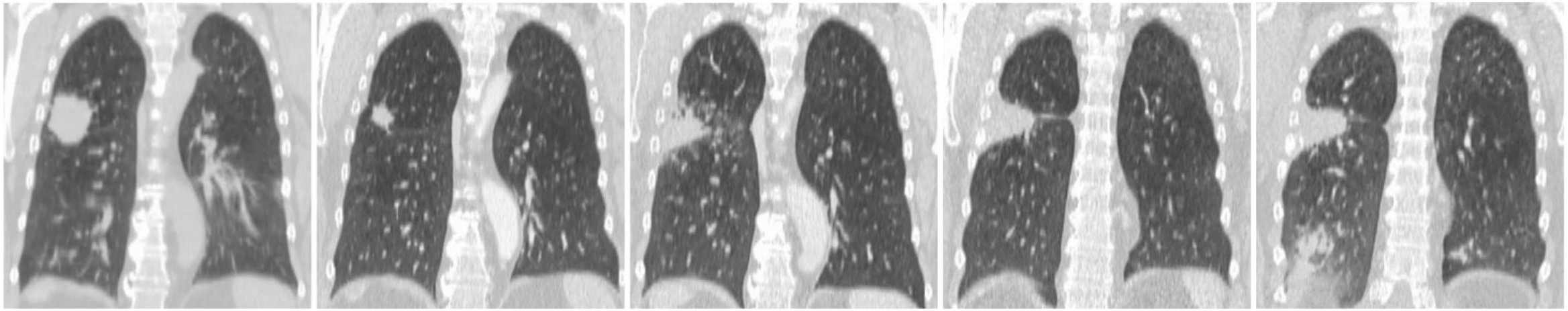
b

Baseline | 5 months | 7 months | 23 months | 32 months

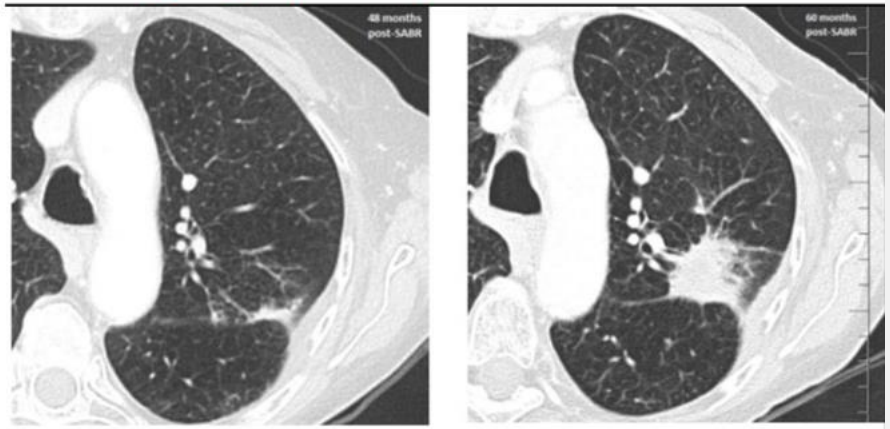


enlarging opacity
cranio-caudal growth

sequential enlarging opacity
enlarging opacity >12 months

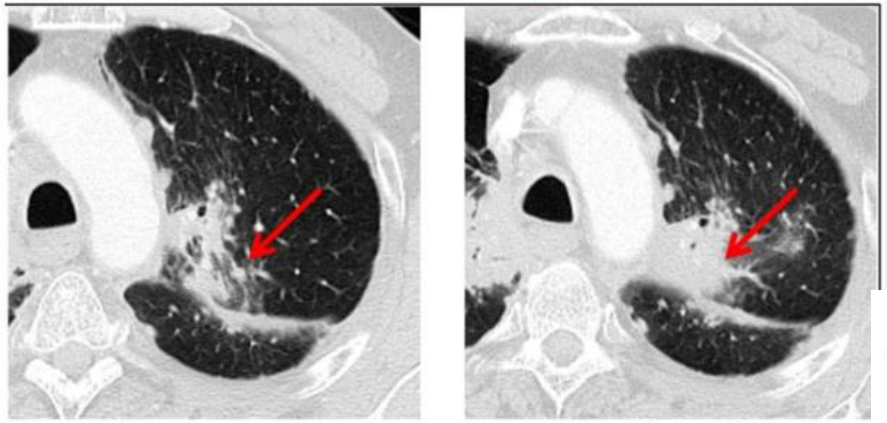


## Enlarging opacity



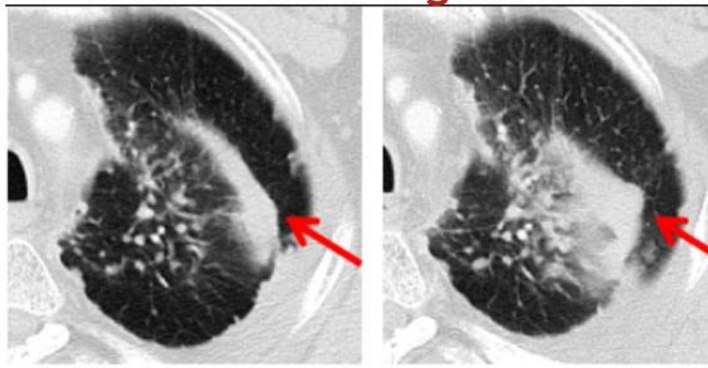
48 months post-SABR | 60 months post-SABR

## Loss of air bronchograms



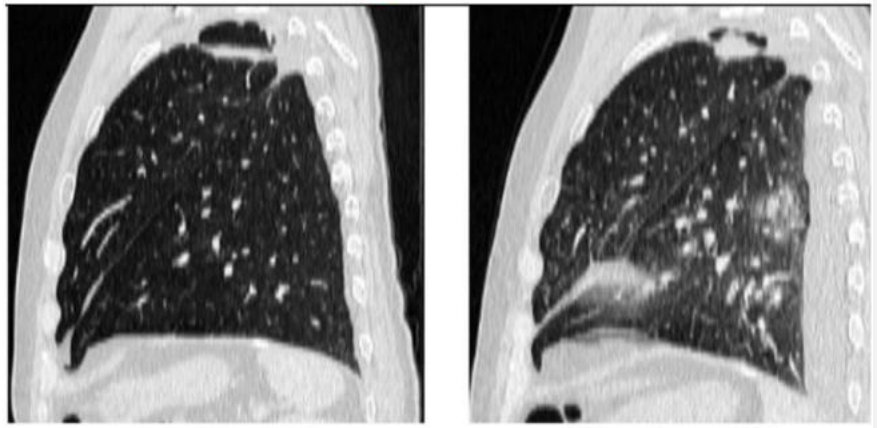
10 months post-SABR | 21 months post-SABR

## Loss of linear margins



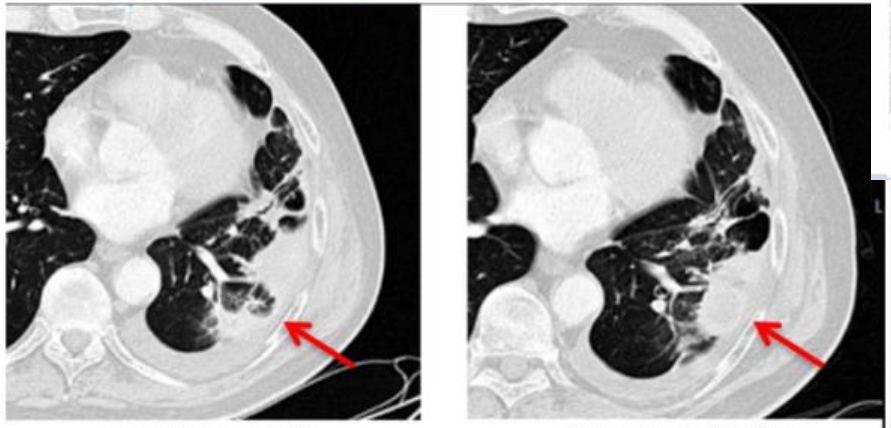
25 months post-SABR | 28 months post-SABR

## Cranio-caudal growth



10 months post-SABR | 16 months post-SABR

## Bulging margins

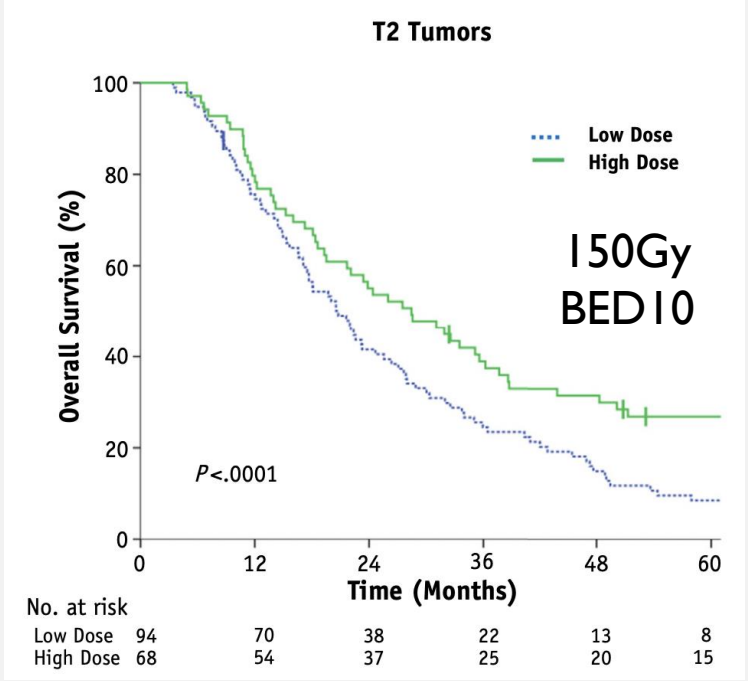


5 months post-SABR | 10 months post-SABR

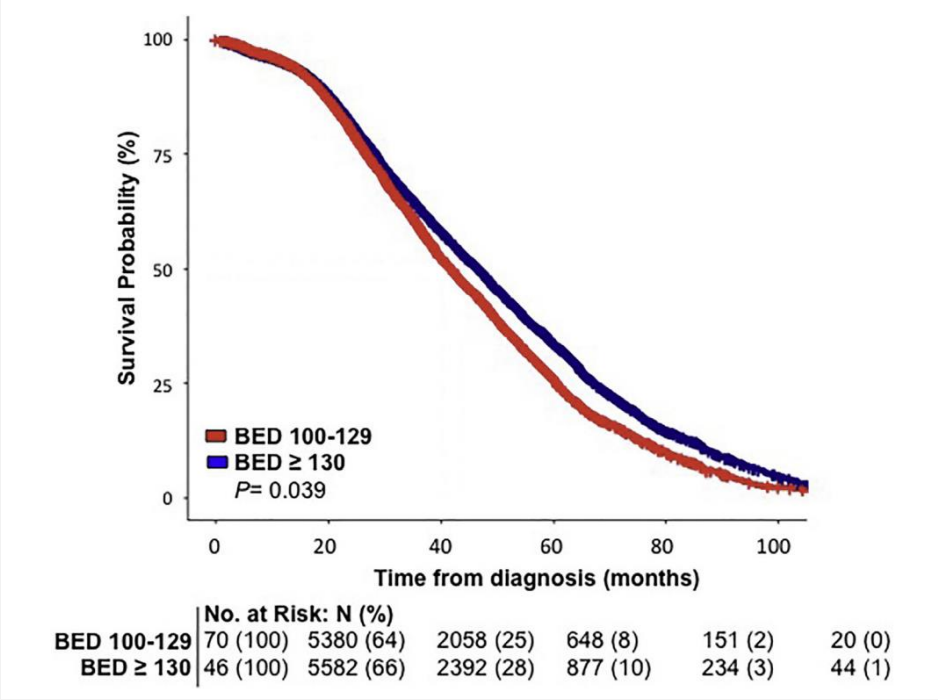
Ronden M, et al J Thoracic Oncol 2018

# DOSE OF SBRT FOR EARLY STAGE LUNG

## Treatment effect OR Impact of tumor burden




Koshy M, et al IJROBP 2015




Moreno, et al JTO 2020

The usual BED10 >100Gy has been an accepted standard

# MY PREFERENCE FOR DOSE FRACTIONATION

| Characteristic | Dose/Fraction |
|---|---|
| Small, Peripheral, <3cm, Away from the chest wall | 54Gy/3# |
| >3cm, Peripheral, broad-based attachment to chest wall | 60Gy/5# |
| Central Tumors, select ultra central tumors | 60Gy/8# |

# CONCLUSION FOR EARLY-STAGE LUNG CANCER

Standard of care in inoperable early-stage lung cancers, improved OS compared to std fractionation

Robust long-term outcomes

Caution preferred while treating central and ultra central, most can be treated safely

Comparable outcomes so far with lobectomy and other surgical approaches

Imaging after SBRT- tricky, need to learn and educate our colleagues (radiologists regarding treatment effects)

Higher BED10 >130Gy seem to be better, need further validation.

Ongoing research will further refine our understanding