TSOG Update

Mara Antonoff, MD
Associate Professor
UT MD Anderson Cancer Center

March 10, 2022

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

General Thoracic Surgical Club

AATS Thoracic Surgery Oncology Group
A joint venture between AATS and Memorial Sloan Kettering Cancer Center

AATS | Thoracic Surgery Oncology Group

A joint venture between AATS and Memorial Sloan Kettering Cancer Center

David R. Jones MD
Chair, TSOG

Executive Committee
Ara Vaporciyan MD
Raphael Bueno MD
David Harpole MD

Project Manager: Maria Singh

AATS Thoracic Surgery Oncology Group

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The Thoracic Surgery Oncology Group (TSOG) supports a network of North American thoracic surgery clinical trials to improve the understanding of thoracic oncologic diseases and enhance patient care.

Formed in 2017 by the Fiona and Stanley Druckenmiller Center for Lung Cancer Research at Memorial Sloan Kettering Cancer Center in conjunction with the American Association for Thoracic Surgery, the Group administers multisite trials focused on recent advances in precision medicine, immunotherapy intraoperative imaging, and related surgical questions. By actively accruing patient to relevant investigator-initiated clinical trials, as well as select industry-sponsored clinical trials, TSOG aims to improve outcomes for patients with thoracic malignancies.

Learn more about the initiative and how to join the network by visiting aats.org.

Thoracic Surgery Oncology Group

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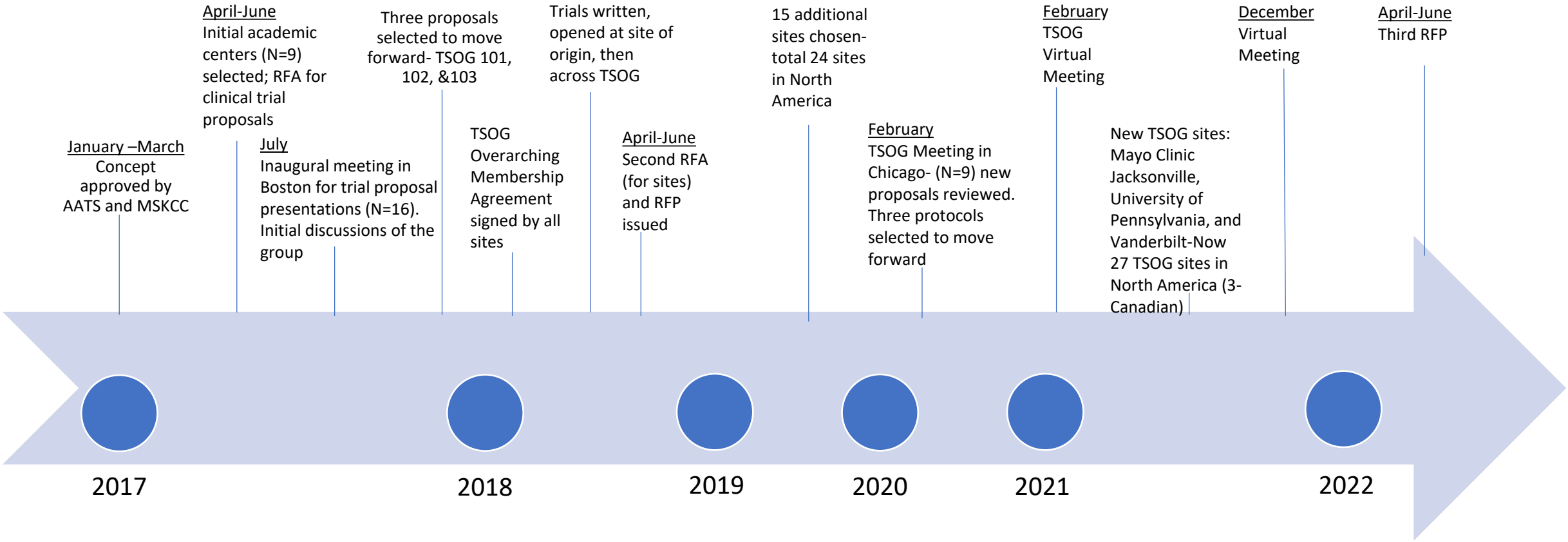
TSOG Timeline



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TSOG 101

PI: James M. Isbell, MD, MSCI
Perioperative Circulating Tumor DNA as a Prognostic Biomarker in Patients Undergoing Neoadjuvant Therapy for Resectable NSCLC

Concept:

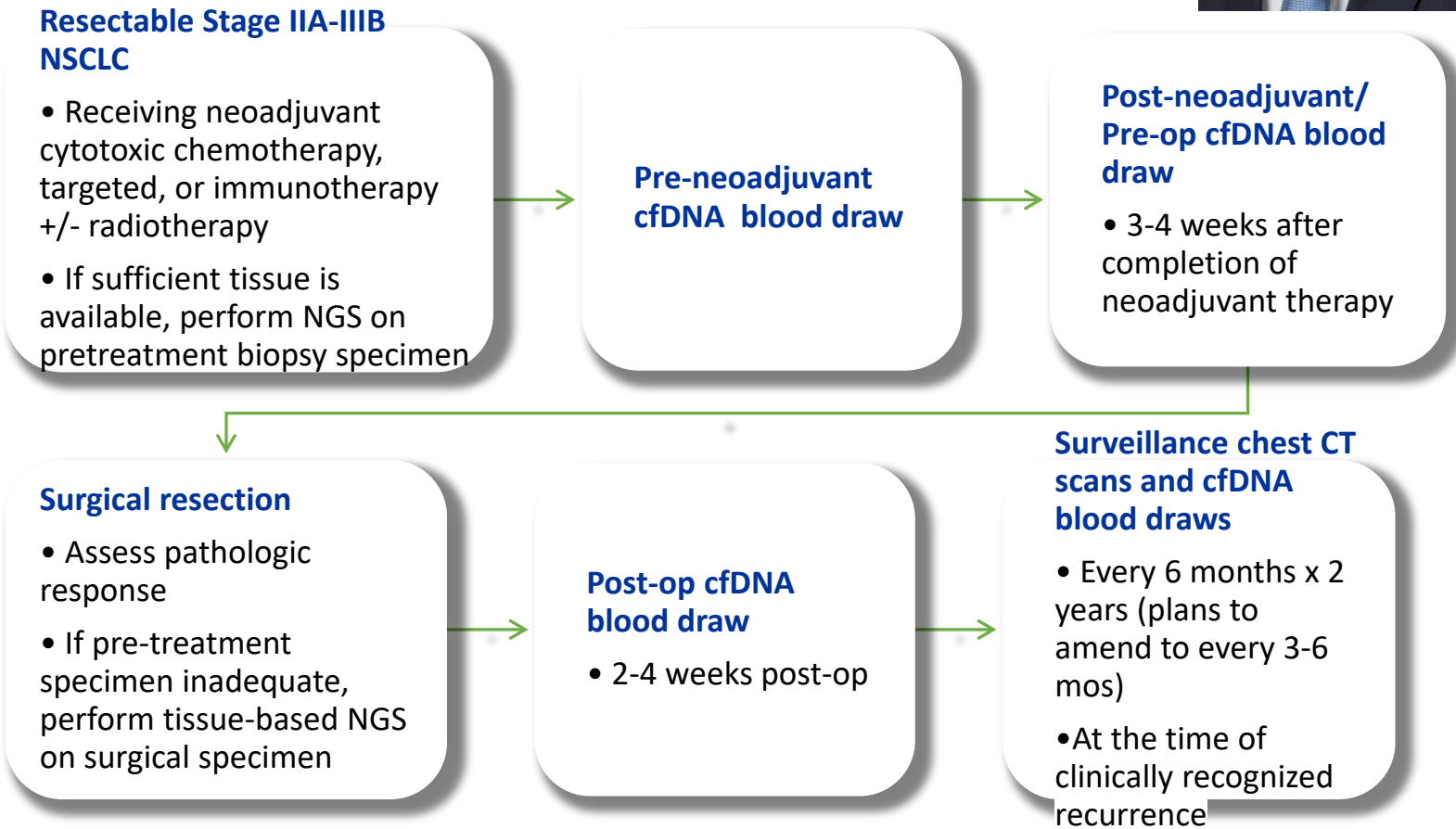
A valid biomarker is needed to assess for treatment response and the presence of minimal residual disease (MRD) in patients undergoing curative-intent treatment for NSCLC

Hypotheses:

- The percentage change in ctDNA variant allele fractions (VAF) before and after neoadjuvant therapy will correlate with pathological response.
- The VAF after complete surgical resection will be predictive of recurrence, disease-free survival and overall survival.

Eligibility Criteria:

- Resectable and medically operable stage IIA-IIIB NSCLC
- Undergoing (any) neoadjuvant cytotoxic, targeted or checkpoint inhibitor therapy with or without radiotherapy



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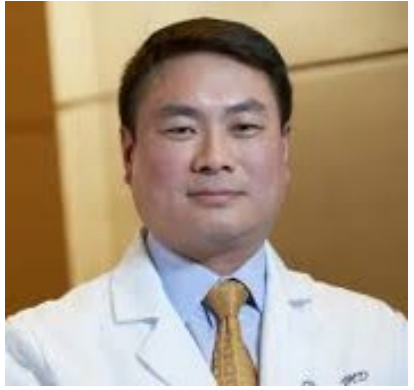
TSOG 102

PI: James Huang, MD

Registry Trial of Active Surveillance for Multifocal Ground Glass Opacities(GGO)



Concept and Hypothesis

- Registry of GGO coupled with active surveillance
  - Mirrors common practice
  - Prospective data about the natural history of these lesions
  - Standardized protocol for surveillance and intervention
- Hypothesis:
  - Active surveillance for GGO is feasible and safe

Study Design:

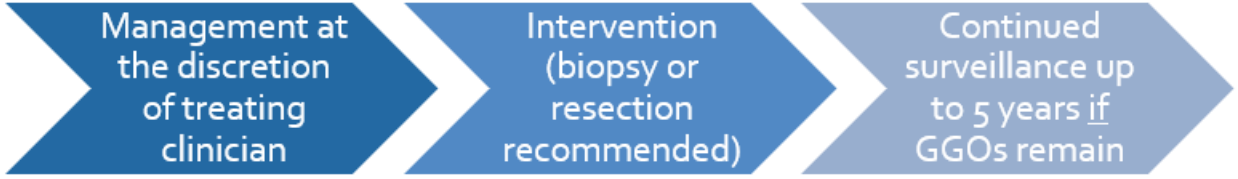
- Patients with 2 or more GGO
- Each lesion tracked in registry
  - CT scan every 6-12 mo
  - Progression defined as:
    - Growth ≥ 50% or more over baseline
    - Increase in solid component > 50% solid
- At progression:
  - Intervention (biopsy or resection) recommended
  - Discretion of treating clinician
- Surveillance on protocol for 5 years

Eligibility:

- Inclusion Criteria
  - 2 or more GGO, each ≥ 0.6cm and ≤ 3cm
- Exclusion Criteria
  - GGO > 3cm
  - GGO > 50% solid
    - (Consolidation/Tumor Ratio > 0.5)
  - Prior history of lung cancer > stage IA
  - Current or prior history of other malignancy

Study Schema

In case of clinical progression:



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TSOG 103

PI: Mara Antonoff MD

The role of multimodality management in risk-stratified patients with lung-limited metastatic colorectal cancer

Thoracic Surgery Oncology Group

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TSOG 104

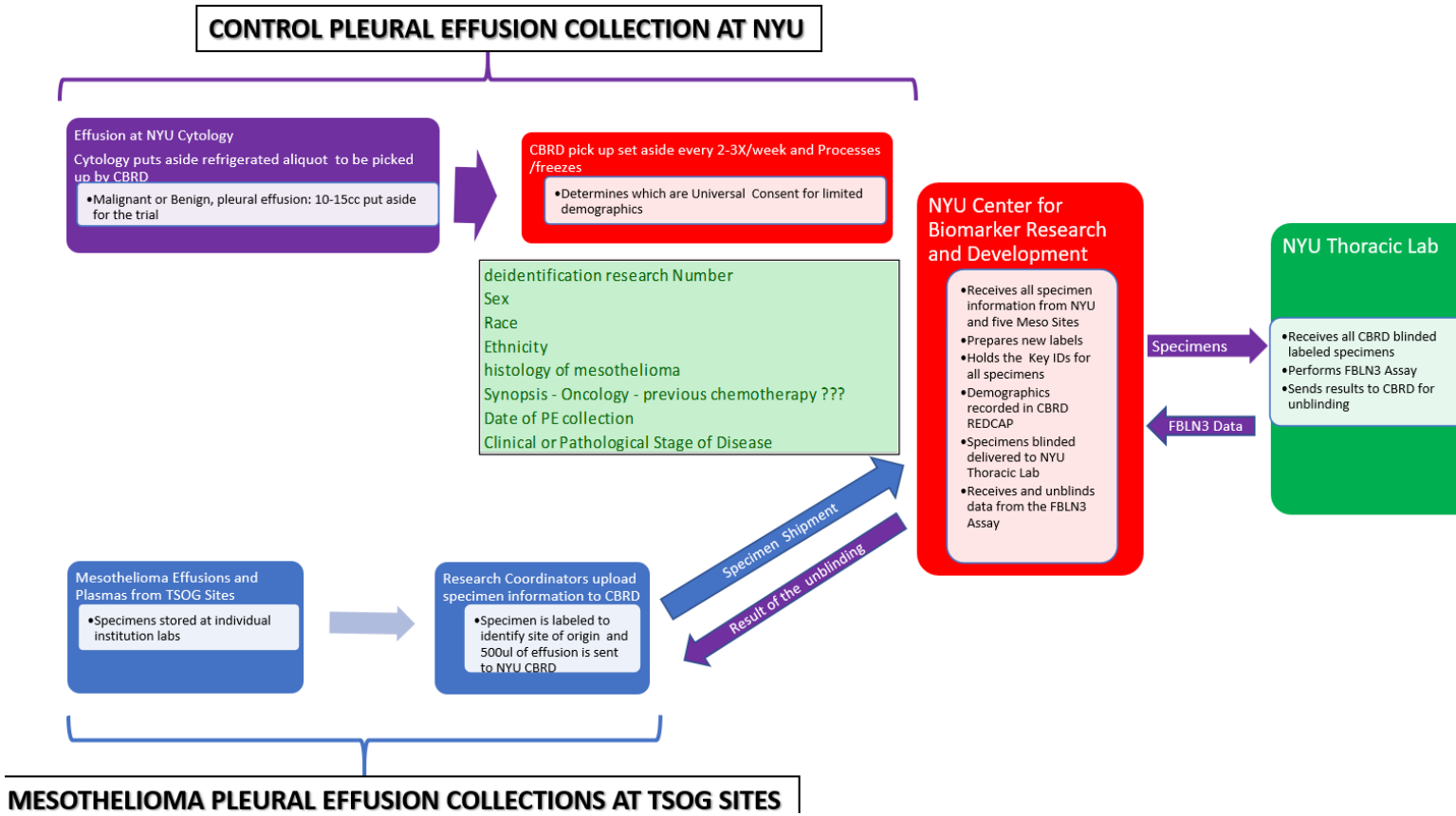
PI- Harvey Pass, MD

Blinded Prospective Validation Trial of Pleural Effusion FBLN3 as a Specific Biomarker of Malignant Pleural Mesothelioma

- **Hypothesis:** FBLN3 is differentially overexpressed in MPM compared to other malignancies that present as pleural effusions
  - **Specific Aim 1:** Prospectively collect pleural fluid from newly diagnosed or treated patients with pleural effusions
  - **Specific Aim 2:** Measure FBLN3 levels in de-identified, blinded prospectively collected specimens using the mab428.2 ELISA in the NYU Thoracic Surgery Laboratory
  - **Specific Aim 3:** Unblind levels of FBLN3, construct ROC curves for pleural effusion for MPM vs other etiology

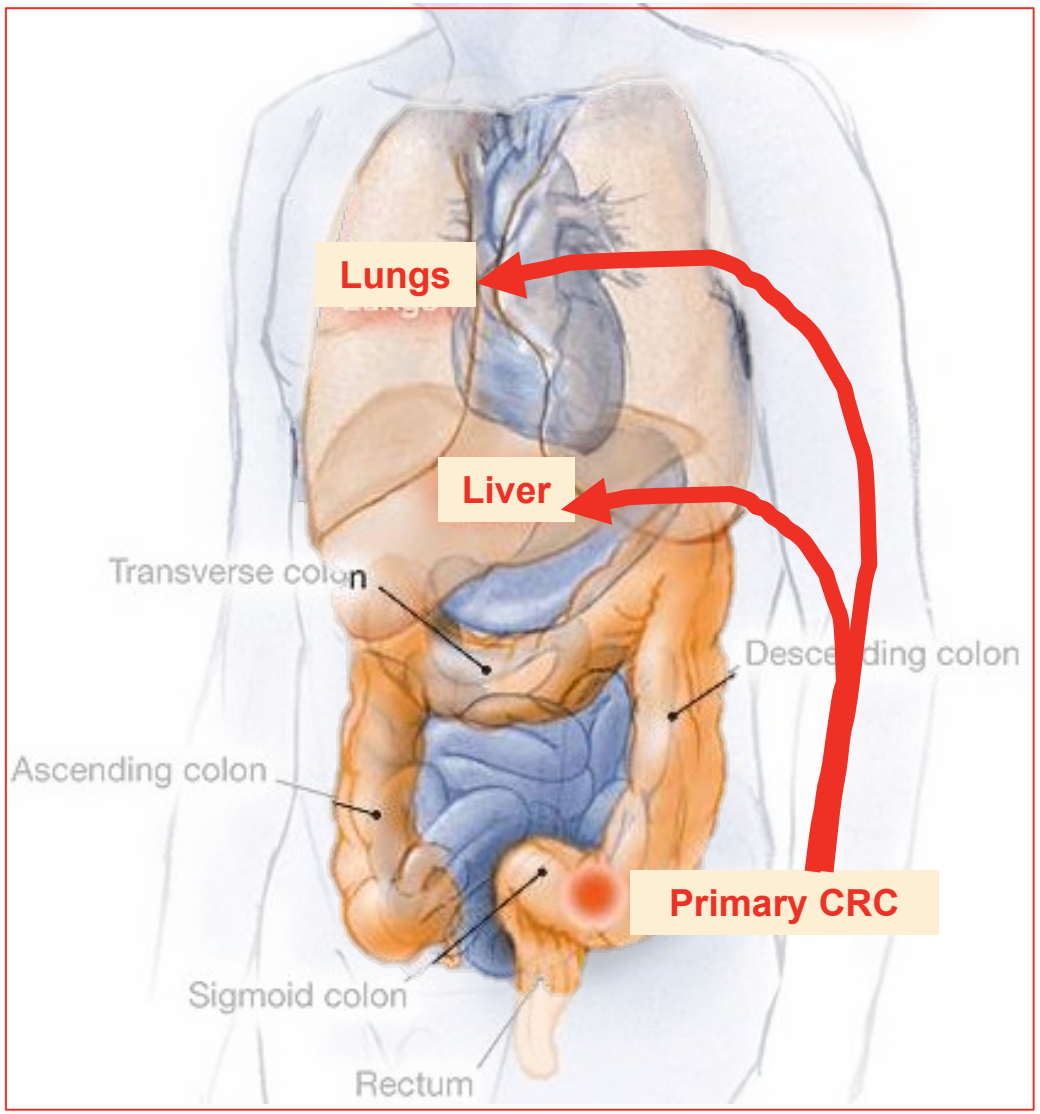
Sites open to Accrual: NYU, University of Toronto/UHN, Brigham and Women's Hospital, Baylor College of Medicine, and Duke University

Site Pending Activation: MSKCC



Colorectal cancer

- 1.3 million new cases yearly worldwide
- 2nd leading cause of cancer-related deaths in US
- 10-20% incidence of pulmonary metastatic disease during disease course
- 25% with Stage IV disease at diagnosis
- Lung is most common extra-abdominal site of distant metastasis



Ferlay J et al, Int J Cancer 2015, 136(5):E359-386; Siegel R et al, CA Cancer J Clin 2014, 64(2):104-117; Mitry et al, Gut 2010,59(10):1383-1388.

Best management for pulmonary metastases?

- The role of multidisciplinary management remains unclear for lung-limited metastatic colorectal cancer (mCRC)
- In many circumstances, pulmonary metastasectomy (PM) can significantly improve survival
- Retrospective reviews have sought those clinical attributes which suggest best outcomes from pulmonary metastasectomy
- **Perioperative chemotherapy improves survival outcomes for patients with resected liver-limited colorectal cancer undergoing metastectomy**
- No prospective trials have been conducted for the role of multimodality therapies in this population **with lung-limited metastatic disease**

Inoue M, Ann Thorac Surg. 2004 78(1):238-24; McCormack PM, Arch Surg. 1992;127(12):1403-1406

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- Retrospective reviews have sought those clinical attributes which suggest best outcomes from pulmonary metastasectomy
- No prospective trials have been conducted for the role of multimodality therapies in this population→ eligibility for PM has been speculated based on retrospective data

Inoue M, Ann Thorac Surg. 2004 78(1):238-24; McCormack PM, Arch Surg. 1992;127(12):1403-1406

Clinical factors predictive of PM outcome

- Prolonged disease-free interval (DFI) and fewer nodules portend better outcome
- MDA experience:
  - >3 lesions at first PM and DFI <3 years predicted lung recurrence
  - # lesions correlated with overall survival
  - Increasing age and male sex associated with shorter survival
- Other series
  - Age, sex: differing, variable results
  - Consistent demonstration of # of metastases as predictive of survival after PM

Blackmon SH, Ann Thorac Surg. 2012, 94(6):1802-1809; Onaitis M, Ann Thorac Surg 2009, 87(6):1684-1688; Rena O, Eur J Cardiothorac Surg. 2002, 21(5):906-912; Zink S, Eur J Cardiothorac Surg 2001, 19(6):908-913; Gonzalez M, Ann Surg Oncol 2013, 20(2):572-579.

Predictors of success after PM

- Preoperative DFI and # metastases at first PM appear to suggest risk of pulmonary recurrence

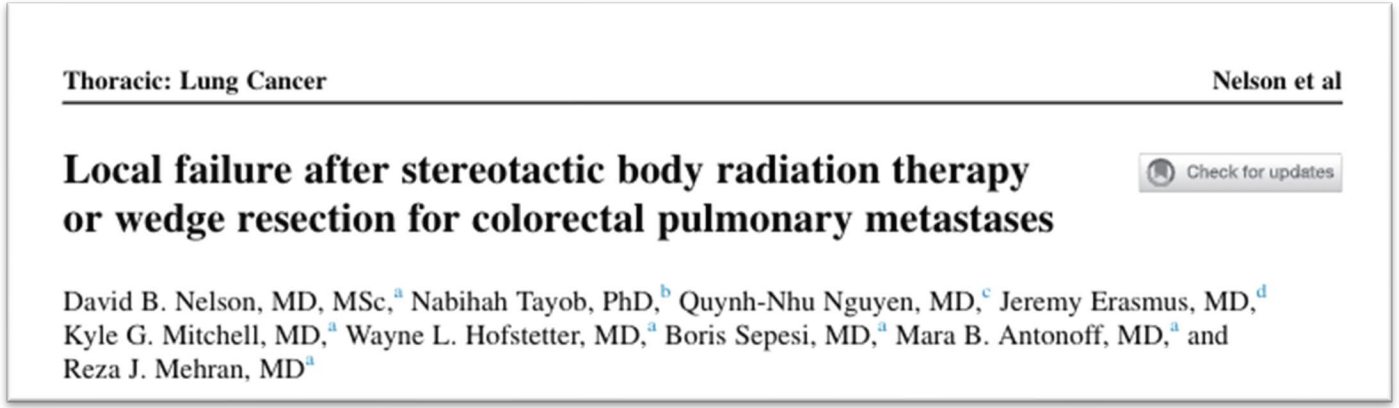
- What is role of systemic therapy among patients being considered for surgical resection of pulmonary disease?

- Uncertainty regarding interplay between surgery and chemotherapy and their impact on recurrence and survival outcomes for such patients

Blackmon SH, Ann Thorac Surg. 2012, 94(6):1802-1809; Onaitis M, Ann Thorac Surg 2009, 87(6):1684-1688;.

Surgery vs other local therapy for mCRC to lungs

- Retrospectively reviewed patients treated for pulmonary colorectal mets at MDACC with SBRT vs wedge, 2006-2016
- N = 381 patients, 826 total nodules
  - 762 wedge resections
  - 64 courses of SBRT



Thoracic: Lung Cancer — Nelson et al

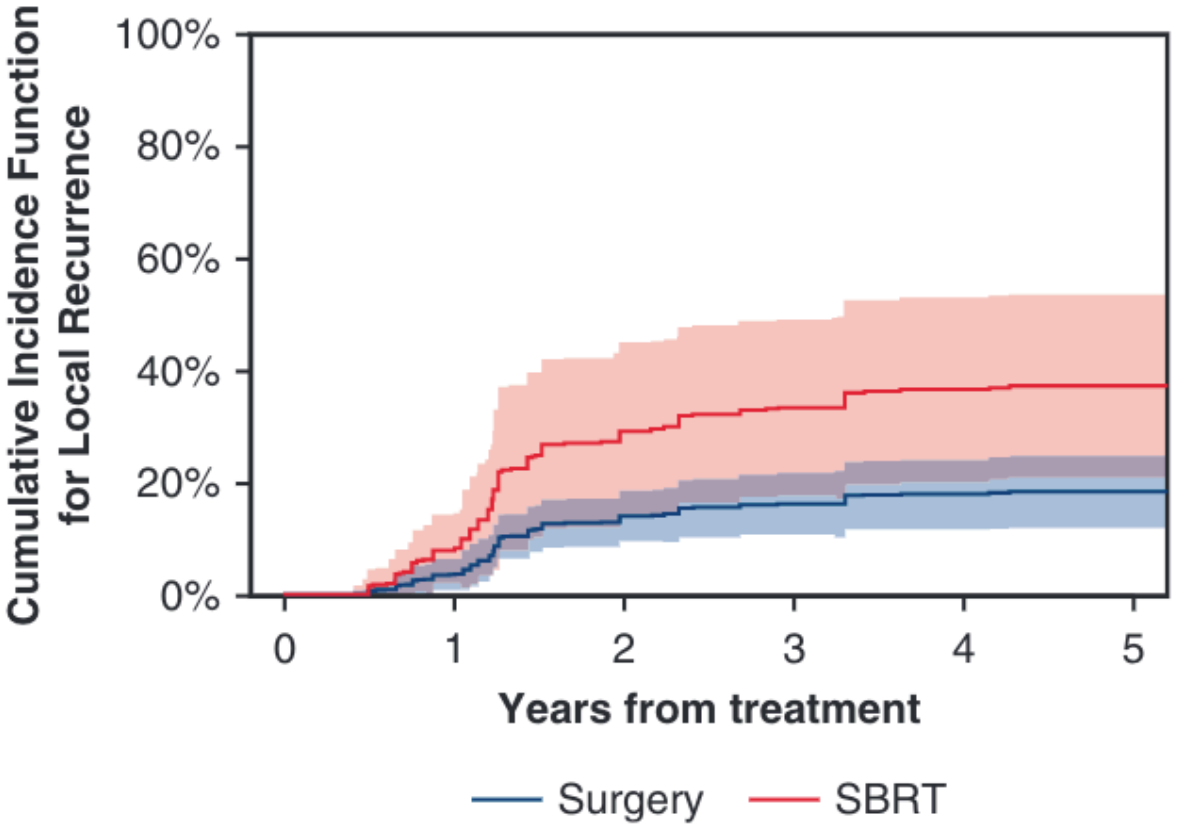
Local failure after stereotactic body radiation therapy or wedge resection for colorectal pulmonary metastases

Check for updates

David B. Nelson, MD, MSc,[a] Nabihah Tayob, PhD,[b] Quynh-Nhu Nguyen, MD,[c] Jeremy Erasmus, MD,[d] Kyle G. Mitchell, MD,[a] Wayne L. Hofstetter, MD,[a] Boris Sepesi, MD,[a] Mara B. Antonoff, MD,[a] and Reza J. Mehran, MD[a]

Nelson DB et al, J Thorac Cardiovasc Surg 2019

Surgery vs other local therapy for mCRC to lungs



- Increased risk local recurrence with SBRT, **HR 3.28**
- Matched weights propensity scoring for local recurrence per nodule:
  - 2-year risk of local recurrence after **wedge**: **14.1%**
  - 2-year risk of local recurrence after **SBRT: 29.4%,** p = 0.02
- *Pulmonary CRC mets treated with SBRT have higher risk of recurrence than those treated with wedge*

Nelson DB et al, J Thorac Cardiovasc Surg 2019

Role of multimodality treatment for mCRC

- Favorable clinical characteristics
  - Surgery fairly well accepted
  - Role of chemotherapy **(for low-risk patients)** perioperatively is unclear (vs surgery alone)

- Poor clinical characteristics
  - Surgical resection after chemotherapy often undertaken if technically feasible
  - Additive benefit of surgery has yet to be elucidated

Novel biologic prognostic factors

- ctDNA highly sensitive and specific biomarker collected from plasma
- Data demonstrating shorter recurrence-free survival for patients after primary CRC resection if they remain ctDNA (+)
- Detection of postoperative ctDNA associated with shorter time to recurrence compared to those without any detectable ctDNA
- Presence of ctDNA following resection of hepatic metastases associated with poorer recurrence-free and overall survival
- Prognostic implication of ctDNA following lung resection remains unclear and could guide clinicians in the decision to administer postoperative chemotherapy

Lanman RB, PLoS One 2015,10(10):e0140712; Diehn MAH, J Clin Oncol. 2017,35:(suppl; abstr 3591); Tie J, Sci Transl Med. 2016, 8(346):346ra392; Overman MJ, J Clin Oncol. 2017:(suppl; abstr 3522).

Questions remain:

- Do “low-risk” patients undergoing pulmonary resection benefit from perioperative chemotherapy?

- Should “high-risk” patients undergoing systemic chemotherapy be offered the possibility of surgery?

- Are there prognostic biomarkers that can better identify patients at higher risk for recurrence following definitive therapy?

“The role of multimodality management in risk-stratified patients with lung-limited metastatic colorectal cancer”

Principal Investigator: Mara Antonoff, M.D.

MD Anderson GI Med Onc Co-PI: Van Morris, M.D.

Departments of Thoracic and Cardiovascular Surgery and Gastrointestinal Medical Oncology

MD Anderson Cancer Center

Activated July 2018 at MD Anderson, Protocol 2017-0905

Thoracic Surgery Oncology Group
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TSOG 103

PI: Mara Antonoff MD
The role of multimodality management in risk-stratified patients with lung-limited metastatic colorectal cancer

Mara Antonoff
The University of Texas MD Anderson Cancer Center

"The role of multimodality management in risk-stratified patients with lung-limited metastatic colorectal cancer." — TSOG 103

The primary objectives of this study are to compare recurrence-free survival in patients with "low-risk" lung-limited mCRC undergoing pulmonary metastasectomy with or without perioperative chemotherapy, as well as to compare overall survival in patients with "high-risk" lung-limited mCRC receiving systemic chemotherapy with or without surgical resection.

Additional exploratory objectives involve the evaluation of changes in ctDNA following surgical resection and/or systemic chemotherapy in patients with lung-limited mCRC.

Objectives:

Primary objectives:

1. To compare progression-free survival in patients with "low-risk" lung-limited mCRC undergoing pulmonary metastasectomy with or without perioperative chemotherapy.
2. To compare overall survival in patients with "high-risk" lung-limited mCRC receiving systemic chemotherapy with or without surgical resection.

Exploratory objective:

- To evaluate for changes in circulating tumor DNA following surgical resection and/or systemic chemotherapy in patients with lung-limited mCRC.

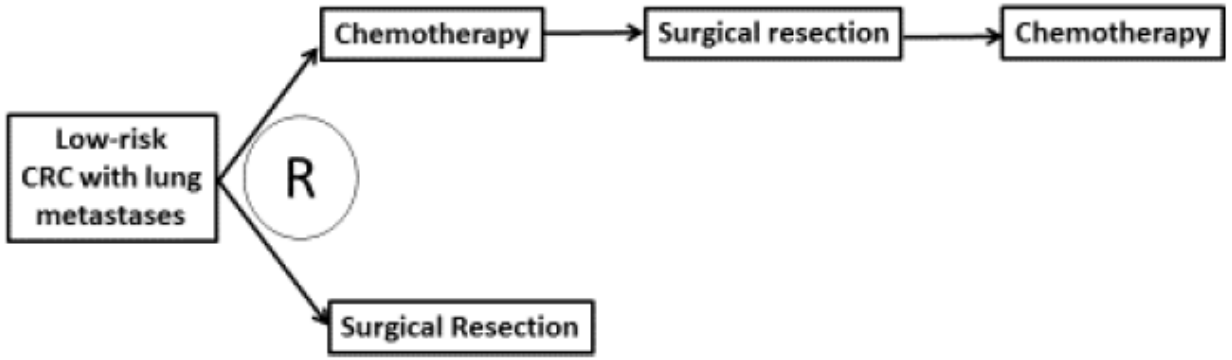
Stratification of lung-limited mCRC by risk group

Risk group	DFI (months)		Number of metastases
LOW	**≥ 12**	**AND**	**≤ 3**
*INTERMEDIATE**	*6-12*	*OR*	*4-6*
HIGH	**< 6**	**OR**	**>6**

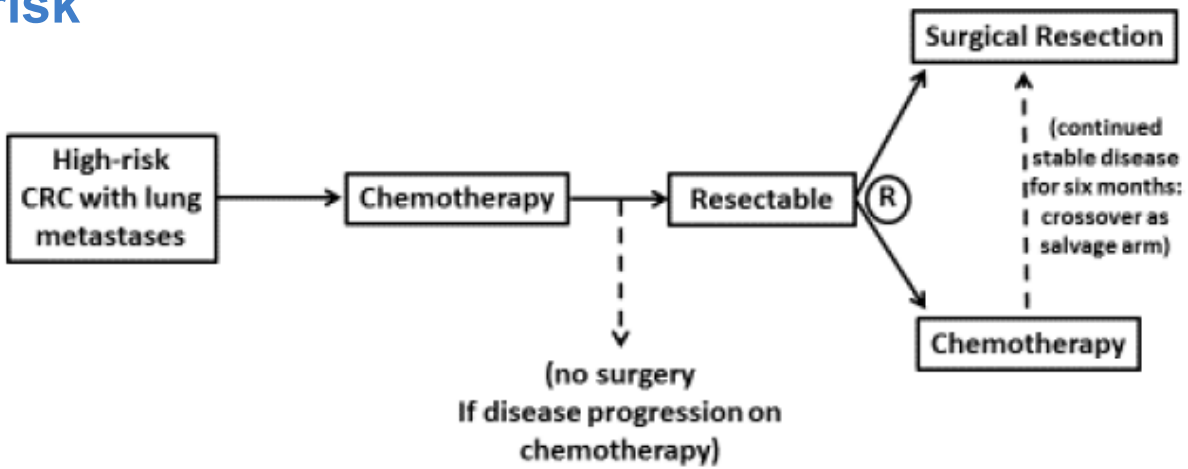
**Intermediate group is not eligible for enrollment at this time*

Schema

Low-risk



High-risk



Eligibility criteria

- Primary tumor history of histologically confirmed colorectal adenocarcinoma and anatomically resectable lung metastases
- Adequate organ function and comorbid conditions to undergo systemic chemotherapy and to undergo surgery
- Prior definitive therapy of primary tumor with no evidence of local recurrence
- Age ≥ 18
- ECOG performance status 0 or 1

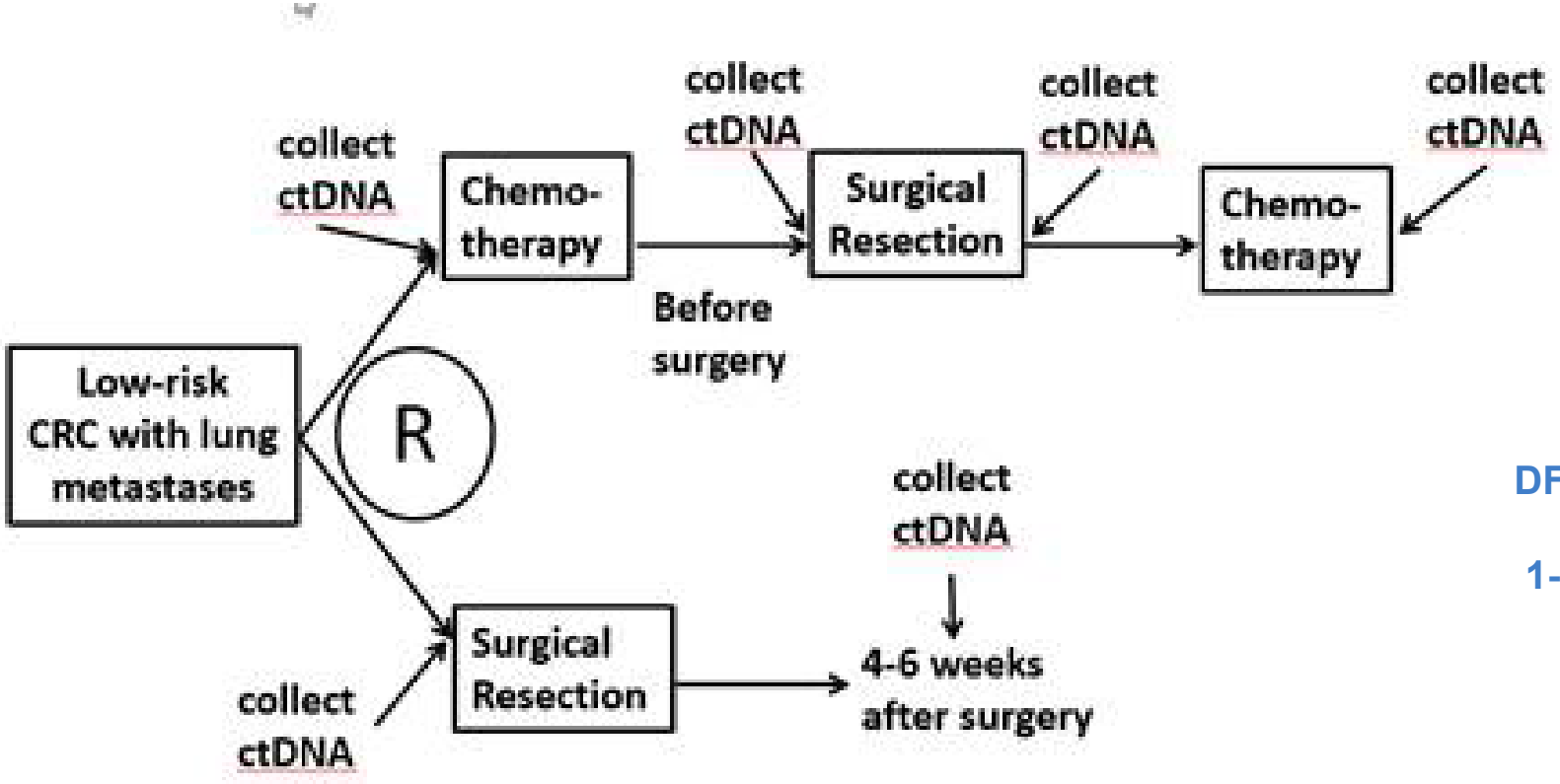
Abbreviated exclusion criteria*

- Presence of non-pulmonary metastatic site of disease that has not been definitively treated
- Prior regorafenib or TAS-102
- Synchronous or prior malignancy in last 5-years (besides nonmelanomtous skin cancer)
- Pregnancy/lactation
- Previous radiotherapy of a lung metastasis that is still radiologically detectable

Please see protocol for complete list of exclusion criteria

Low-risk lung-limited mCRC

Does perioperative chemotherapy offer benefit compared to surgery alone in patients with **low-risk** lung-only mCRC?

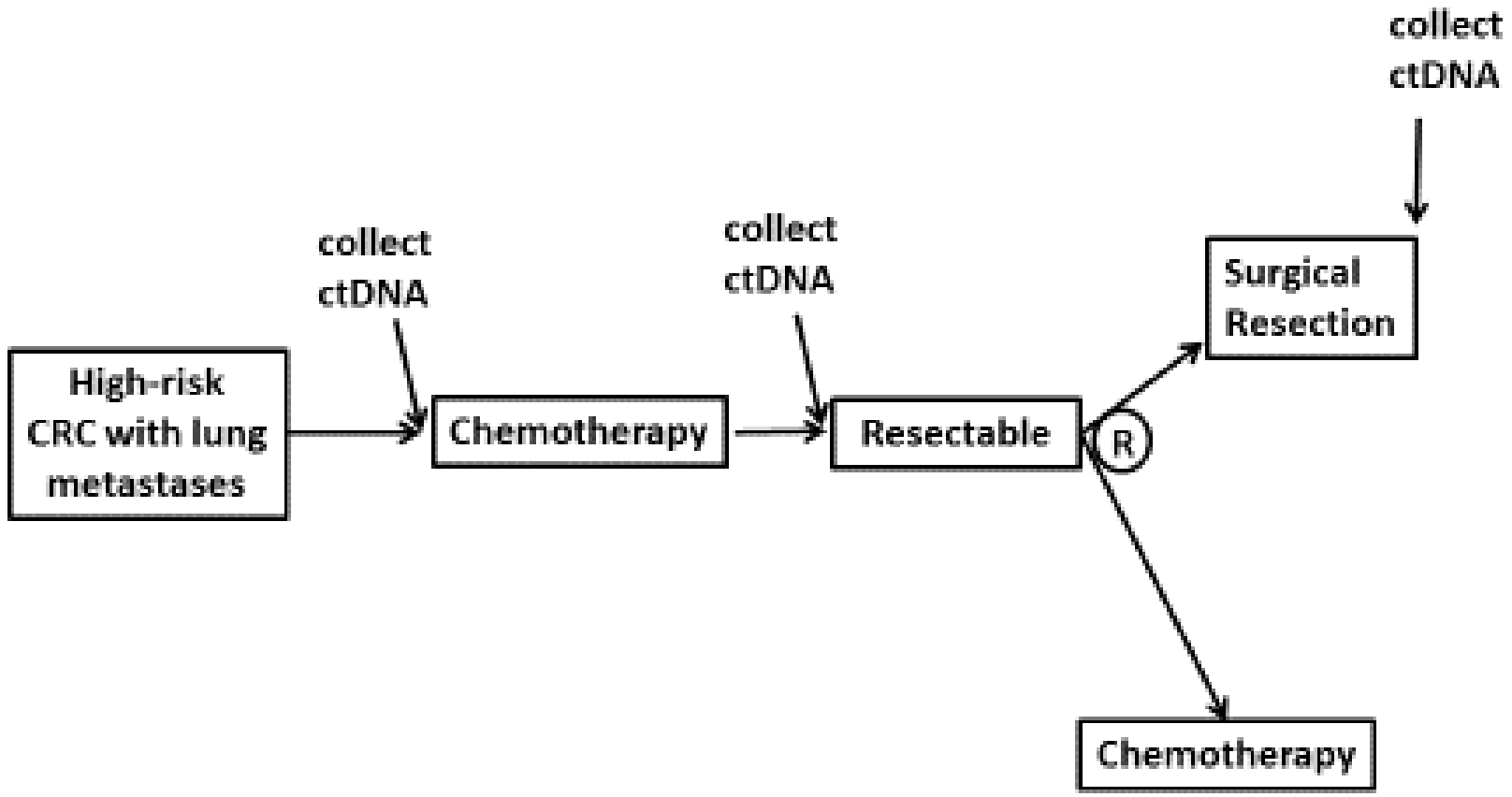


*Low risk=

DFI > 12months
AND
1-3 metastases

High-risk lung-limited mCRC

Do patients with **high-risk** lung mCRC benefit from surgery following an initial response to chemotherapy?



***High risk=**

DFI < 6 months
OR
6 or > metastases

OR
nonpulmonary met <12 mos
(eg liver)

ctDNA as a prognostic biomarker for recurrence

- Detection of circulating tumor DNA (ctDNA) from patients' plasma is a non-invasive method of assessing for tumor burden in solid tumors like NSCLC and CRC in both the limited-stage and metastatic settings
- For both risk groups, ctDNA will be collected at specific time points to monitor changes following surgery and/or chemotherapy for further assessment as a prognostic biomarker for recurrence
- Resected tumor will be sequenced to identify mutation(s) to be followed with ctDNA. In patients not undergoing surgery, available archival tumor will be sequenced

Additional stratification within risk groups

- By primary tumor laterality
  - Left- vs right-sided tumors

- By KRAS mutational status
  - Mutant vs wild-type

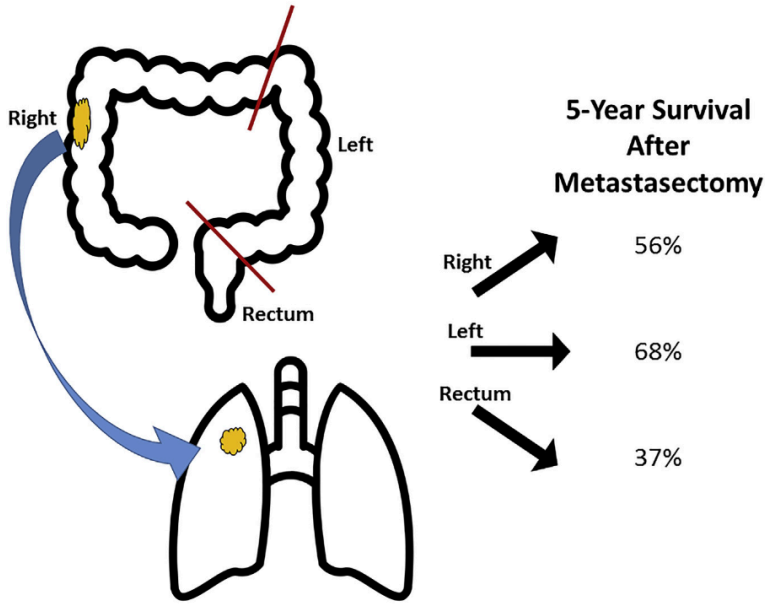
Rationale for stratification by laterality

- Superior survival for patients with left-sided disease (splenic flexure to distal colorectum)
- CRC laterality implicated in locoregional disease control following primary tumor resection
  - Right-sided tumors → 5Y LR recurrence rate double that of left-sided CRC

Charlton ME, et al. J Natl Compr Canc Netw, 2017; Park JH, et al. Dis Colon Rectum, 2015

Rationale for stratification by laterality

- Laterality furthermore implicated in OS following pulmonary metastasectomy
  - Left-sided HR 0.31 (0.10-0.93), *p*=0.036

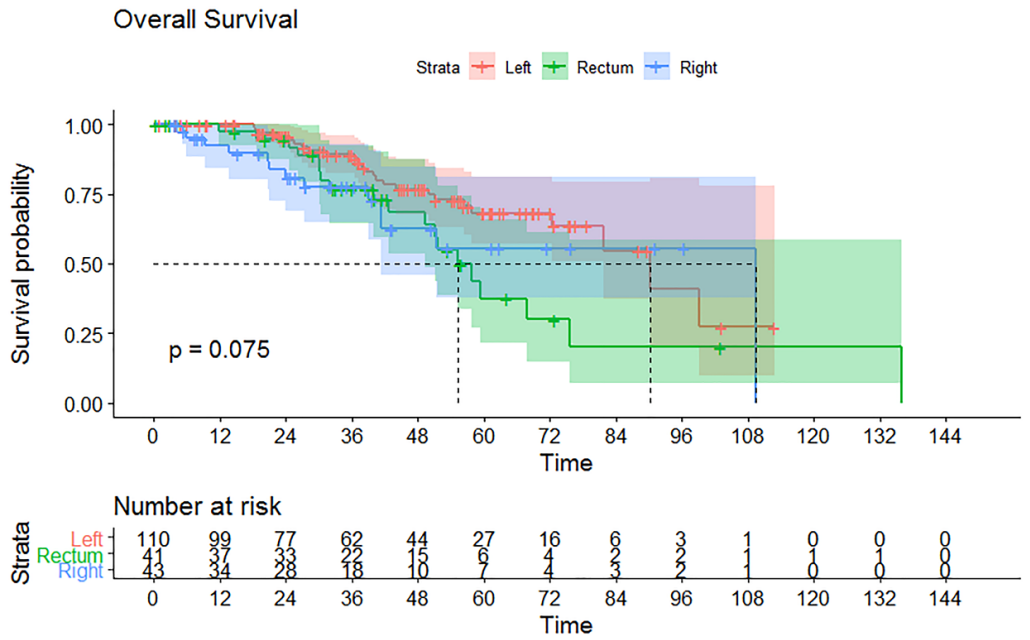


Corsini EM, et al. J Thorac Cardiovasc Surg 2021

THORACIC: LUNG METASTASECTOMY

Effect of primary colorectal cancer tumor location on survival after pulmonary metastasectomy

Erin M. Corsini, MD, MSc,[a] Kyle G. Mitchell, MD, MSc,[a] Arlene Correa, PhD,[a] Van K. Morris, MD,[b] and Mara B. Antonoff, MD,[a] the MD Anderson Pulmonary Metastasectomy Working Group*



@maraantonoff

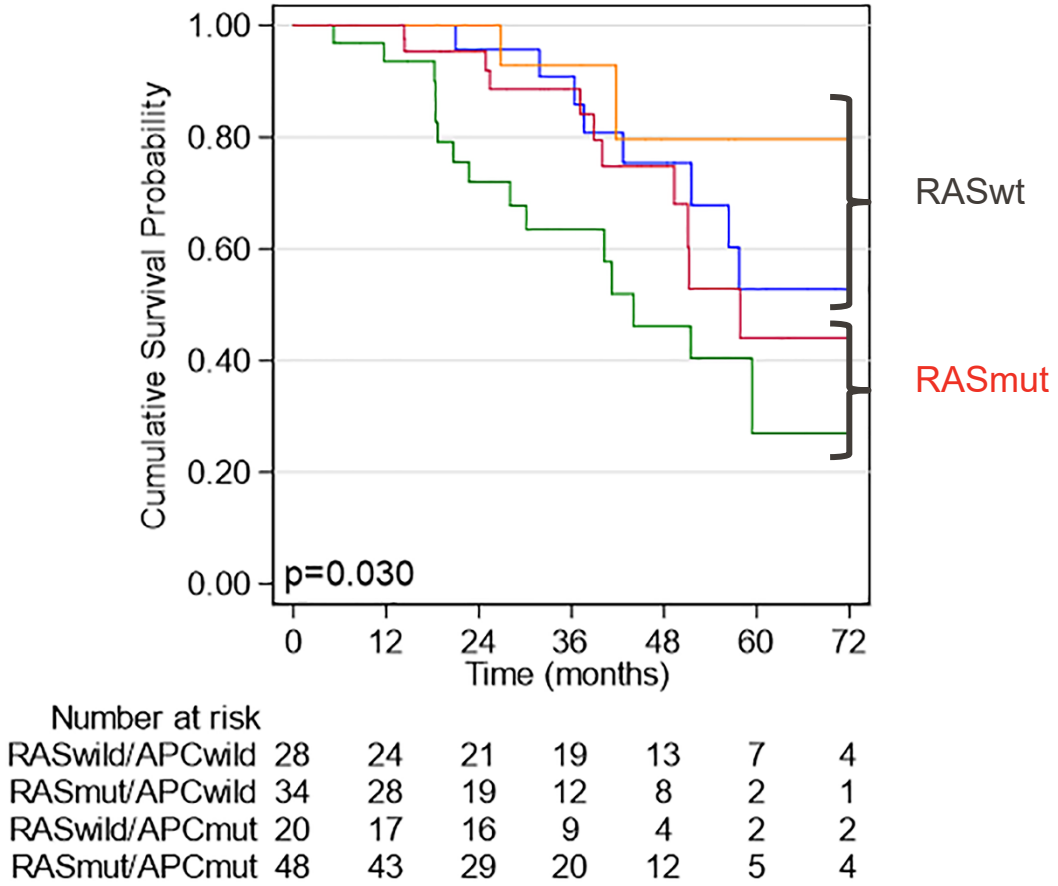
Rationale for stratification by KRAS mutation status

- RAS mutant → poorer outcomes with respect to primary disease control, and in setting of hepatic metastatic disease
- Impact in lung?

Taieb J, et al. J Natl Cancer Inst, 2017; Tosi F, et al. Clin Colorectal Cancer, 2017

Rationale for stratification by KRAS mutation status

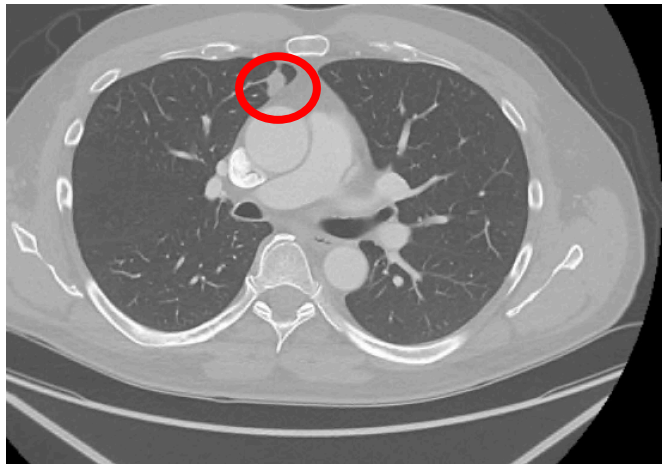
- RAS mutant disease demonstrated poorer OS and DFS following pulmonary metastasectomy
  - OS HR: 3.25 (1.39-7.59), *p*=0.006
  - DFS HR: 2.14 (1.35-3.39), *p*<0.001

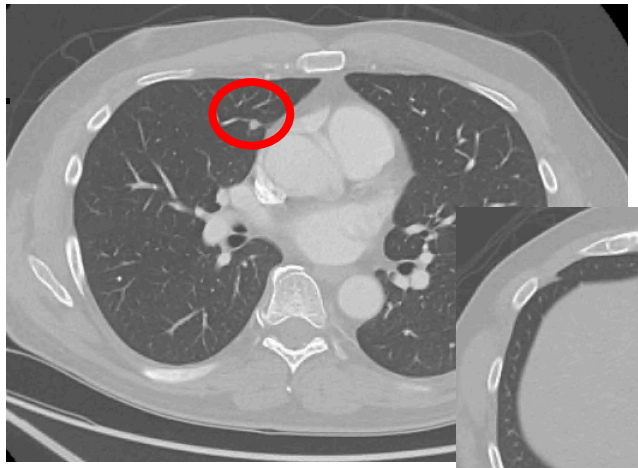


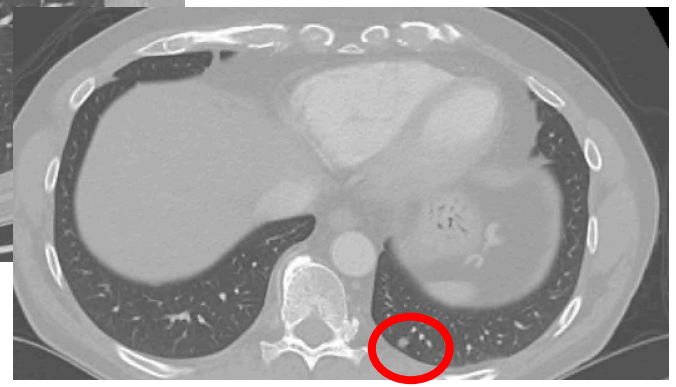
Corsini EM, et al. J Surg Onc, 2019.

Sample patient:

- 50 yo male with hx of rectal adenocarcinoma, dx 10/2017
- Pulmonary nodule noted in 02/2018
- Received chemo, LAR completed 3/2018
- Adjuvant chemo 4/2018-7/2018
- 2/2019: interval increase in bilateral pulmonary nodules
- Number of lesions: 3
- Disease-free interval: 0







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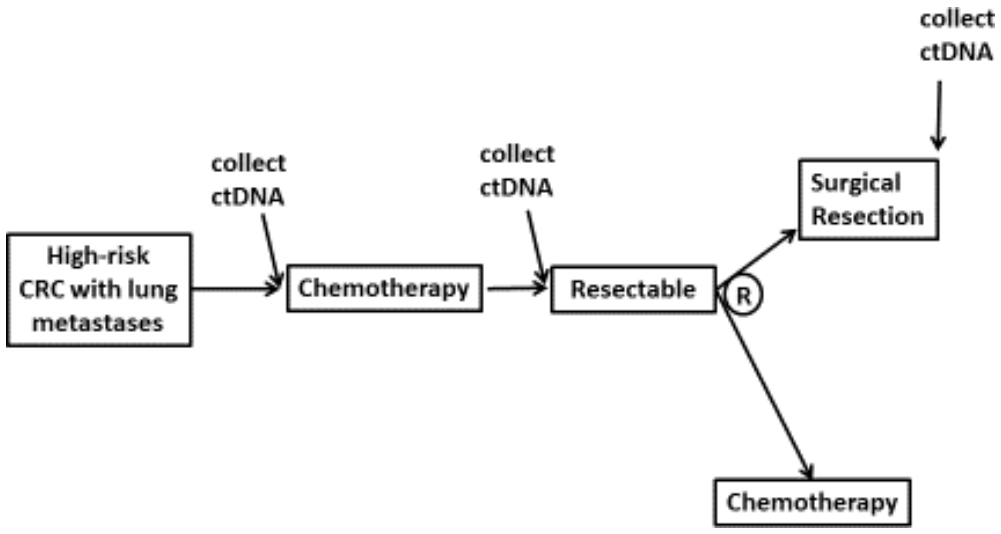

Sample patient:

- High risk
- No progression after 3 months chemo
- Randomized to surgery
- Staged sequential procedures on right then left lung

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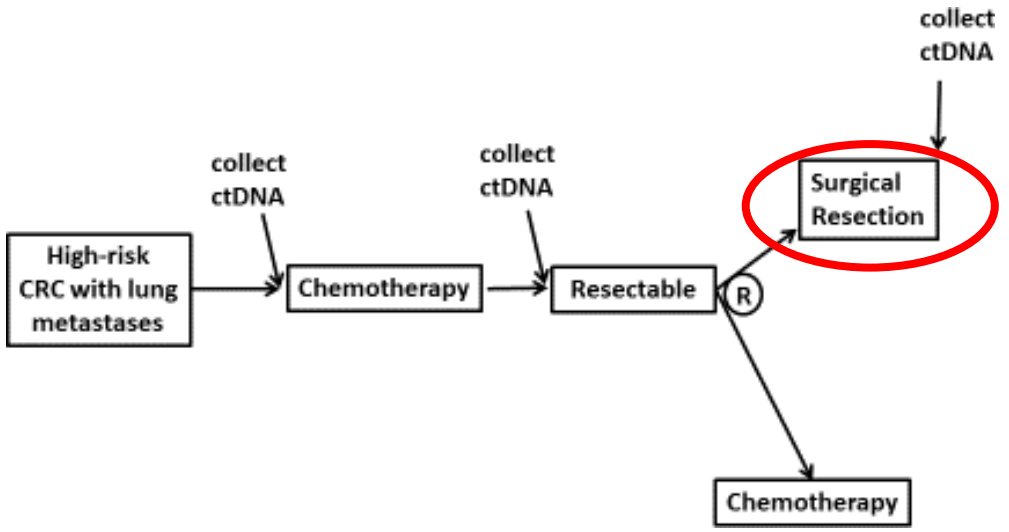

Enrollment/Accrual

- 173 patients screened
- 35 consented
  - 32 MDACC
  - 1 Univ Toronto
  - 2 Thomas Jefferson
- 65 ctDNA samples collected
  - 6 for recurrence

TSOG 103 Site	Date of Activation	PI
MD Anderson Cancer Center	06/16/2018	Mara Antonoff, M.D.
Washington University in St. Louis *(Closed to new patient accrual)*	11/14/2019	Benjamin Kozower, M.D.
Centre Hospitalier Universitaire de Montreal	12/05/2019	Moishe Liberman, M.D.
Brigham and Women's Hospital	06/15/2020	M. Blair Marshall, M.D.
University of Toronto/ University Health Network	09/17/2020	Marcelo Cypel, M.D.
Thomas Jefferson University Hospital	08/16/2021	Nathaniel Evans III, M.D.
Memorial Sloan Kettering Cancer Center	11/17/2021	Bernard Park, M.D.
Baylor College of Medicine	01/31/2022	Bryan Burt, M.D.

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Questions about TSOG 103: Mara Antonoff → mbantonoff@mdanderson.org

Questions about TSOG Overall: Maria Singh → singhm1@mskcc.org