Surgical, Radiation, and Medical Oncology

Brendon Stiles, MD

Raymond Osarogiagbon, MBBS

Anurag Singh, MD

Gregory Riely, MD, PhD

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ENFORCING THE NEED FOR STATE-OF-THE-ART SURGICAL INTERVENTIONS

Brendon Stiles, MD
Weill Cornell Medicine, Department of Cardiothoracic Surgery
Lung Cancer Research Foundation
Disclosures: AstraZeneca, Pfizer, Flame Biosciences, Genentech, BMS, LCRF

What is “state-of-the-art”?

- Minimally invasive surgery
- Enhanced recovery after surgery
- Consideration of sublobar resection
- Individualized patient therapy
- Reflex comprehensive biomarker testing
- Access to neoadjuvant and adjuvant trials

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Minimally Invasive Surgery and ERAS

- National rates
  - STS GTSD: 70.6%
- Implications for screening
  - NLST: Just 30%
- Effects on complications and enhanced recovery

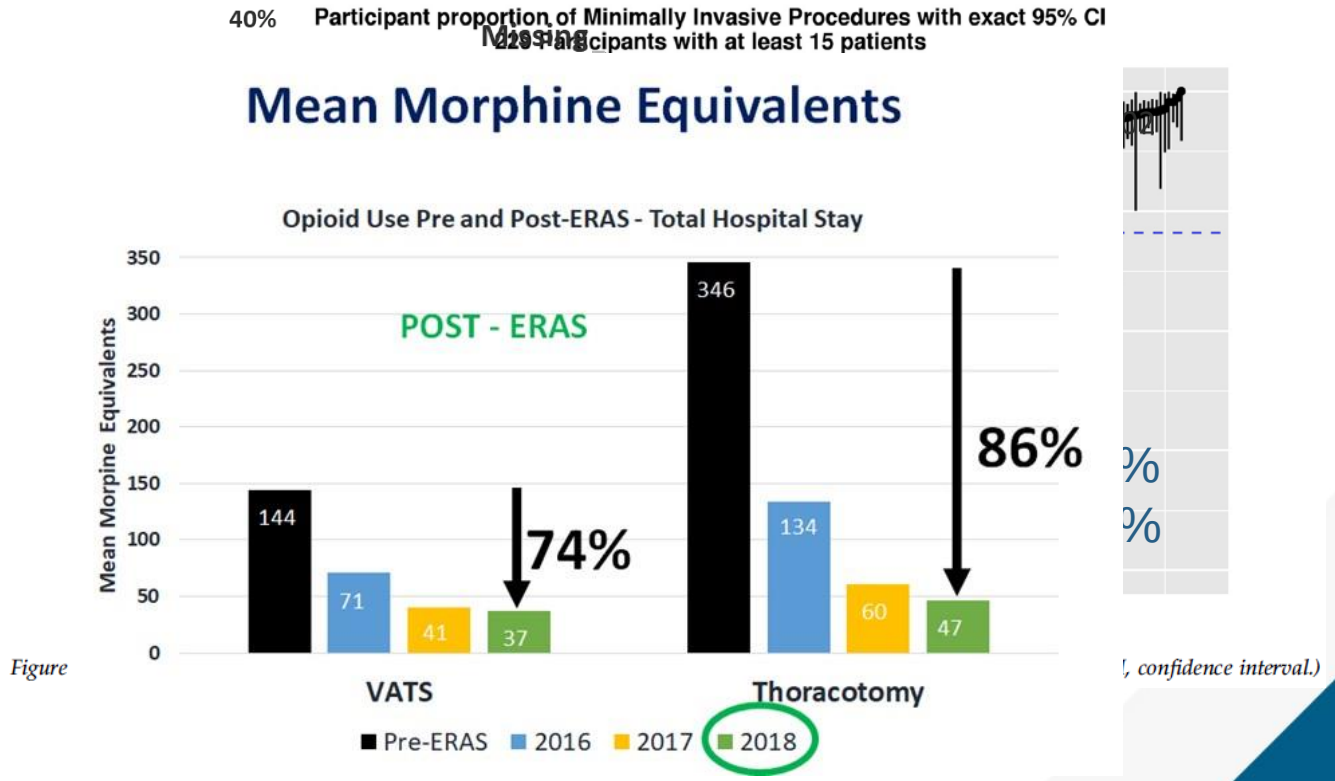

Figure , confidence interval.)

Ann Thorac Surg 2020:109:848-55
Lancet Respir Med 2018;6:915-24
N Engl J Med 2011;365:395-409
Ann Thorac Surg 2018;105:1597-604

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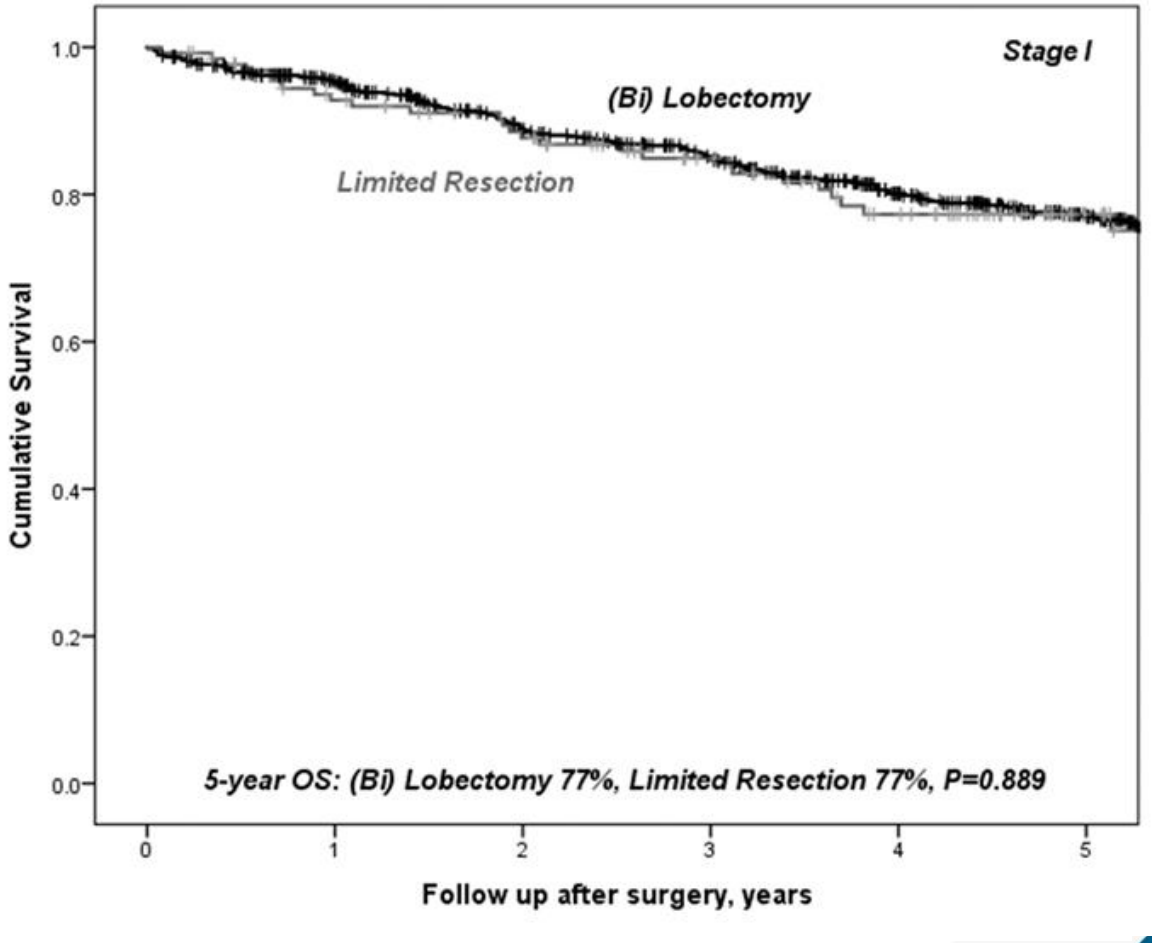
Sublobar resection

- CALGB 140503 and JCOG 0802
- Implications for screen-detected cancers



Lancet Respir Med 2018;6:915-24
J Thorac Cardiovasc Surg 2019;158:895-907
WCLC Oral presentation 2018

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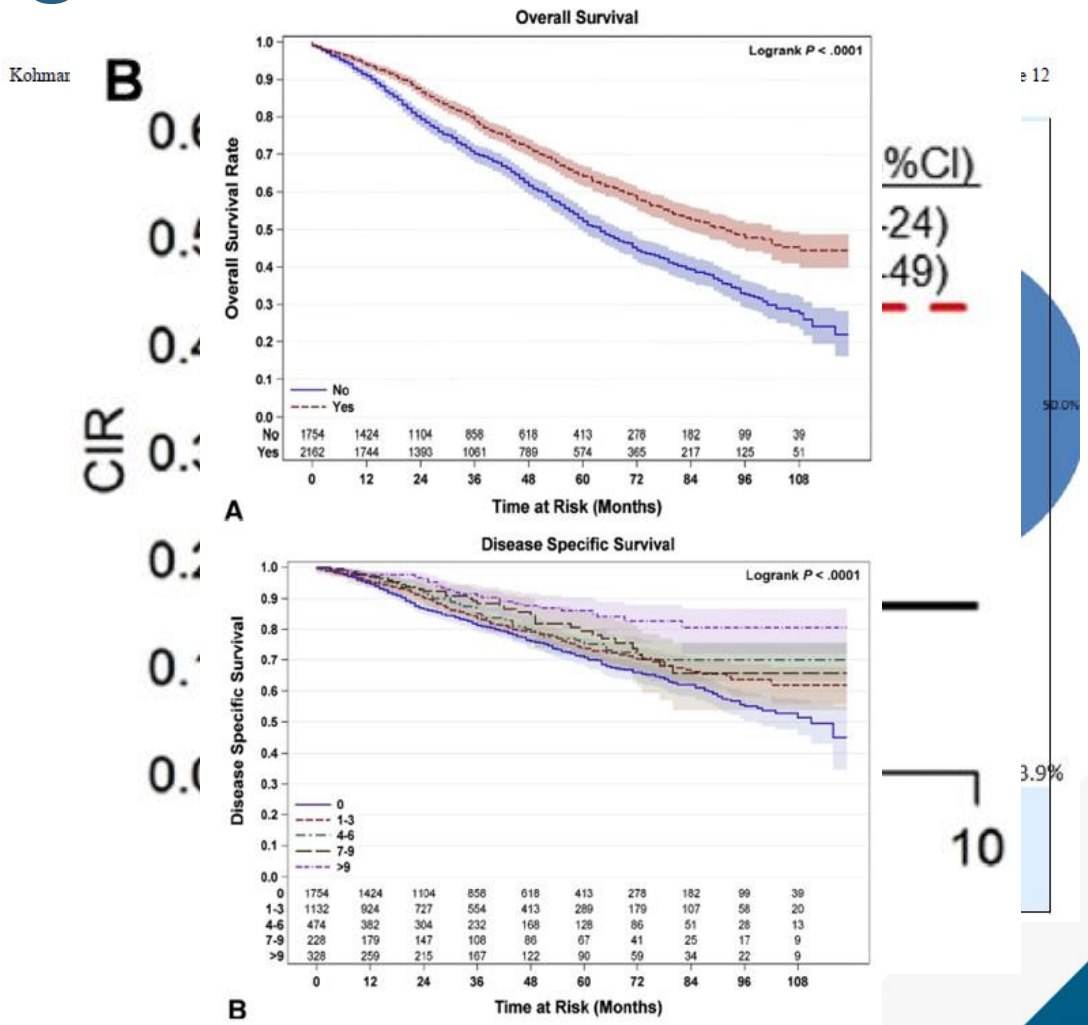
Individualized Surgical Therapy

- Biopsy first
- Consideration of radiographic and pathologic features for individualized surgery with appropriate lymph node evaluation
- Offer trial enrollment when appropriate



J Thorac Cardiovasc Surg 2017;153:1592-1597
J Thorac Onc 2018;14:87-98
J Thorac Cardiovasc Surg 2018;156:394-402

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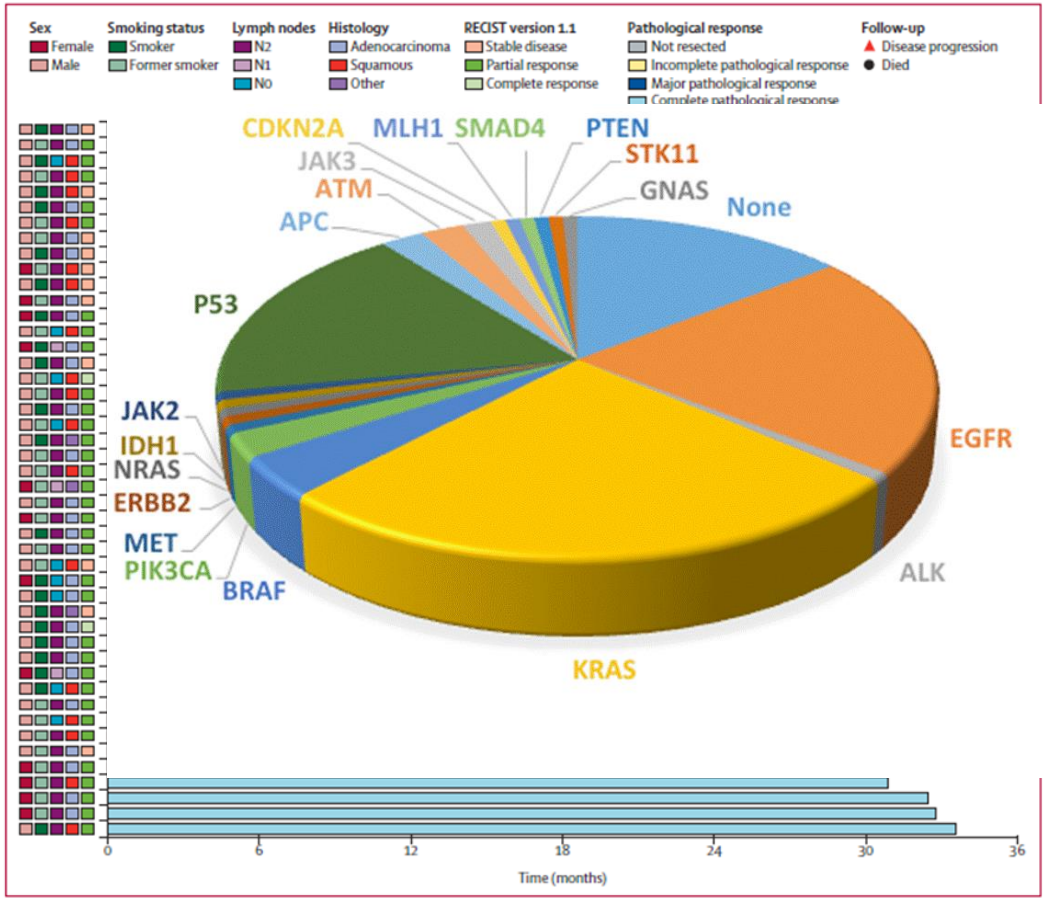
Reflex Comprehensive Biomarker Testing and Access to Neoadjuvant/Adjuvant Trials

- Increasingly “actionable”
- Numerous neoadjuvant and adjuvant options
- RIOT – Return to Intended Oncologic Therapy



N Engl J Med 2020;383:1711-1723
Lancet Onc 2020;21:1413-1422
J Thorac Cardiovasc Surg 2019;158:279-86

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In conclusion

Thank you for your time and thank you NLCRT!

@BrendonStilesMD

- Surgery *must* be state-of-the-art
- Personalized therapy is here to stay, even for screen detected and early stage lung cancer
- Multidisciplinary care facilitates great surgery

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Thank You

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STEREOTACTIC BODY RADIATION THERAPY (SBRT) FOR LUNG CANCER

Anurag K. Singh MD
Professor of Oncology
Director of Radiation Research
Leader, Cell Stress and Biophysical Therapy Program
Associate Dean of Graduate Medical Education for Career Development

December 2020

Disclosures

Conflicts: None

- **I have no intention to discuss off-label and/or investigational use of pharmaceuticals or devices.**

Employer: Roswell Park Comprehensive Cancer Center

Honoraria: None

Non-Financial: None

Trial Funding: N/A

My Other Grant Support

- National Cancer Institute
  - 1R01CA099326-16
  - 1R01CA204636-01
  - 1R01CA236390-A1
  - 5UG1CA233191-01
  - 5P30CA016056-42
- Braun Foundation
- Louis Sklarow Memorial Trust
- Roswell Park Alliance Foundation

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Definition of Terms

- **Conventional Fractionated Radiation Therapy**:
  - 1.8- 2 Gy per fraction
    - 2 Dimensional (2D) Radiation Therapy
    - 3 Dimensional (3D) Conformal Radiation Therapy

TOTAL TIME: 6-7 weeks
TOTAL DOSE: 60-70 Gy

- **SBRT: Stereotactic Body Radiation Therapy**
  - More than 5 Gy per fraction
    - Image Guidance
    - Tight margins
    - Fixation
    - 5 Fractions or less
    - Large doses per fraction

TOTAL TIME: 1-14 days
TOTAL DOSE: 30-60 Gy

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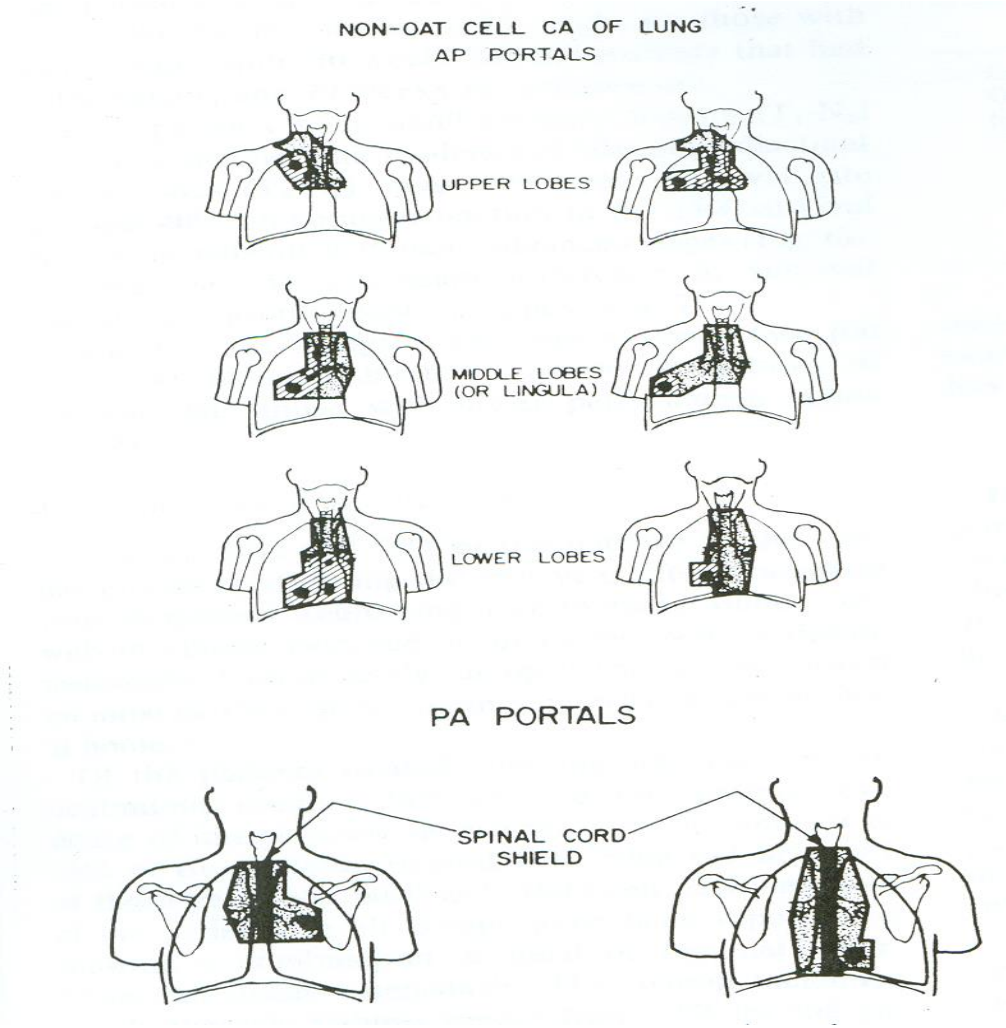
2D (Conventional) Radiotherapy

Perez. Cancer. 1987.



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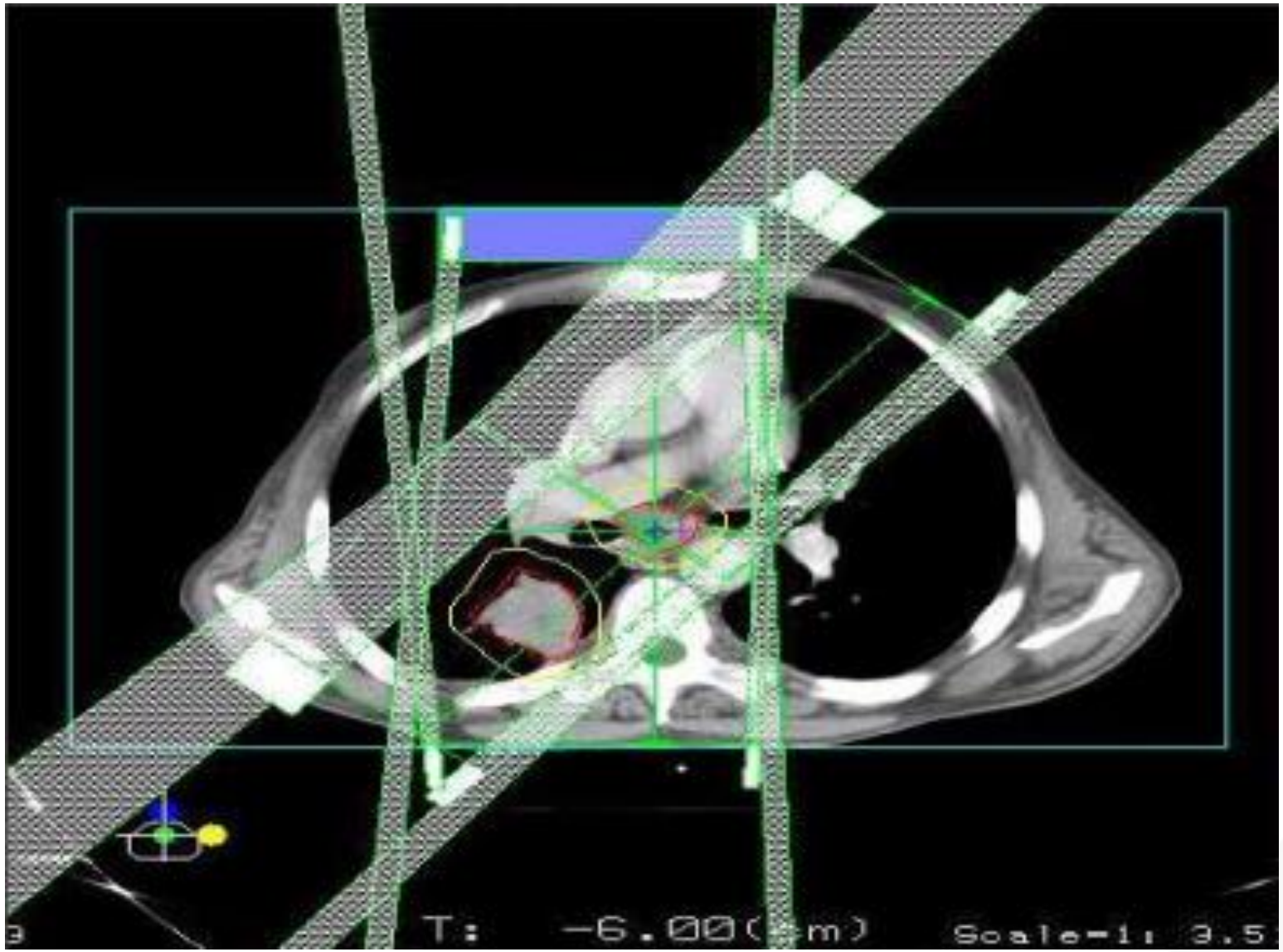
3D Conformal (Conventional) RT



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Stereotactic Body Radiation Therapy (SBRT)

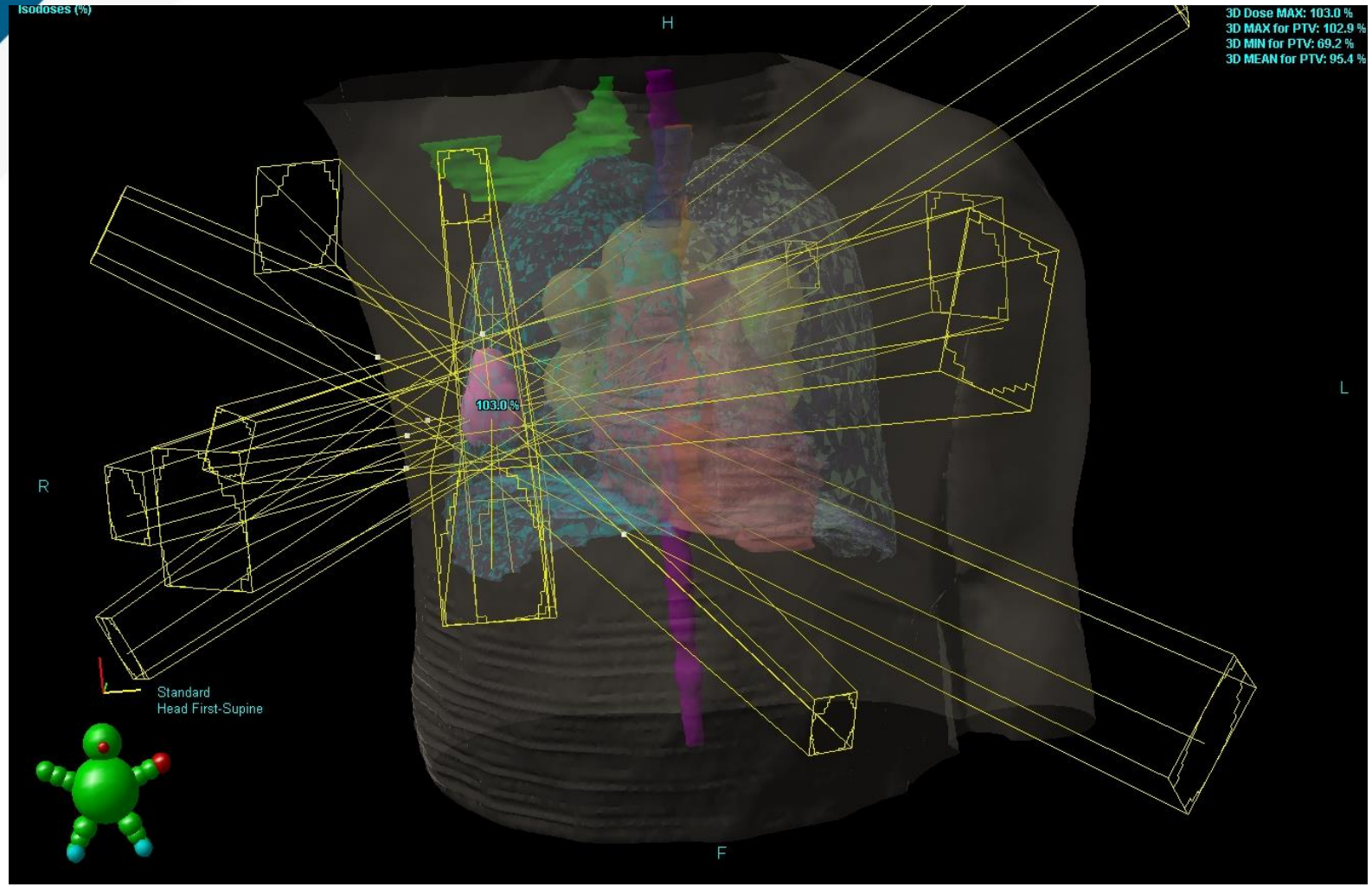

Image Guided Radiation Therapy (IGRT) Volumes

- **Gross Tumor Volume (GTV):**
  - Gross palpable or visible/demonstrable extent and location of malignant growth
- **Clinical Target Volume (CTV):**
  - Anatomical concept.
  - Tissue volume that contains a GTV and/or subclinical microscopic malignant disease, which has to be eliminated.
- **Internal Target Volume (ITV):**
  - Accounts for tumor motion during treatment
- **Planning Target Volume (PTV):**
  - Defined to select appropriate beam sizes and beam arrangements, taking into consideration the net effect of all the possible geometrical variations and inaccuracies in order to ensure that the prescribed dose is actually absorbed in the CTV

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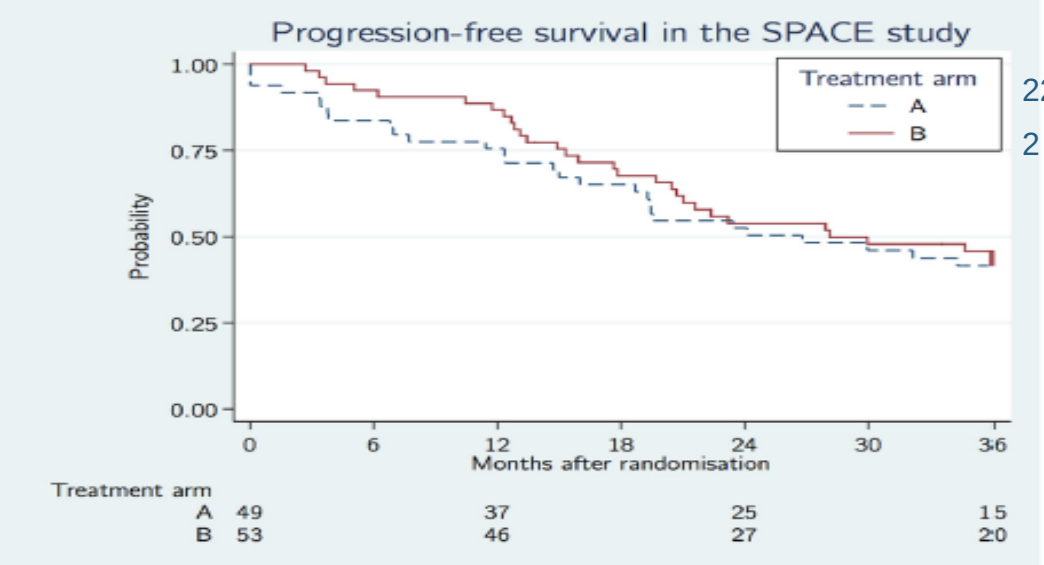
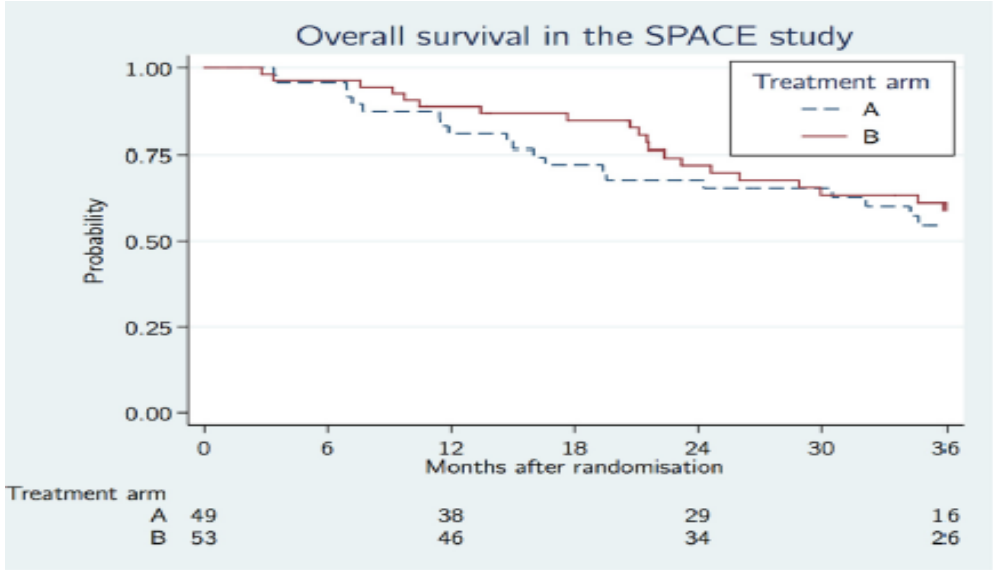
SPACE Trial: 3 SBRT vs 35 Standard 3D Txs

Nyman. Radioth Oncol. 2017.



22 Gy x 3

2 Gy x 35



Progression free survival by treatment arm (A = SBRT, B = 3DCRT), ITT analysis. HR = 0.85, 95% CI: 0.52–1.36.

Overall survival by treatment arm (A = SBRT, B = 3DCRT), ITT analysis. HR = 0.75, 95% CI: 0.43–1.30.

Maximal toxicity CTC-AE v. 3.0, grade 1–3, by treatment arm.

Toxicity	A: SBRT *n* = 48, grade:			B: 3DCRT *n* = 53, grade:			*p*-Value for difference between arms
	1	2	3	1	2	3	
Esophagitis	4 (8%)	0	0	15 (28%)	1 (2%)	0	0.006
Pneumonitis	7 (15%)	2 (4%)	0	13 (24%)	4 (8%)	1 (2%)	0.085
Dyspnea	19 (40%)	8 (17%)	5 (10%)	22 (42%)	16 (30%)	5 (9%)	0.097
Fibrosis	20 (42%)	4 (8%)	0	24 (45%)	2 (4%)	1 (2%)	0.925
Cough	19 (40%)	5 (10%)	1 (2%)	31 (58%)	3 (6%)	0	0.22
Skin reactions	13 (27%)	2 (4%)	1 (2%)	17 (32%)	5 (10%)	0	0.40
Rib fractures	6 (13%)	2 (4%)	0	5 (9%)	1 (2%)	0	0.44

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SBRT 1 versus 3 Fraction: One and Done

Clinical Investigation

One Versus Three Fractions of Stereotactic Bo Radiation Therapy for Peripheral Stage I to II Non-Small Cell Lung Cancer: A Randomized, Multi-Institution, Phase 2 Trial

Anurag K. Singh, MD,* Jorge A. Gomez-Suescun, MD,*
Kevin L. Stephans, MD,† Jeffrey A. Bogart, MD,‡
Gregory M. Hermann, MD, MPH,* Lili Tian, PhD,§
Adrienne Groman, MS,§ and Gregory M. Videtic, MD†

Int Jn Radiat Oncol Phys. 2019.

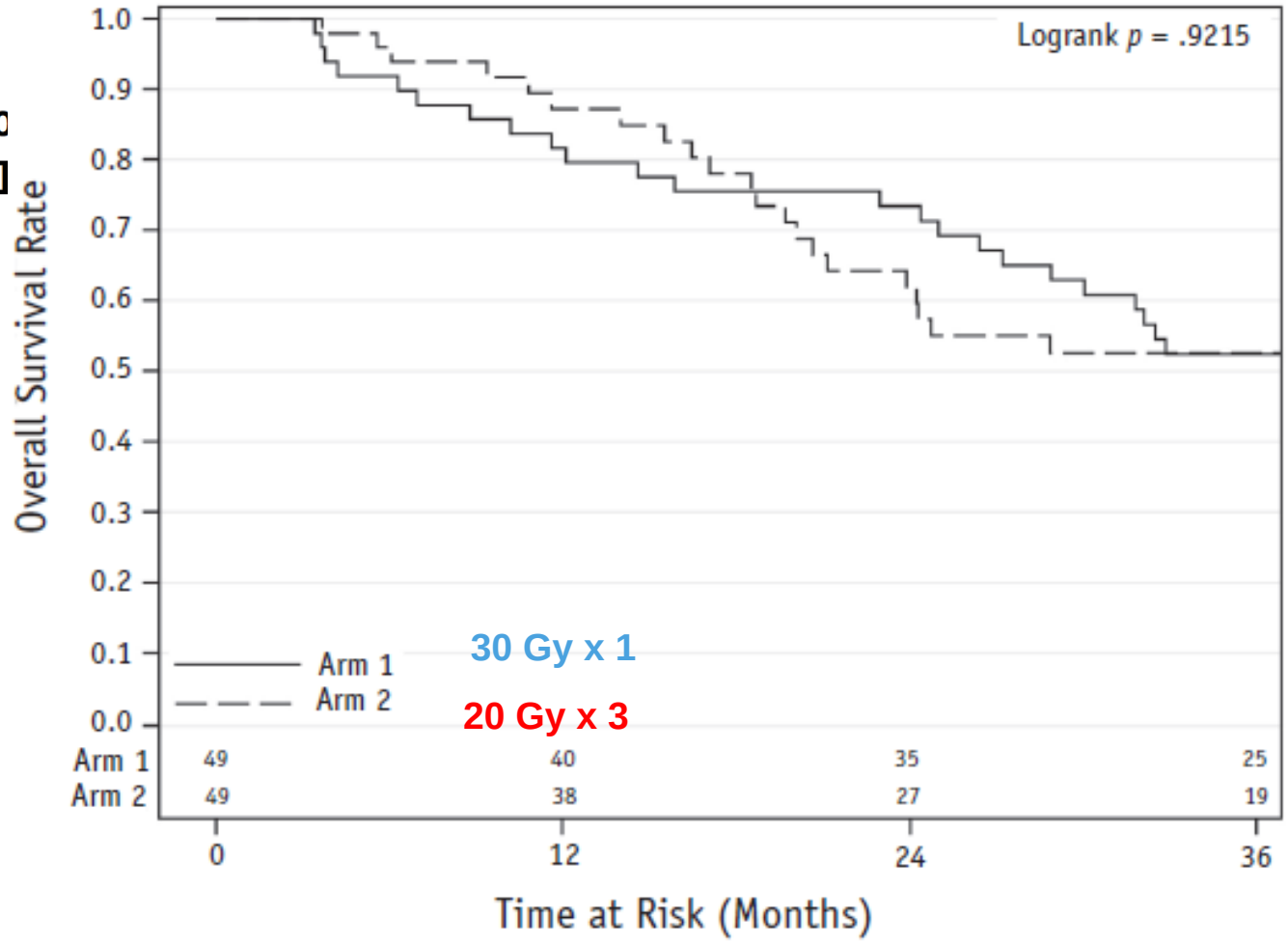

Fig. 2. Overall survival.

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Lung SBRT Works… there is lots of data

Submit a Manuscript: https://www.f6publishing.com

World J Clin Oncol 2019 January 10; 10(1): 14-27

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ISSN 2218-4333 (online)

MINIREVIEWS

Stereotactic body radiation therapy for non-small cell lung cancer: A review

Kavitha M Prezzano, Sung Jun Ma, Gregory M Hermann, Charlotte I Rivers, Jorge A Gomez-Suescun, Anurag K Singh

Table 1 Study characteristics and tumor control results

Study	No.	F/u (median)	Age (median)	Loc	Stage	Dose/fx	OS	LC	RC	DC
Miyakawa *et al*[20], 2017	71	44	77	C + P	T1-2N0M0	48-52 Gy/ 4 fx	5-yr 65%	5-yr 85%	NA	NA
Sun *et al*[30], 2017	65	86	71	C + P	T1-2N0M0	50 Gy/4 fx	7-yr 48%	7-yr 92%	7-yr 86%	7-yr 86%
Singh *et al*[22], 2017, I-124407	98	27	NA	P	T1-2N0M0	30 Gy/1 fx and 60 Gy/3fx	2-yr 71% (30 Gy) 2-yr 61% (60 Gy)	NA	NA	NA
Bezjak *et al*[24], 2016, RTOG 0813	71	33 (57.5 Gy) 30 (60 Gy)	NA	C	T1-2N0M0	57.5-60 Gy/5 fx	2-yr 70% (57.5 Gy) 2-yr 88% (60 Gy)	2-yr 90% (57.5 Gy) 2-yr 88% (60 Gy)	2-yr 95% (57.5 Gy) 2-yr 88% (60 Gy)	2-yr 84% (57.5 Gy) 2-yr 85% (60 Gy)
Navarro-Martin *et al*[11], 2016	38	42	74	P	T1-3N0M0	54 Gy/3 fx	3-yr 66%	3-yr 94%	3-yr 79%	3-yr 87%
Nyman *et al*[14], 2016, SPACE	102	37	74 (mean)	P	T1-2N0M0	66 Gy/3 fx	3-yr 54%	3-yr 86%	3-yr 93%	3-yr 76%
Chang *et al*[15], 2015, STARS and ROSEL	31	40	67	C + P	T1-2N0M0	54 Gy/3 fx, 50 Gy/4 fx, 60 Gy/5 fx	3-yr 95%	3-yr 96%	3-yr 90%	3-yr 97%
Lindberg *et al*[19], 2015	57	42	75 (mean)	P	T1-2N0M0	45 Gy/3 fx	5-yr 30%	5-yr 79%	3-yr 81% for regional/distant control	NA
Nagata *et al*[17], 2015, JCOG 0403	169	47 (inop) 67 (op)	78	NA	T1N0M0	48 Gy/4 fx	3-yr 60% 5-yr 43% (inop) 3-yr 77% 5-yr 54% (op)	3-yr 87% (inop) 3-yr 85% (op)	3-yr 92% (inop) 3-yr 75% (op)	3-yr 78% (inop) 3-yr 67% (op)
Shibamoto *et al*[9], 2015	180	53	77	C + P	T1-2N0M0	44-52 Gy /4 fx	5-yr 52%	5-y 83%	5-yr 84%	5-yr 76%
Videtic *et al*[13], 2015, RTOG 0915	94	30	75	P	T1-2N0M0	34 Gy/1 fx and 48 Gy/4 fx	3-yr 56%	3-yr 98%	NA	NA
Timmerman *et al*[18], 2014, RTOG 0236	55	48	72	P	T1-2N0M0	54 Gy/3 fx	5-yr 40%	5-yr 80%	5-yr 62% (local-regional control)	5-yr 79%
Taremi *et al*[28], 2012	108	19	73 (mean)	C + P	T1-2N0M0	48 Gy/4 fx or 54-60 Gy/3 fx (P) 50-60 Gy /8-10 fx (C)	4-yr 30%	4-yr 89%	4-yr 87%	4-yr 83%
Bral *et al*[16], 2011	40	16	73 (mean)	C + P	T1-3N0M0	60 Gy/3-4 fx	2-yr 52%	2-yr 84%	2 nodal recurrences	6 distant recurrences
Ricardi *et al*[16], 2010	62	28	74	P	Stage I	45 Gy/3 fx	3-yr 57%	3-yr 88%	3-yr 94%	3-yr 76%
Fakiris *et al*[17], 2009	70	50	70	C + P	T1-2N0M0	60-66 Gy/ 3 fx	3-yr 43%	3-yr 88%	3-yr 91%	3-yr 87%
Koto *et al*[10], 2007	31	32	77	C + P	T1-2N0M0	45 Gy/3 fx or 60 Gy/8 fx	3-yr 72%	3-yr 78% (T1) 3-yr 40% (T2)	3-yr 94%	3-yr 81%
McGarry *et al*[7], 2005	47	27 (Stage IA) 19 (Stage IB)	71 (Stage IA) 74 (Stage IB)	C + P	T1-2N0M0	24-72 Gy/ 3 fx	NA	2-yr 81%	2-yr 81%	2-yr 79%
Nagata *et al*[8], 2005	45	30 (Stage IA)	77 (Stage IA)	C + P	T1-2N0M0	48 Gy/4 fx	2-yr 90% (Stage IA)	1-yr 100%	2-yr 91%	2-yr 88% (Stage IA)

SBRT for Oligomets

Study	N	Tumor Type	Arm 1	Arm 2	Findings
SABR-COMET Palma et al. Lancet. 2019	**99**	**Several Histologies Oligomets (5 or less)**	**Conventional Systemic Tx**	**Conventional Systemic Tx + SBRT**	**1. Median OS Improved from 28 to 41 mos (p =0.09)** **2. More Grade 2+ toxicity: 9 vs 29%, (p=0.02)**
Gomez et al. JCO. 2019	**49**	**Oligomets (3 or less) NSCLC**	**Conventional Systemic Tx Or Observation**	**ARM 1 + Local Tx (Surg or RT)**	**Median OS Improved 17 vs 41 mos (P=0.017)**
PEMBRO-RT Theelen et al. JAMA Onc.	**92**	**Stage IV NSCLC**	**PEMBRO**	**PEMBRO + SBRT (8 Gy x 3)**	At 12 weeks, favored SBRT: 1. Response rate= 8% vs 36% (P = .07) **2. Disease control rate (64% vs 40%; P = .04)** 3. Median survival=7.6 mo vs. 15.9 mo (HR,0.66;P=.16).
Singh et al. Clin Can Res. 2017. **Chow et al. PNAS. 2020.**	**30**	**Renal Cell Cancer**	**Surgery alone**	**SBRT followed by Surgery**	**1. greater tumor associated antigen release** **2. antigen presentation** **3. T-cell infiltration following RT** **4. Enhanced peripheral T-cell response**

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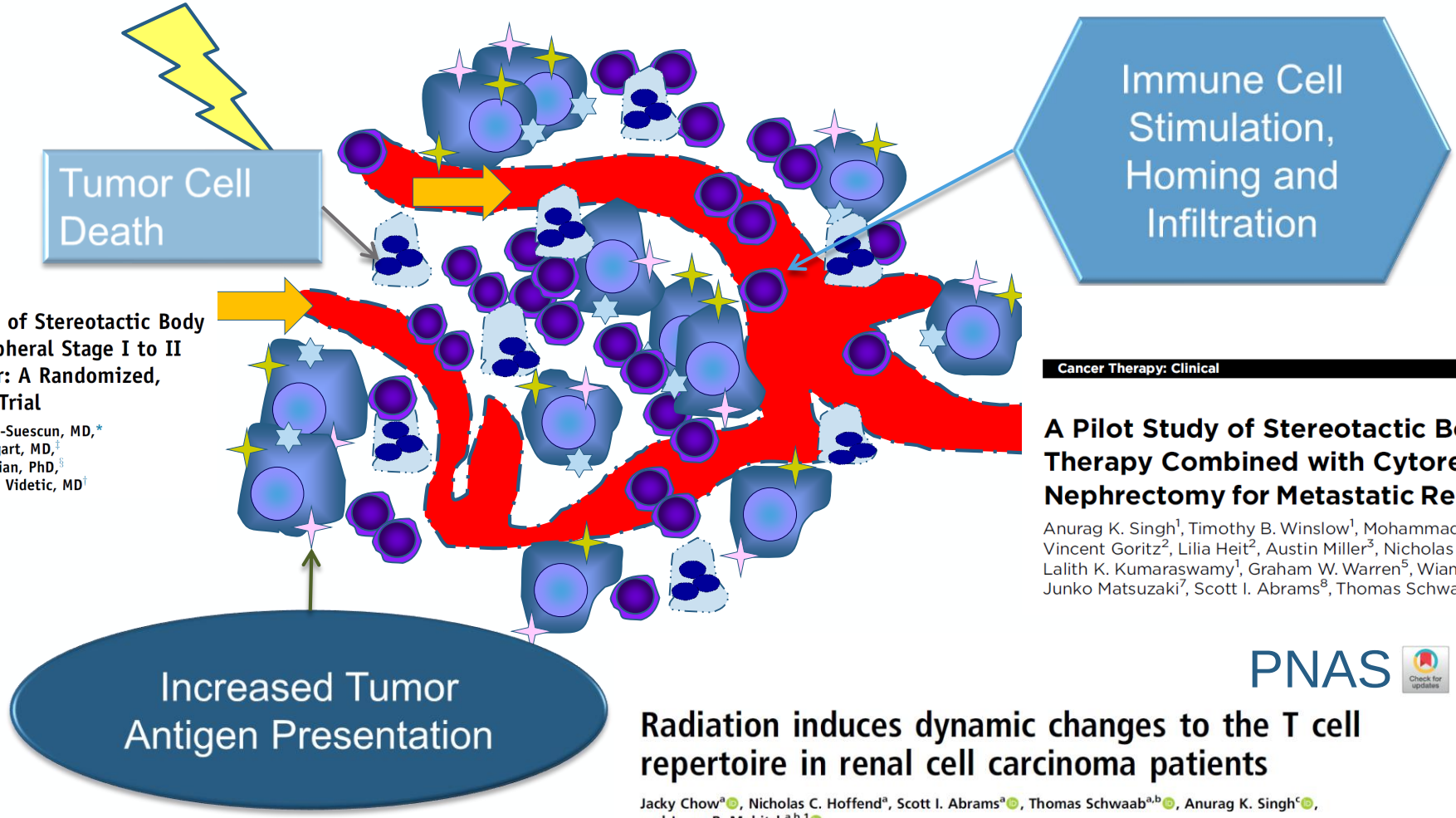
Effects of Stereotactic Body Radiation Therapy (SBRT) in Humans



Clinical Investigation

One Versus Three Fractions of Stereotactic Body Radiation Therapy for Peripheral Stage I to II Non-Small Cell Lung Cancer: A Randomized, Multi-Institution, Phase 2 Trial

Anurag K. Singh, MD,* Jorge A. Gomez-Suescun, MD,* Kevin L. Stephans, MD,† Jeffrey A. Bogart, MD,‡ Gregory M. Hermann, MD, MPH,* Lili Tian, PhD,§ Adrienne Groman, MS,§ and Gregory M. Videtic, MD†

Cancer Therapy: Clinical

Clinical Cancer Research

A Pilot Study of Stereotactic Body Radiation Therapy Combined with Cytoreductive Nephrectomy for Metastatic Renal Cell Carcinoma

Anurag K. Singh[1], Timothy B. Winslow[1], Mohammad Habiby Kermany[2], Vincent Goritz[2], Lilia Heit[2], Austin Miller[3], Nicholas C. Hoffend[2], Leighton C. Stein[4], Lalith K. Kumaraswamy[1], Graham W. Warren[5], Wiam Bshara[4], Kunle Odunsi[6,7,8], Junko Matsuzaki[7], Scott I. Abrams[8], Thomas Schwaab[2,8], and Jason B. Muhitch[2,8]

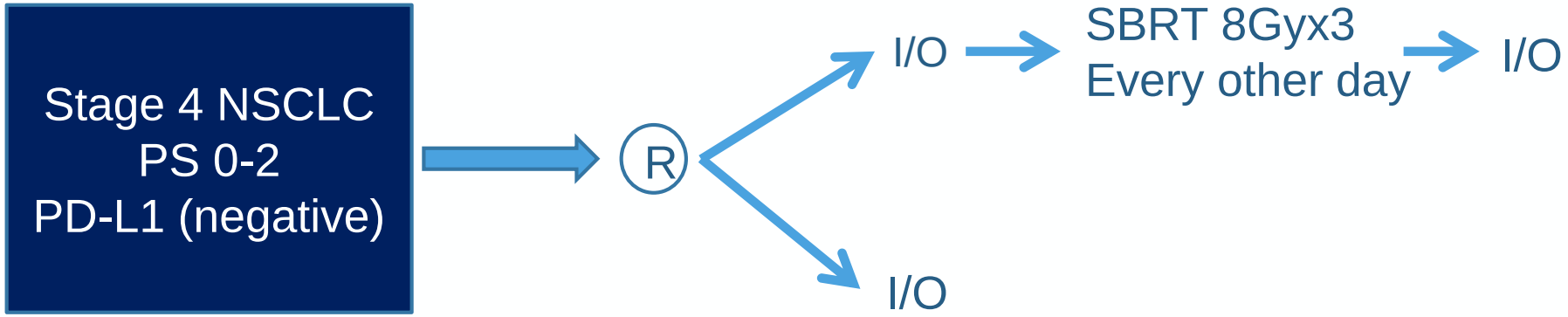
PNAS

Radiation induces dynamic changes to the T cell repertoire in renal cell carcinoma patients

Jacky Chow[a], Nicholas C. Hoffend[a], Scott I. Abrams[a], Thomas Schwaab[a,b], Anurag K. Singh[c], and Jason B. Muhitch[a,b,1]

[a]Department of Immunology, Roswell Park Comprehensive Cancer Center, Buffalo, NY 14263; [b]Department of Urology, Roswell Park Comprehensive Cancer Center, Buffalo, NY 14263; and [c]Department of Radiation Medicine, Roswell Park Comprehensive Cancer Center, Buffalo, NY 14263

Alliance Cooperative Group: Phase 3 Trial Concept (Schild PI)



Primary endpoint is survival

I/O: **Nivolumab (NIVO) + low-dose ipilimumab (IPI)**

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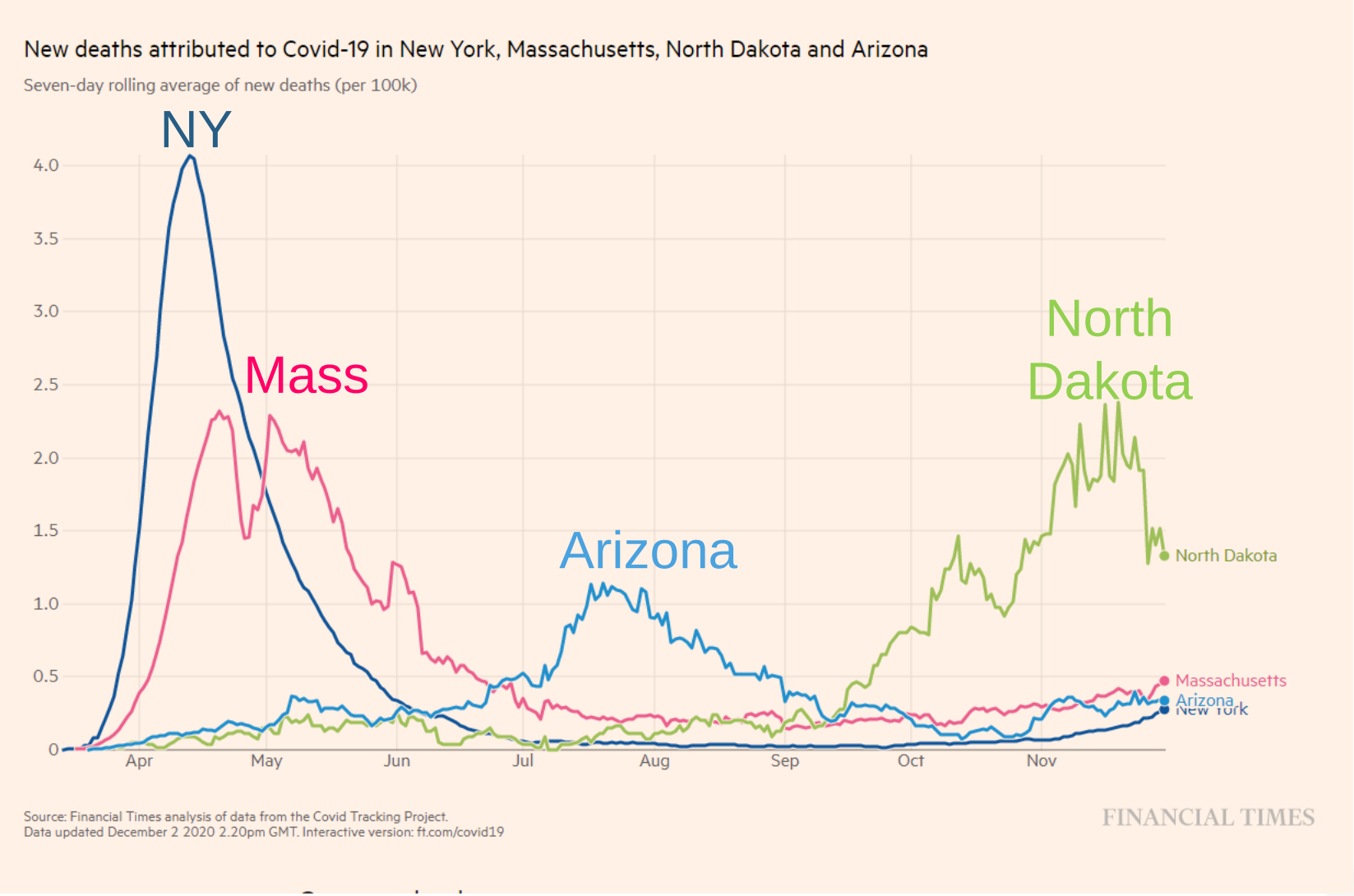
COVID-19 AND LUNG CANCER

Gregory J. Riely, MD, PhD

Memorial Sloan Kettering Cancer Center

Reminder of the timing of COVID-19 in the US



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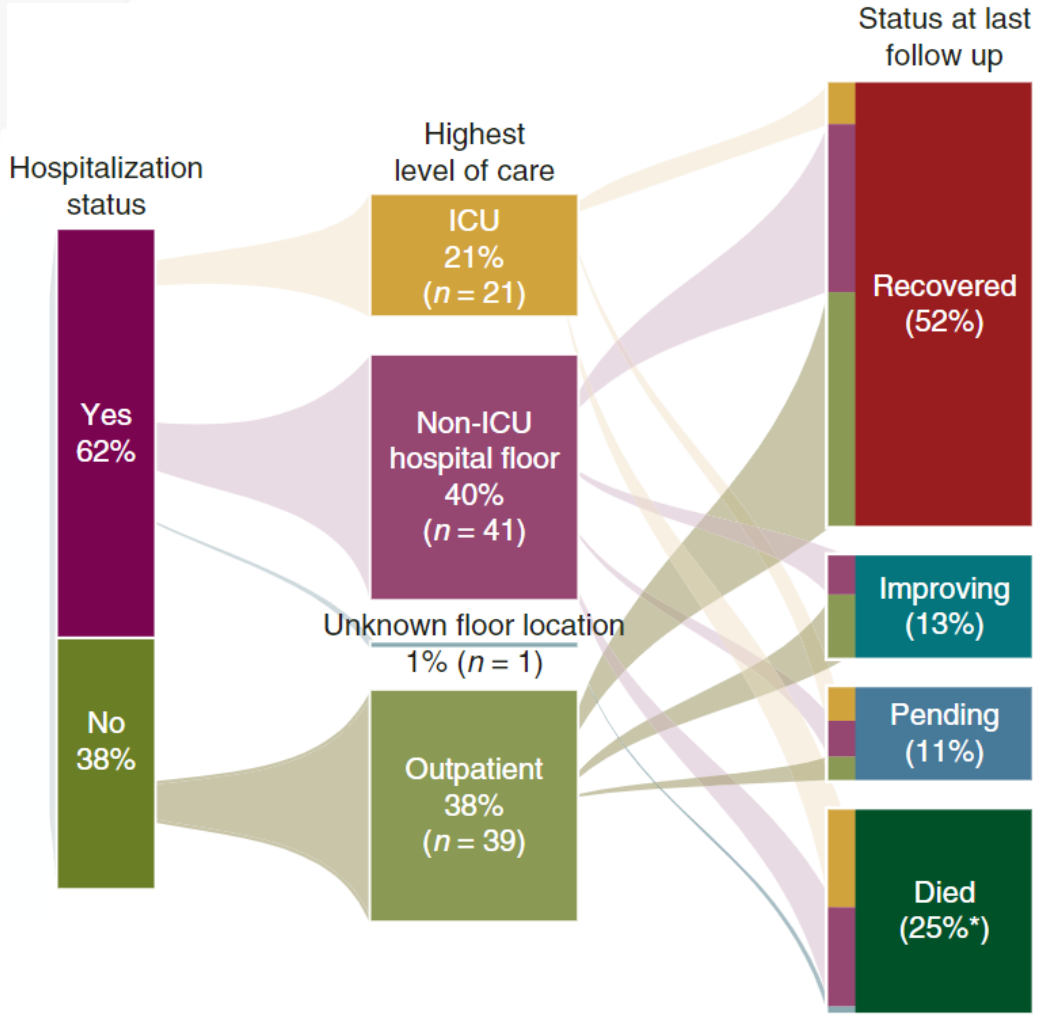
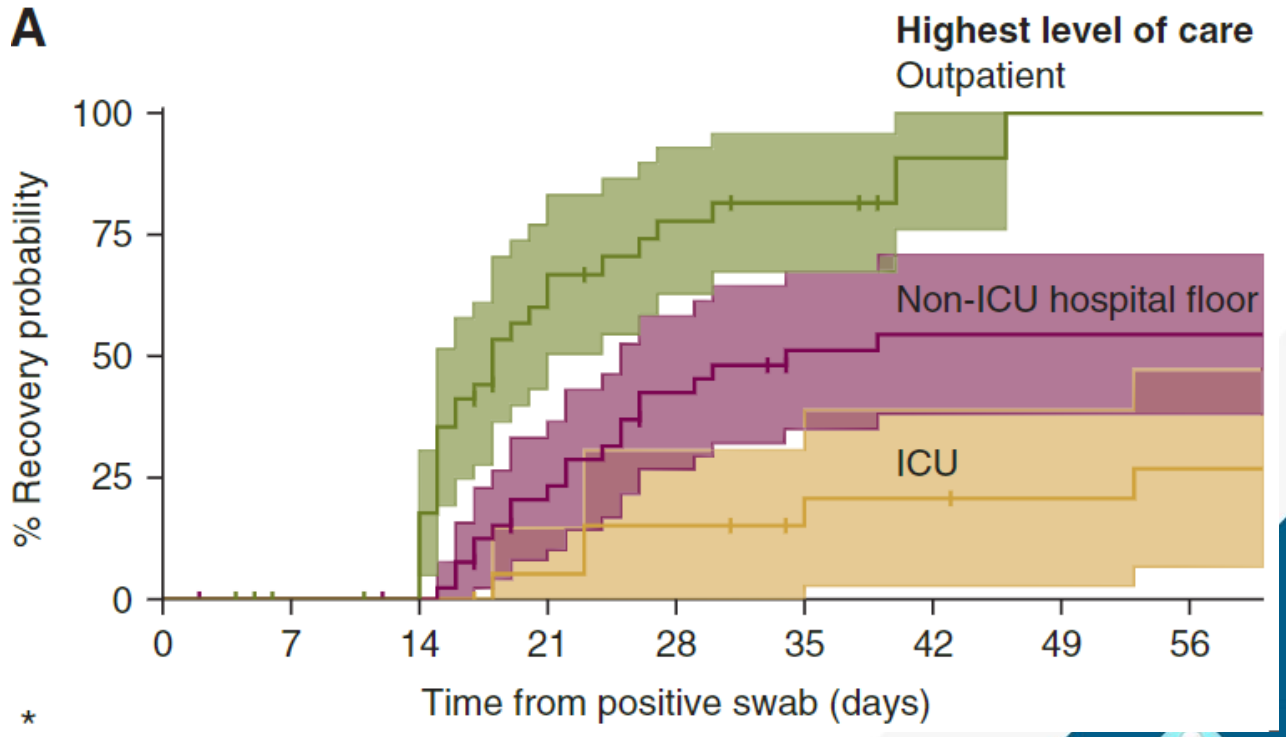
Outcomes of lung cancer and COVID-19
(NYC, first wave 2020)





Luo et al, Annals of Oncology 2020

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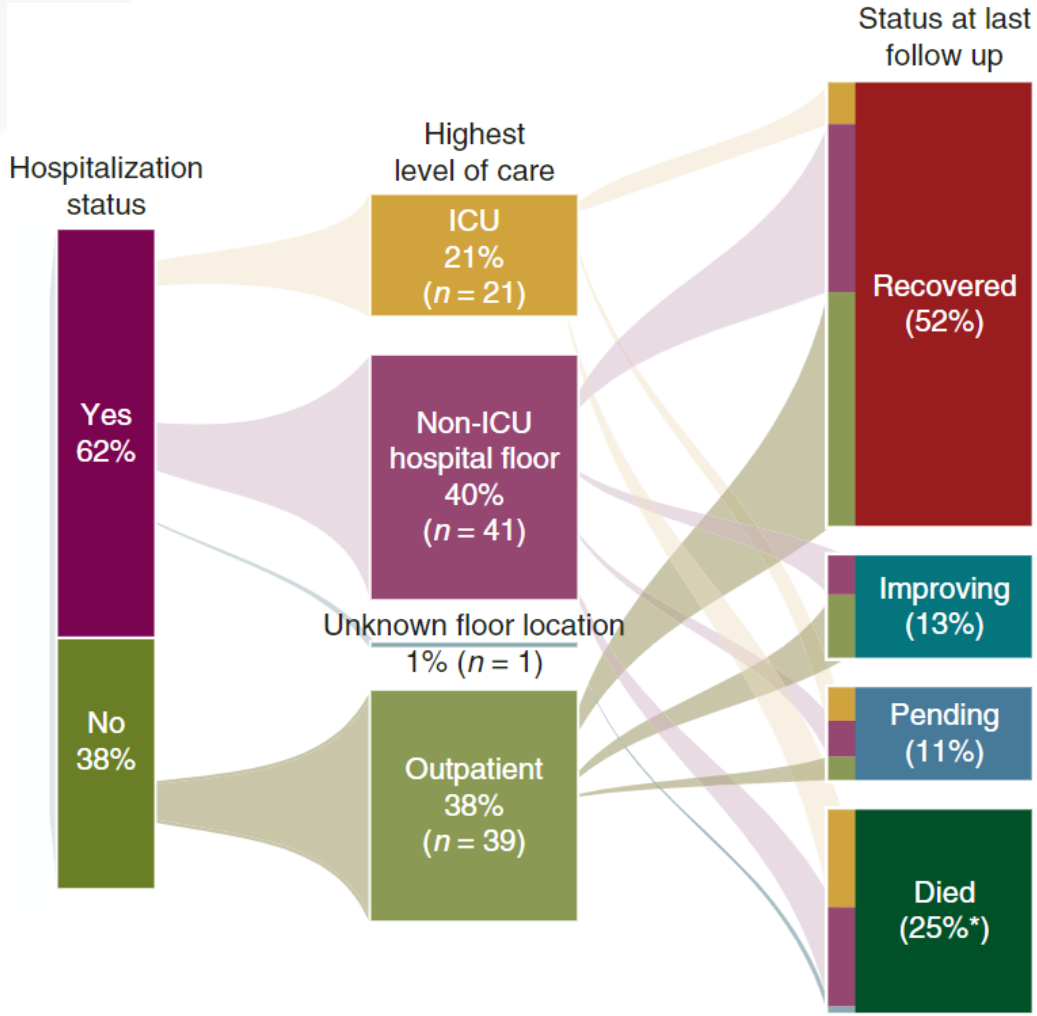
(NYC, first wave 2020)



Predictors of worse outcome:

- Age
- Cigarette Smoking (pack years)
- COPD
- Hypertension

<u>Not</u> predictive:

- Prior thoracic radiation
- Prior thoracic surgery
- Recent chemotherapy (<3 wks)

Luo et al, Annals of Oncology 2020

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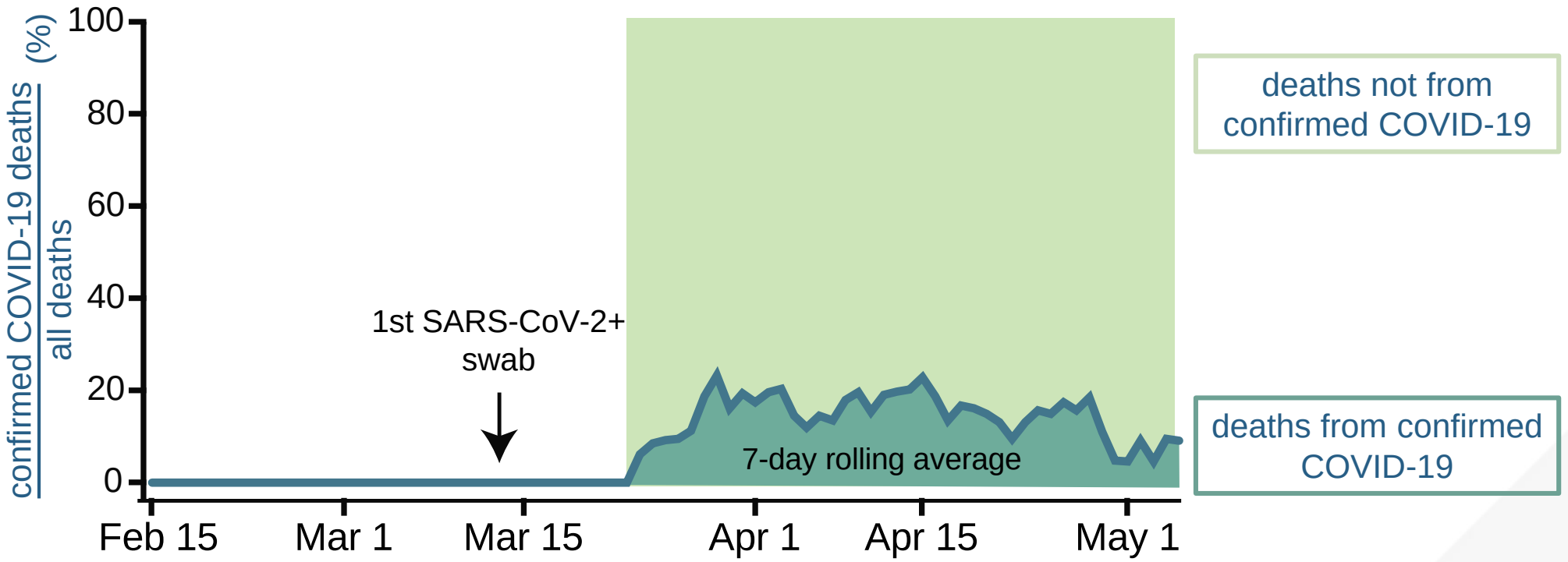
Lung cancer is still the problem



Modified from Luo et al, Annals of Oncology 2020

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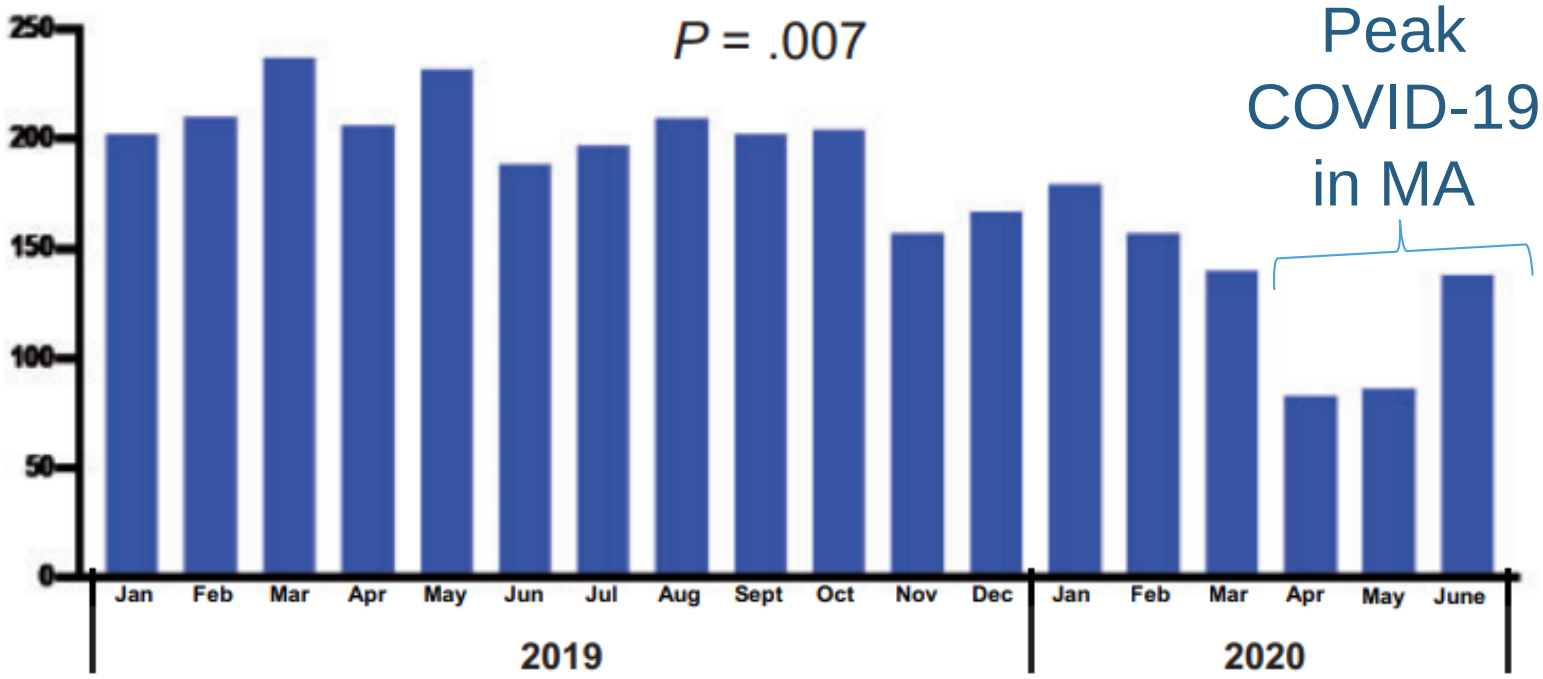
The Impact of COVID-19 on Clinical Trial Execution at the Dana-Farber Cancer Institute

Sara M. Tolaney, MD, MPH,[1] Christine A. Lydon, BA,[1] Tianyu Li, MS,[2] Jiale Dai, PhD, RPH,[3] Andrea Standring, PharmD,[3] Kristen A. Legor, JD, RN, OCN,[4] Caryn M. Caparrotta, BSN, RN, OCN,[4] Matthew P. Schenker, MD,[5] Daniel I. Glazer, MD,[5] Nabihah Tayob, PhD,[2] Steven G. DuBois, MD,[6] Jeffrey A. Meyerhardt, MD,[1] Mary-Ellen Taplin, MD,[1] Bruce E. Johnson, MD[1,*]

Therapeutic Clinical Trial Activity



Tolaney et al JNCI 2020

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Conclusions

- Outcomes with COVID-19 are worse in patients with COVID-19, but significant majority recover
- Lung cancer is still the underlying problem that we need to address, with prioritization of clinical trials
- Ongoing collaborative initiatives to look at interplay of COVID-19 and lung cancer: CCC-19, Terravolt, ASCO

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