Cancer and Ischemic Stroke: When to Search for and How to Treat

Babak Navi MD, MS

Chief, Division of Stroke and Hospital Neurology

Associate Professor, Neurology & Neuroscience

Medical Director, Stroke Center

Weill Cornell Medicine

Affiliate Associate Member

Memorial Sloan Kettering Cancer Center

Conflicts/Disclosures

- NIH grants K23NS091395 (PI), R01HL144541 (co-I)
- PCORI grant HIS-1511-33024 (subaward PI)
- NIDILRR grant 90REGE0012-01-11 (co-I)
- Weill Cornell Covid-19 Seed grant (co-PI)
- Associate Editor for the *Neurohospitalist* journal
- DSMB Member for TRAVERSE trial
- Medicolegal consulting on stroke

Objectives

- Define epidemiological relationship between cancer and stroke
- Describe risk and predictors for occult cancer in patients with stroke, and when and how to screen
- Review stroke mechanisms in cancer patients
- Evaluate antithrombotic treatment strategies for patients with cancer and stroke

Background

- 1.6M cancers and 800K strokes each year in USA
- Estimated lifetime incidences are 40% for cancer and 16% for stroke
- Leading causes of death and disability
- Intertwined diseases with shared risk factors

SEER Cancer Statistics Review, http://seer.cancer.gov/csr/1975_2013/; Furie KL et al, Stroke 2011; Graus F et al, Medicine 1985; Oneal WT et al, Am J Cardiol 2015; Conen D et al, JAMA Cardiol 2016; Sanossian N et al, J Stroke Cerebrovasc Dis 2013.

Cancer the Chronic Disease?

- Earlier detection, decreased smoking, and improved treatments have prolonged cancer survival
  - In USA, by 2015, two-thirds were surviving >5 years
- Further advances through targeted agents and immunotherapy leading to even more cancer survivors
- Increased emphasis on preventing disabling cardiovascular events, including stroke

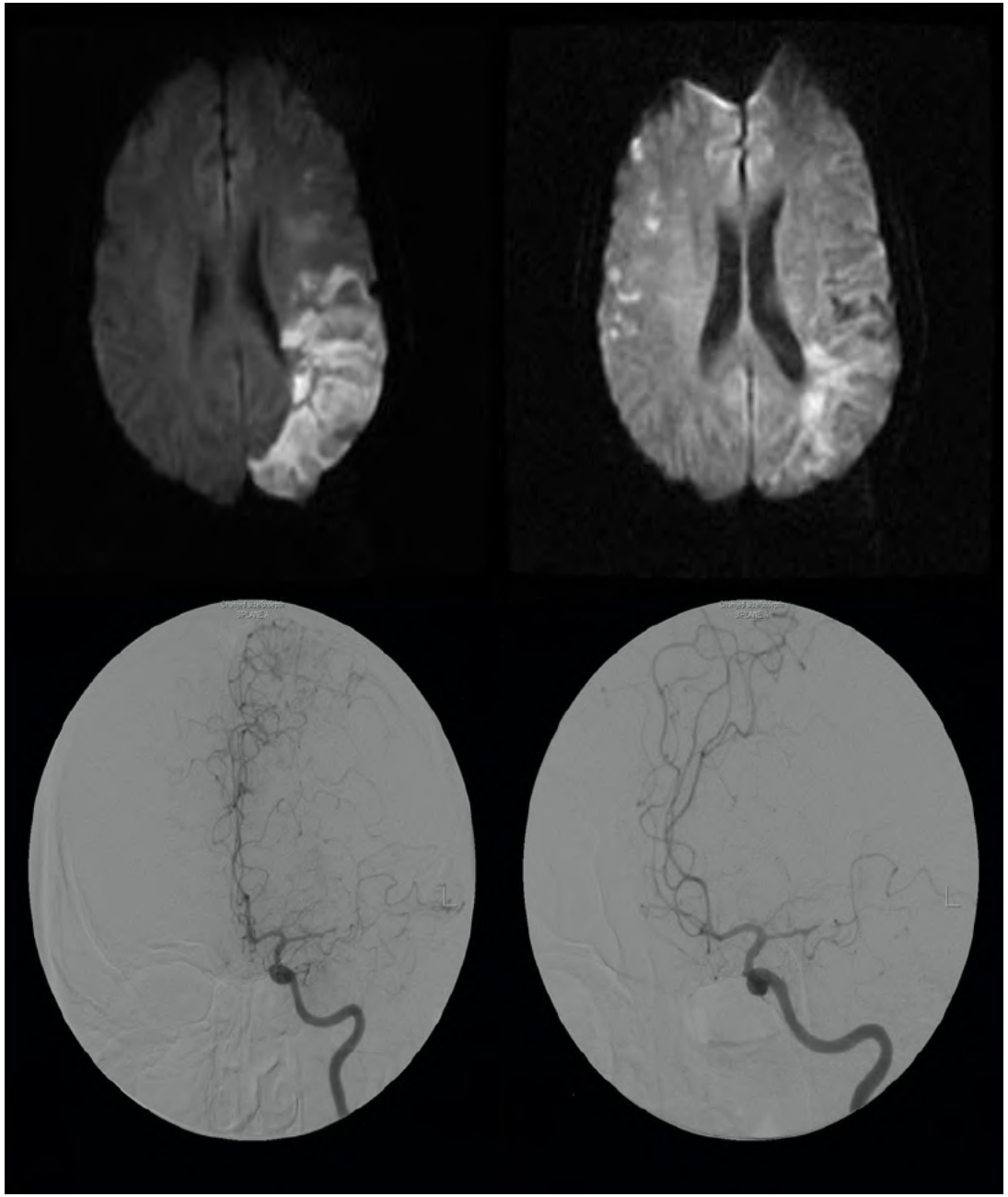
Henley SJ et al, MMWR 2015. Welch HG et al, N Engl J Med 2019; Howlader N et al N Engl J Med 2020.

Cancer is Common in Stroke Patients

- 10% of stroke patients have a known cancer history
  - Rates as high as 20% in certain Asian populations
- 50% of these cancers are active at the time of stroke
- Coprevalence of diseases increasing

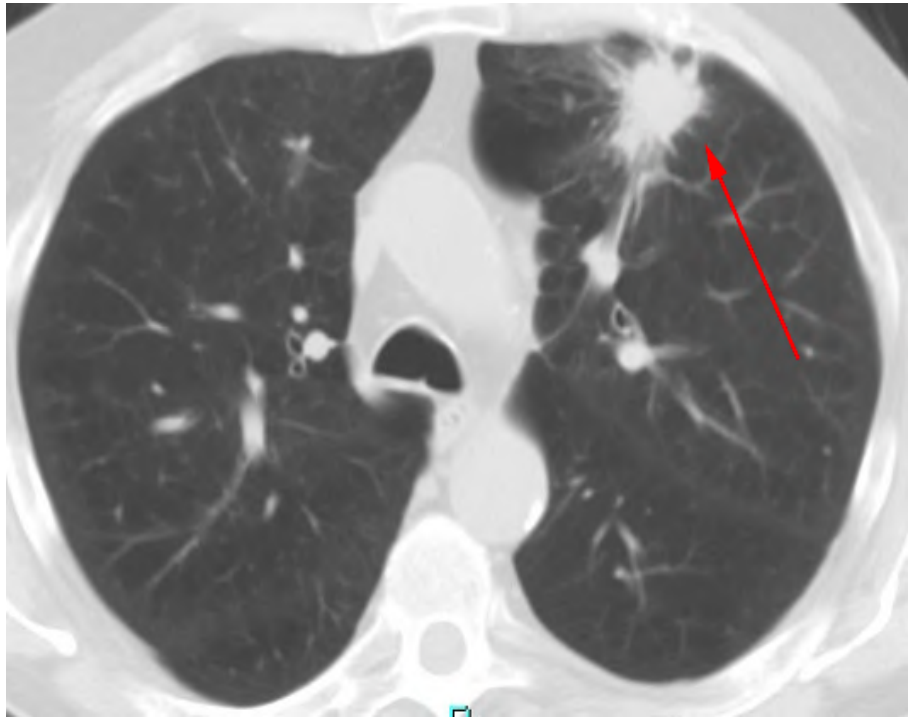
Sanossian N et al, J Stroke Cerebrovasc Dis 2013; Kim SJ et al, Plos One 2012

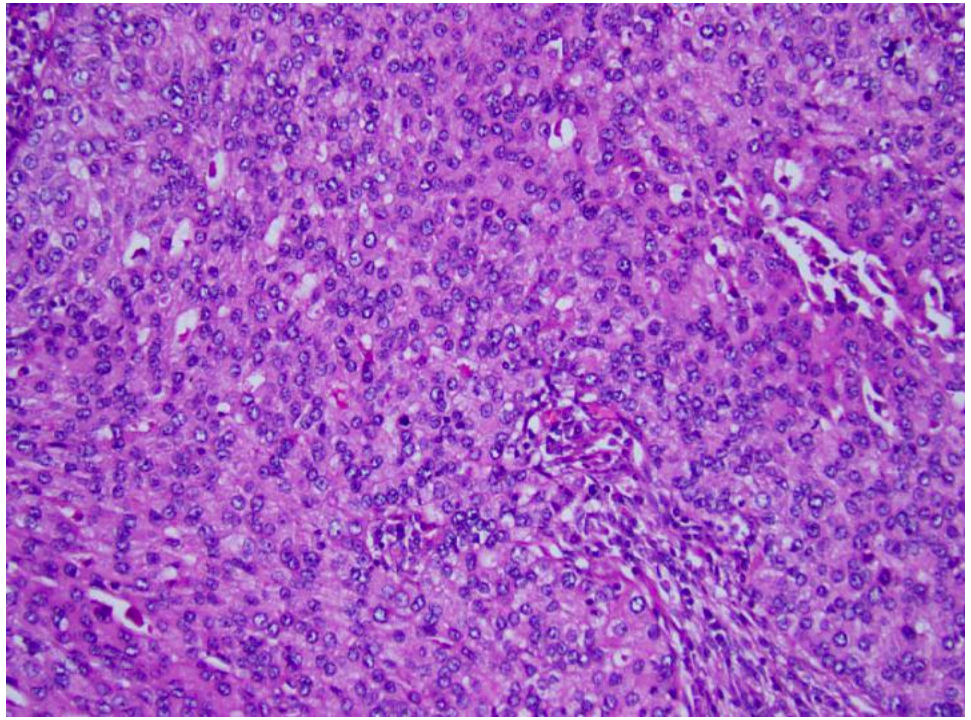
- 46 year old woman
- History of smoking
- 1 month of recurrent multifocal strokes despite aggressive medical therapy
- Also had NSTEMI
- Ultimately tissue obtained and diagnosis made



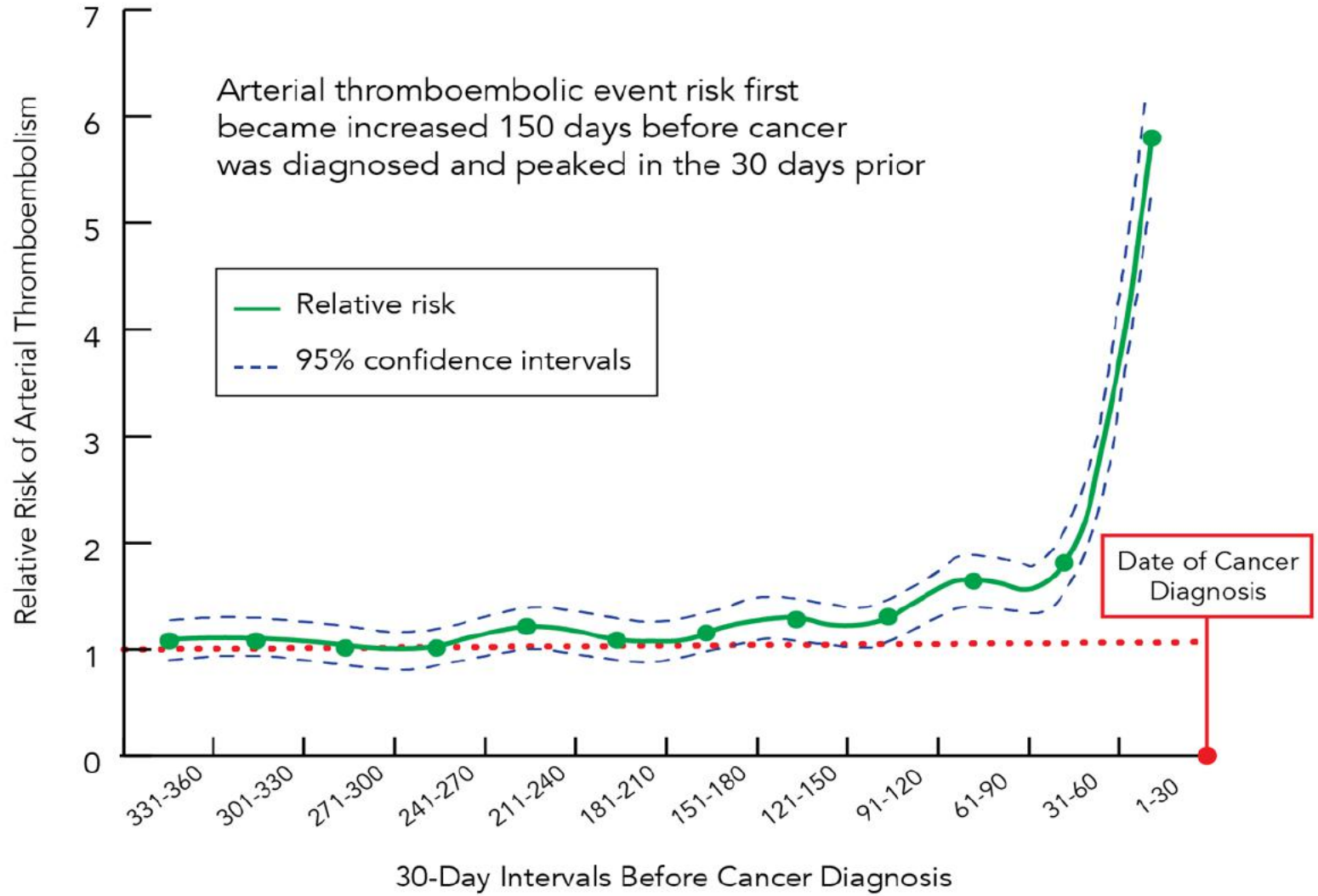
Navi BB et al, J Neurooncol 2007

Cancer Presenting as Stroke





Relative Risk Of Arterial Thromboembolic Events Preceding Cancer Diagnosis Between 374,331 Pairs of Cancer Patients and Matched Cancer-Free Controls



Navi BB et al, Blood 2018.

Occult Cancer in Ischemic Stroke Patients

- 2-10% of AIS patients without known cancer are diagnosed with cancer in the year after stroke

- Possible predictors include
  - **Cryptogenic (or ESUS) mechanism**
  - **Elevated D-dimer**
  - **3-territory sign**
  - **History of smoking**
  - Increased CRP
  - Anemia
  - Hypoalbuminemia

- Body CT vs. PET-CT vs. tumor markers?

Gon Y et al, Eur J Neurology 2017; Cocho D et al, J Stroke Cerebrovasc Dis 2015; Kim SJ et al, Plos One 2012; Selvik HA et al, Cerebrovasc Dis Extra 2015; Selvik HA et al, Cerebrovasc Dis 2018; Kassubek R et al, J Neurol 2017.

Pitfalls to Cancer Screening

- Cost
- Incidental findings
- Radiation exposure
- Effect on outcomes?

Screening for Occult Cancer in Unprovoked Venous Thromboembolism

Marc Carrier, M.D., Alejandro Lazo-Langner, M.D., Sudeep Shivakumar, M.D., Vicky Tagalakis, M.D., Ryan Zarychanski, M.D., Susan Solymoss, M.D., Nathalie Routhier, M.D., James Douketis, M.D., Kim Danovitch, C.C.R.P., Agnes Y. Lee, M.D., Gregoire Le Gal, M.D., Philip S. Wells, M.D., Daniel J. Corsi, Ph.D., Timothy Ramsay, Ph.D., Doug Coyle, Ph.D., Isabelle Chagnon, M.D., Zahra Kassam, M.D., Hardy Tao, M.D., and Marc A. Rodger, M.D., for the SOME Investigators*

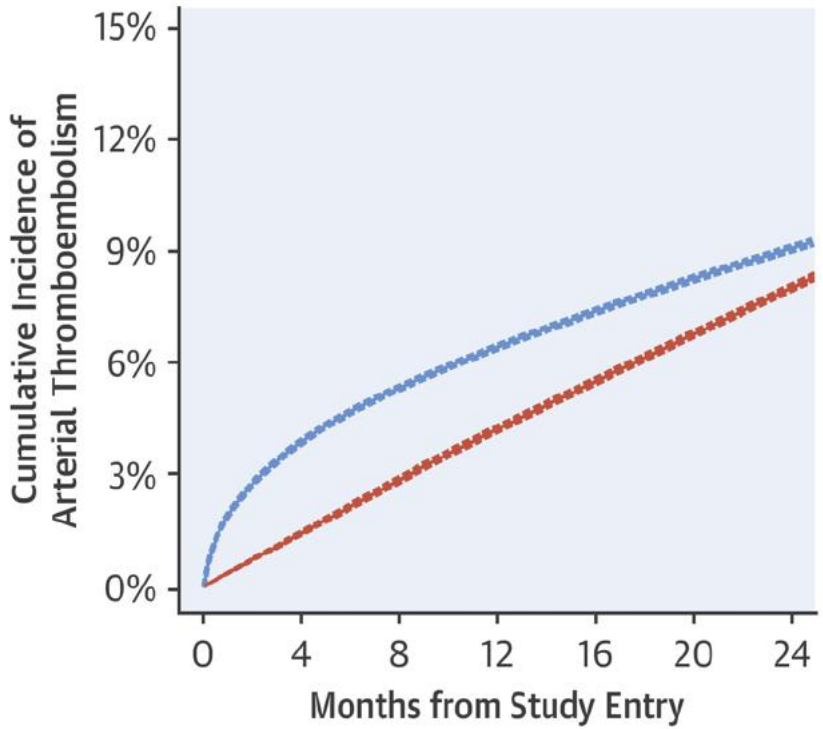
Carrier M et al, N Engl J Med 2020.

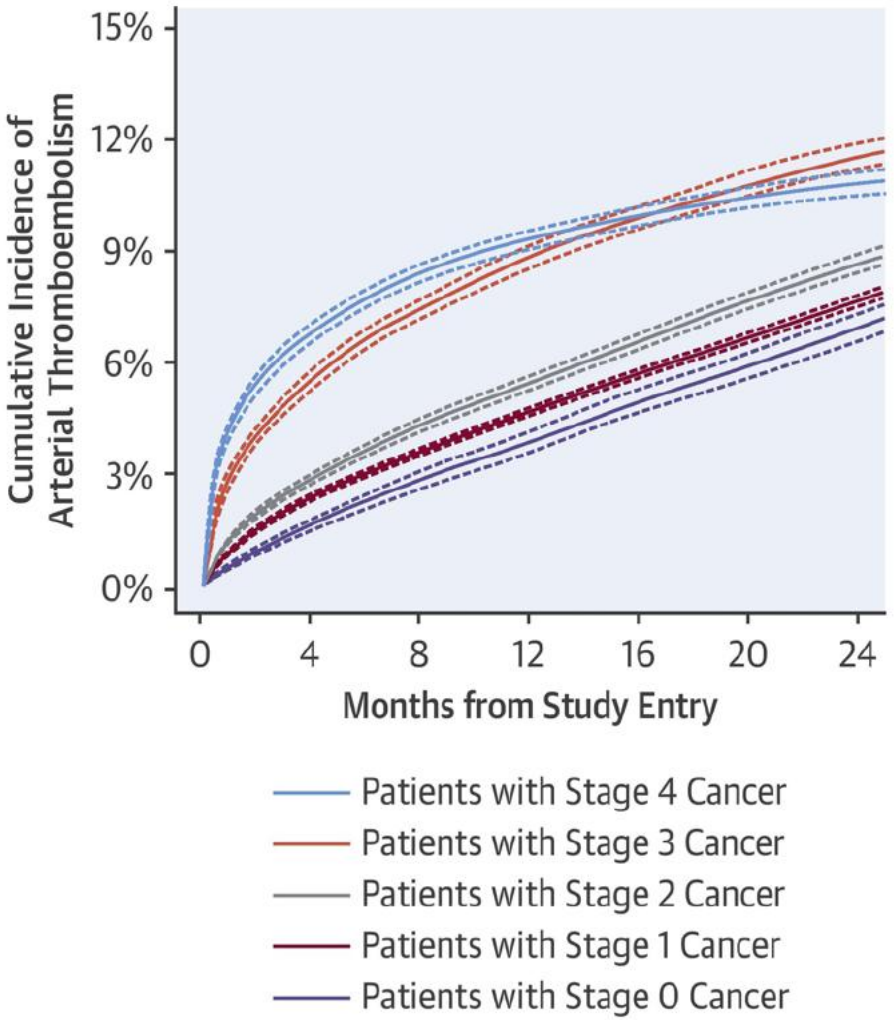
Arterial Thromboembolism Risk after Cancer Diagnosis

- Using SEER-Medicare, identified 279,719 patients with new diagnoses of breast, prostate, lung, colorectal, bladder, NHL, pancreatic, and gastric cancers from 2002-2011
  - 64% of all cancer in USA, 5 most common solid tumors, most common hematologic tumor, and 2 cancers with highest VTE risk
  - Median age 74 years
  - 30% of cancers stages 3 or 4 at diagnosis
- Identified controls without cancer matched 1:1 to cancer patients by demographics and comorbidities
- Excluded patients with prior coronary and cerebrovascular disease
- Followed until death, MI, AIS, or Dec 31, 2012
- Primary composite outcome of MI and AIS identified through validated ICD-9 codes

Navi BB et al, J Am Coll Cardiol 2017.

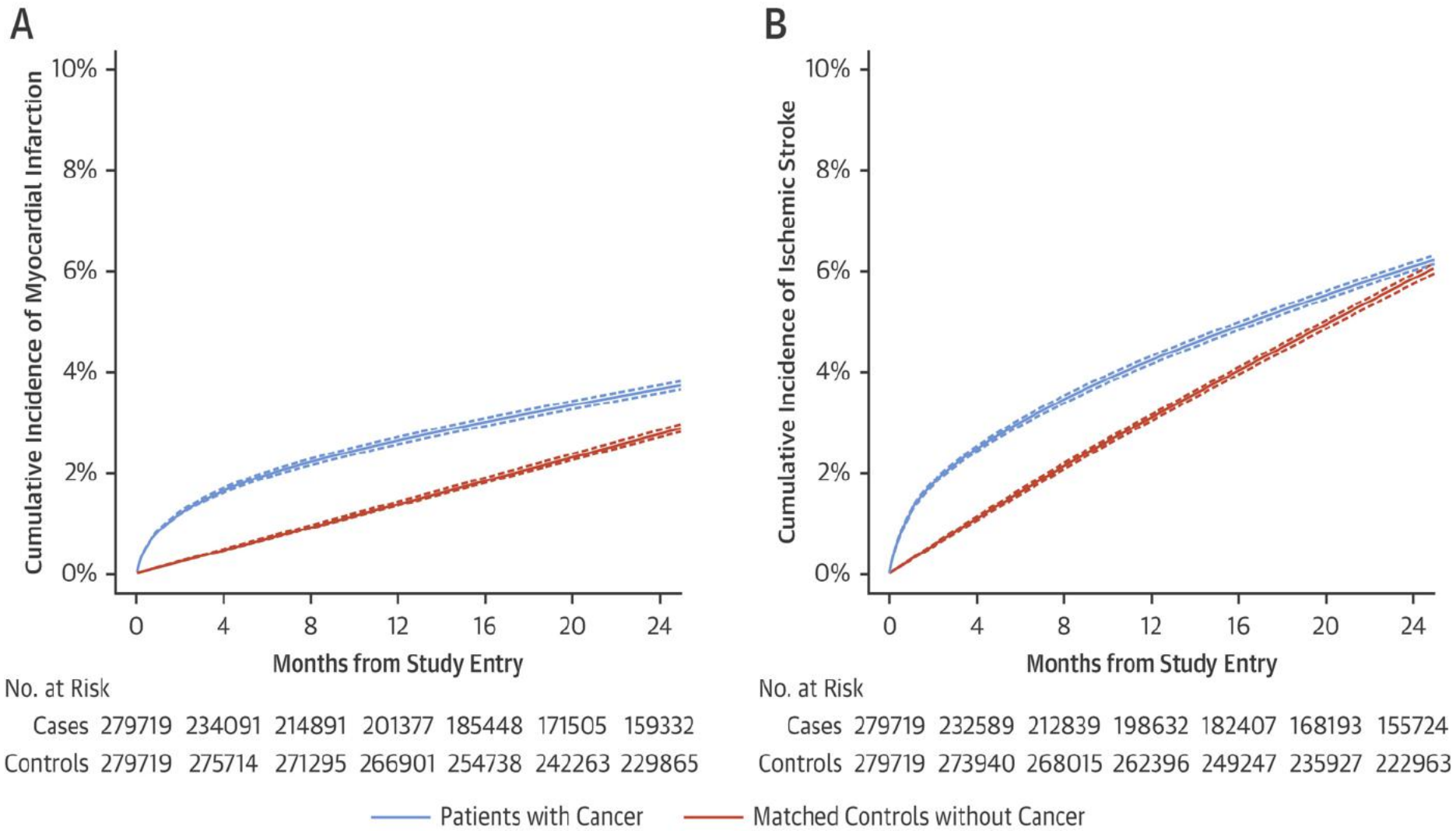
CENTRAL ILLUSTRATION: Cumulative Incidence of Arterial Thromboembolism in Cancer Patients





Navi, B.B. et al. J Am Coll Cardiol. 2017;70(8):926-38.

Cumulative Incidence of MI and AIS in Cancer Patients and Matched Controls



Navi BB et al, J Am Coll Cardiol 2017.

Relative Hazards of Stroke during Discrete Time Periods

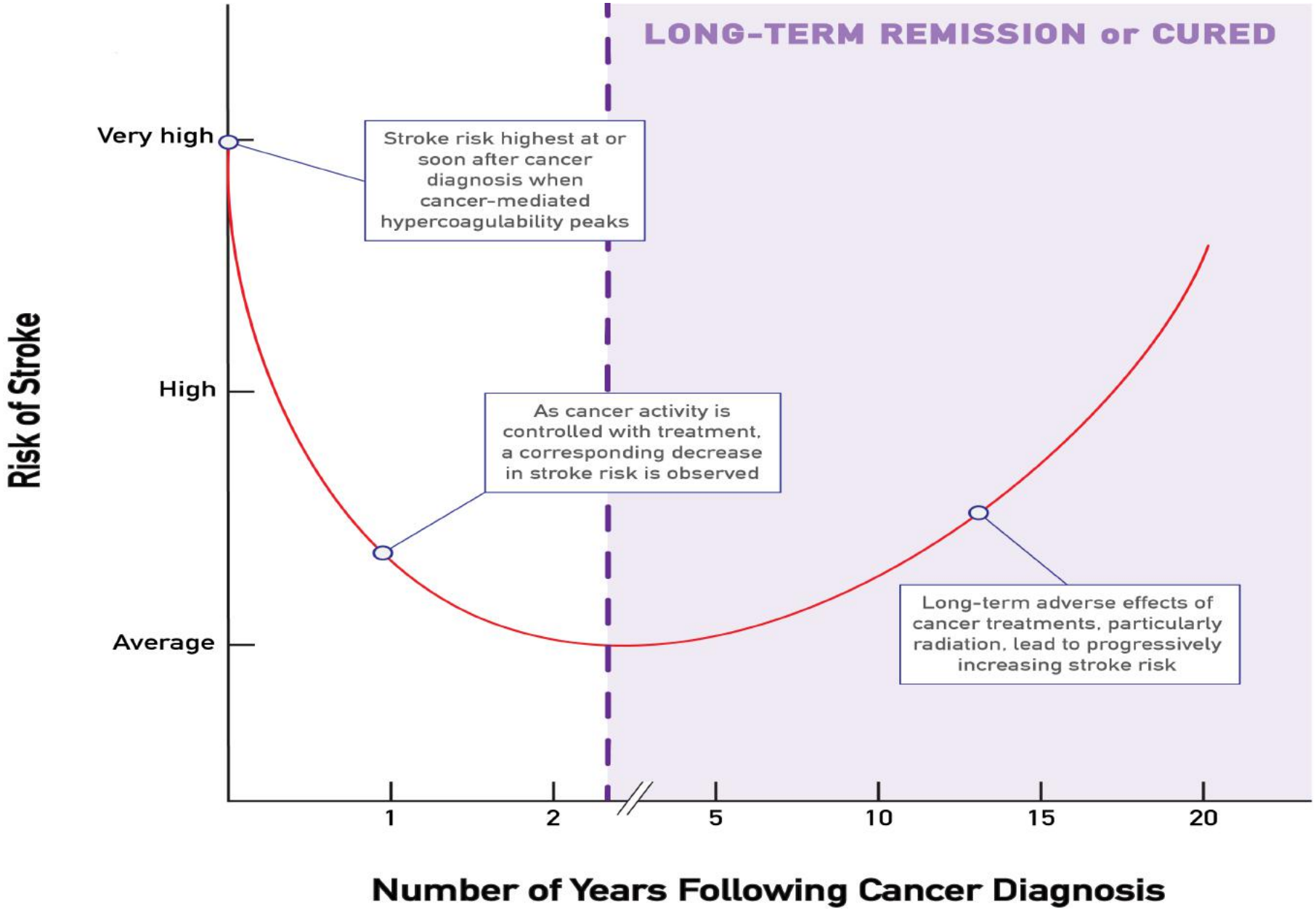
	Time Periods After Cancer Diagnosis				
	0-1 Month	***1-3 Months***	***3-6 Months***	***6-9 Months***	***9-12 Months***
Lung	7.4 (6.7-8.3)	2.7 (2.4-2.9)	2.0 (1.8-2.1)	1.6 (1.5-1.8)	1.7 (1.5-1.9)
Pancreas	4.3 (3.3-5.5)	2.1 (1.7-2.7)	1.6 (1.3-2.0)	--	--
Colorectal	4.2 (3.7-4.7)	1.8 (1.6-2.0)	1.4 (1.3-1.5)	0.9 (0.8-1.0)	0.9 (0.8-1.0)
Breast	1.7 (1.5-2.0)	1.2 (1.0-1.3)	0.9 (0.8-1.0)	0.9 (0.8-1.0)	0.9 (0.8-1.0)
Prostate	1.3 (1.1-1.4)	1.0 (0.9-1.1)	1.0 (0.9-1.1)	0.9 (0.8-1.0)	0.9 (0.8-1.0)

Navi BB et al, Ann Neurol 2015.

Link between Cancer and Cerebrovascular Events in REGARDS

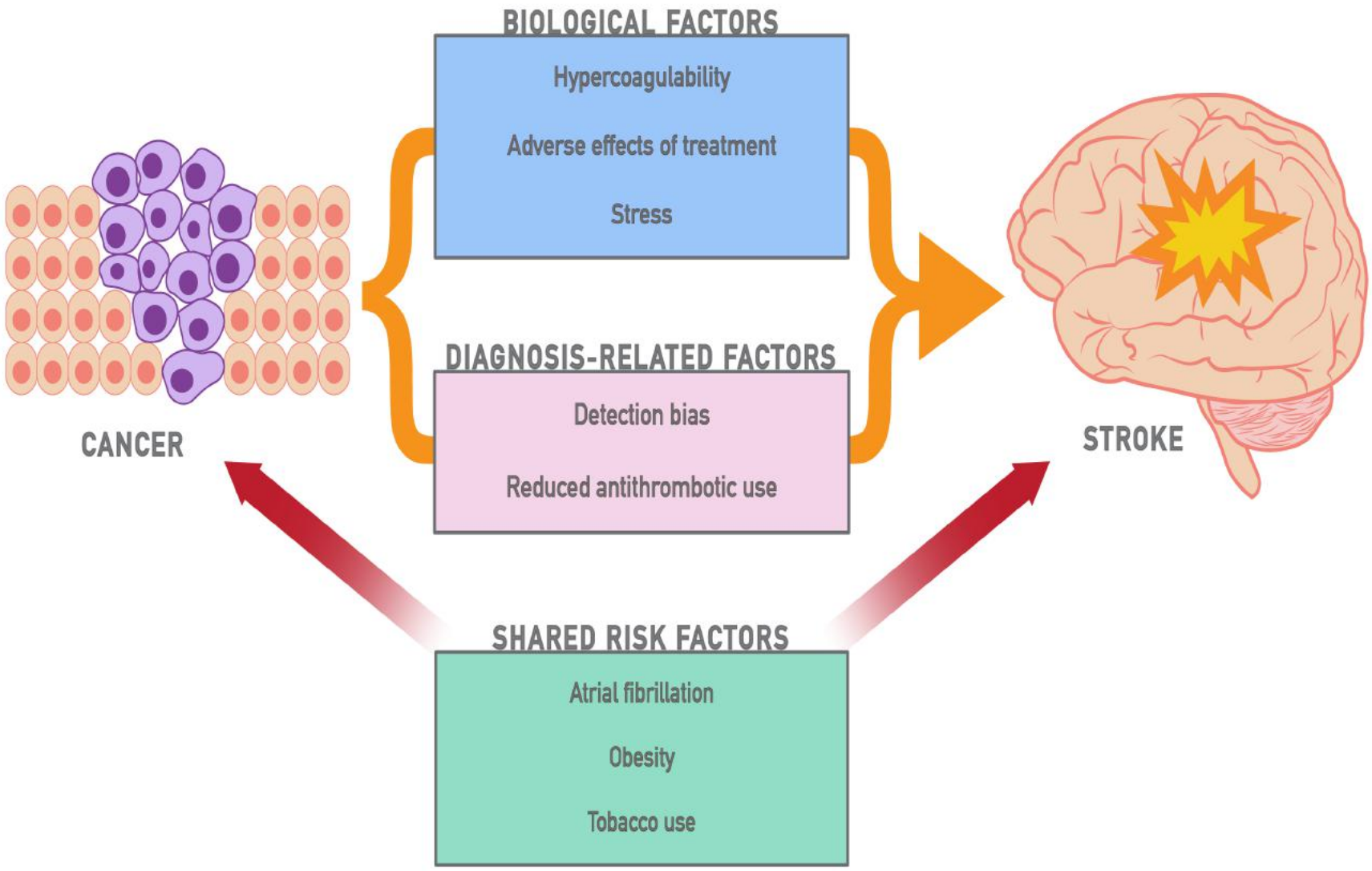
- 6,602 REGARDS participants met eligibility criteria
- 1,149 diagnosed with cancer during follow-up
- New cancer diagnosis strongly associated with subsequent cerebrovascular events in the first month after cancer diagnosis (**HR 6.1, 95% CI 2.7-13.7**)
- Association stronger after adjustment for demographics, region of residence, and stroke risk factors (**HR 6.6, 95% CI 2.7-16.0**)
- Significant association in 1-3 month period for high-risk cancers, particularly lung, pancreatic, and colorectal cancers, but not for all cancers though analysis underpowered

Navi BB et al, Neurology 2018.



Fullerton HJ et al, Neurology 2015; Campen CJ et al, Stroke 2012; Navi BB et al, Ann Neurol 2015.

Reasons for Increased Stroke Risk in Cancer Patients



Navi BB, Iadecola C, Ann Neurol 2018.

Pathobiology of Hypercoagulability of Cancer

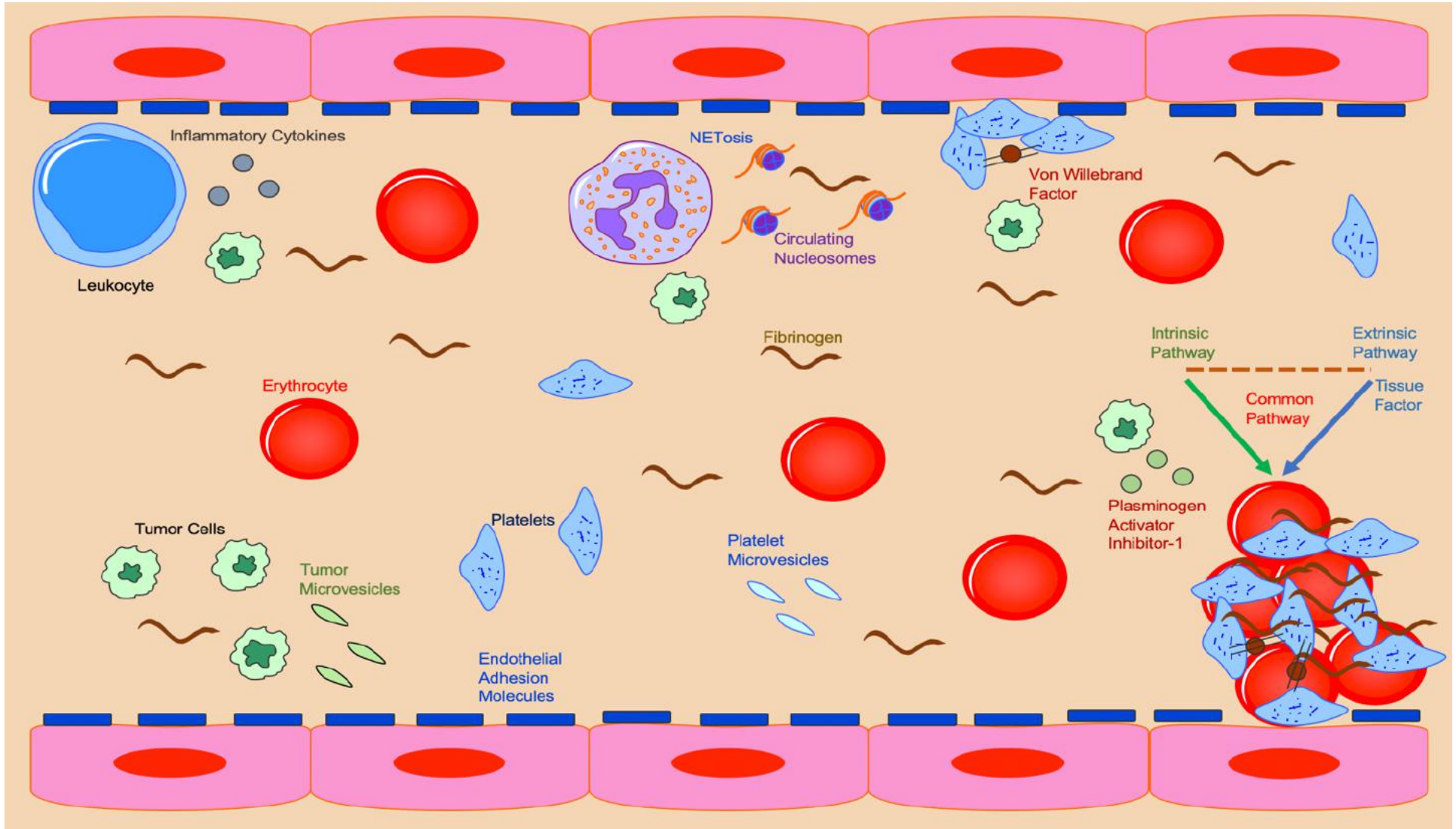
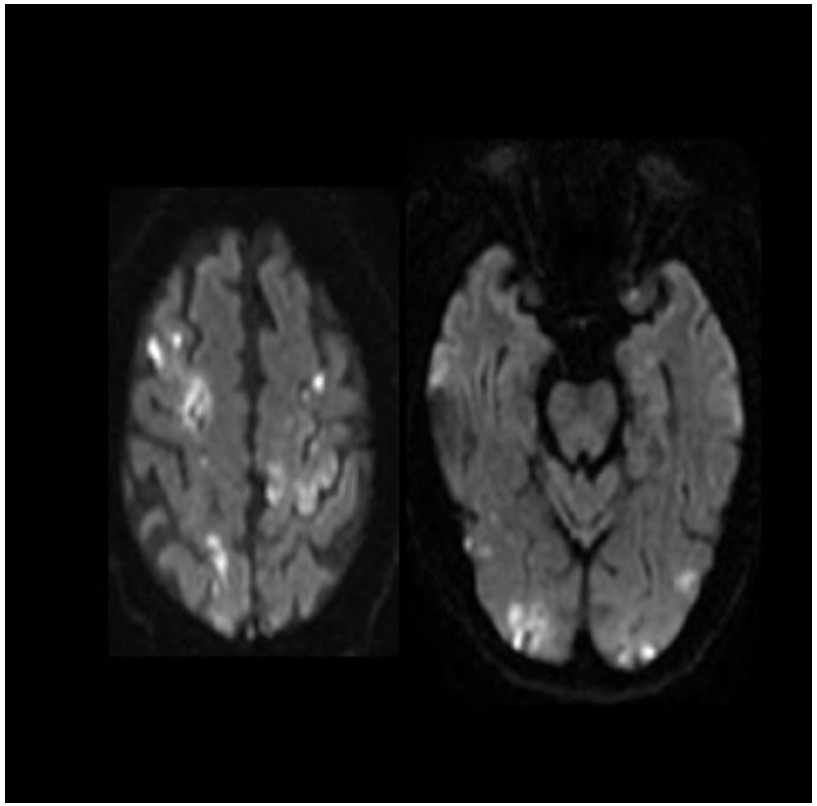


Figure created by Babak Navi

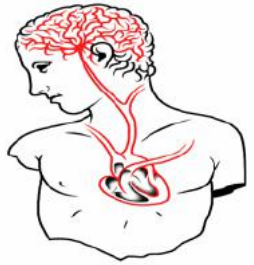
Ischemic Stroke Mechanisms in Cancer Patients

- Often unconventional (~50-60%)
- Commonly related to cancer properties or its treatment
- Frequently embolic appearing
  - 3-territory sign



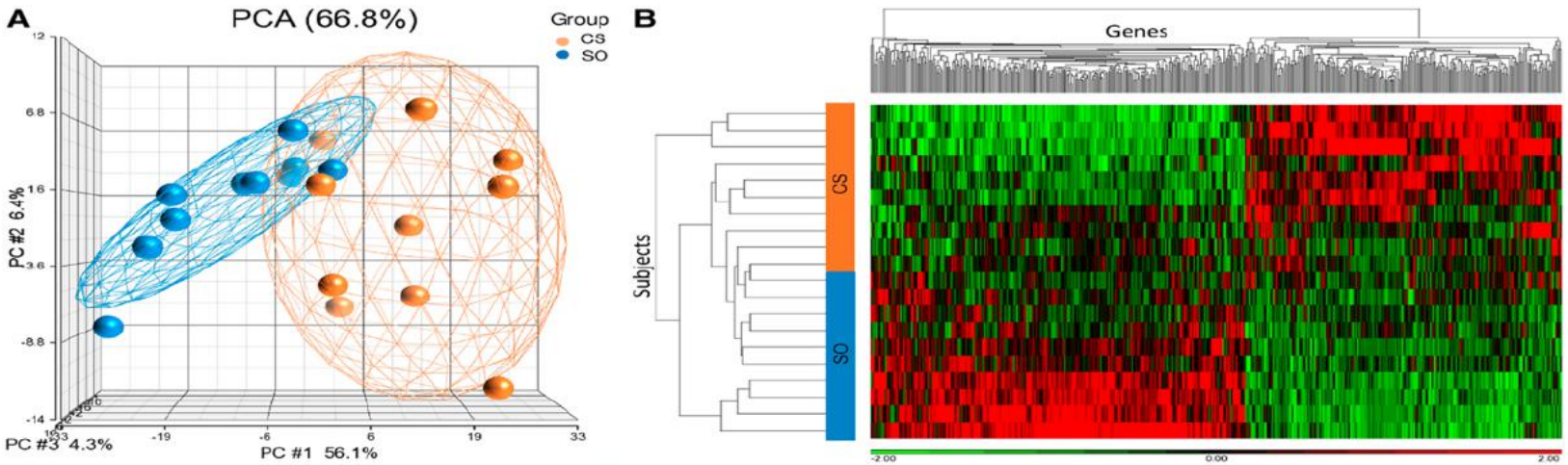
Seok JM et al, Ann Neurol 2010; Cestari DM et al, Neurology 2004; Schwarzbach CJ et al, Cerebrovasc Dis Extra 2015.

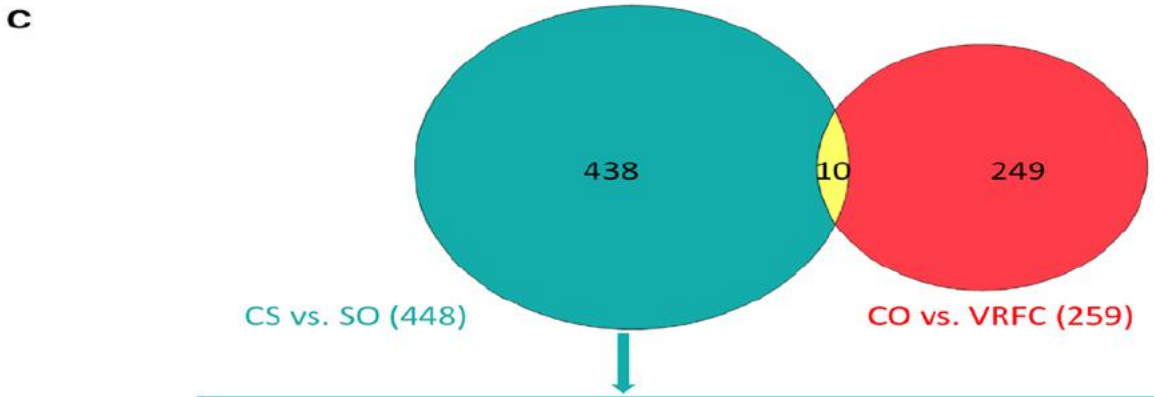
MOST-Cancer Study



- NIH-funded, prospective, cross-sectional, biomarker study evaluating mechanisms of ischemic stroke in patients with cancer
- 3 groups of 50 subjects matched by age, gender, and cancer type
  - Active solid tumor cancer and AIS
  - Active solid tumor cancer only
  - AIS only
- Testing includes hematological biomarkers, blood leukocyte RNA gene expression, and TCD-microemboli detection study

Distinct RNA Expression Profile in Cancer-Stroke





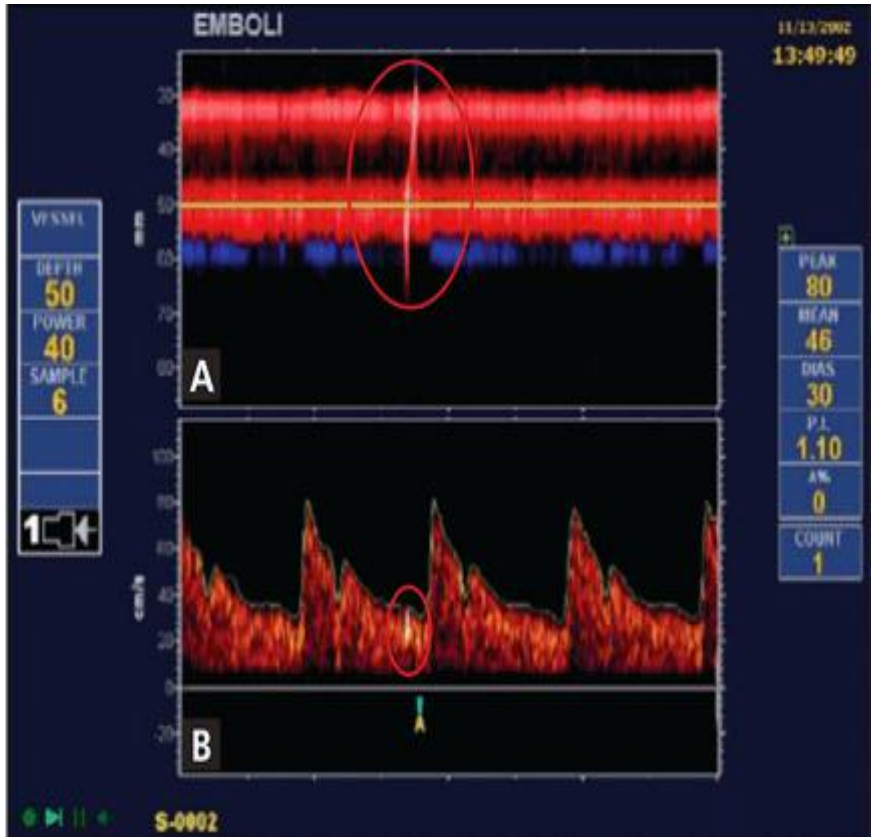
Over-Represented Pathways in the 438 Unique Genes in CS vs. SO

Canonical Pathway	Genes
Autophagy	ATG13, CTSA, CTSD, CTSF, SQSTM1
IL-1 Signaling	GNA15, GNG5, IRAK2, MAP3K7, MRAS, MYD88
mTOR Signaling	AKT1S1, ATG13, EIF3F, EIF4B, EIF4EBP1, FKBP1A, MRAS, RHOT2, RPS29
BER (base extension repair) Pathway	APEX1, LIG1
Interferon Signaling	IFITM3,IRF9,IFITM1
Relaxin Signaling	APEX1, CREB1, GDE1, GNA15, GNG5, GUCY1B1, MRAS
RAN Signaling	KPNA5, RANBP2
Estrogen Receptor Signaling	CARM1, MRAS, PHB2, TAF1, TAF7, TAF10
Gαs Signaling	CREB1, GNG5, MRAS, PTGDR, PTGIR

Navi BB et al, Stroke 2019.

TCD Microemboli Study in Cancer-Stroke Patients

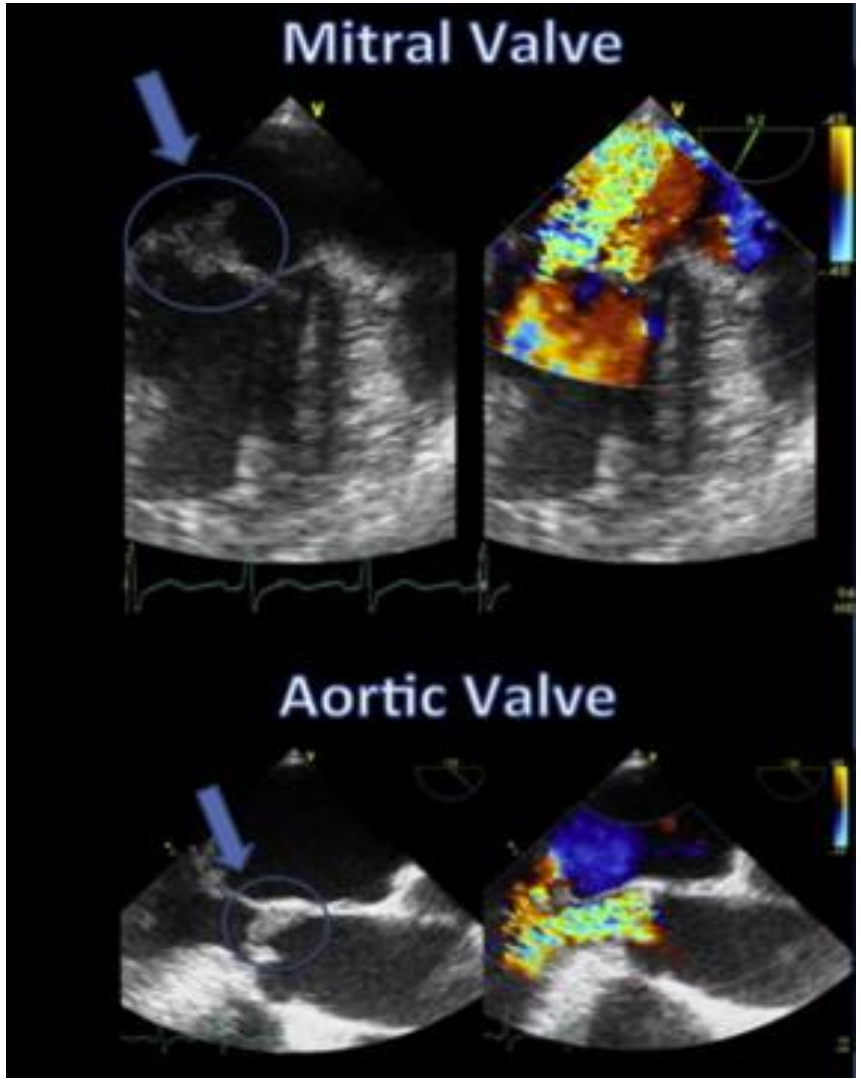
- Prospective TCD study of 74 active cancer patients with MCA distribution strokes
- Microemboli observed in 46% of overall cohort and 58% of those with unconventional stroke mechanisms
- Microemboli associated with high D-dimer levels and adenocarcinoma cancer histology



Seok JM et al, Ann Neurol 2010.

Nonbacterial Thrombotic Endocarditis (NBTE)

- Frequent cause of AIS in patients with cancer
- Sterile, small platelet-fibrin vegetations on normal cardiac valves
- Manifestation of cancer-mediated hypercoagulability
- More common with advanced metastatic disease but can herald cancer diagnosis
- Difficult to confirm with echo, though TEE superior to TTE



Graus F et al, Medicine 1985; Merkler AE et al, J Neurooncol 2015.

Atherosclerosis

- About one-third of ischemic strokes in patients with active cancer
- Likely most common cause in those whose cancer is in remission
- Prior radiation accelerates disease
  - ICA stenosis with head and neck cancers
  - Great vessel stenosis with breast cancer and lymphoma
  - CNS vasculopathy with brain tumors

Kim SG et al, Stroke 2010; Plummer C et al, Stroke 2011; De Bruin ML et al, J Natl Cancer Inst 2009.

Other Causes of Ischemic Stroke in Cancer Patients

- Venous infarction
  - Hypercoagulability
  - Neoplastic compression (breast, meningioma)
- Paradoxical embolism
- Tumor embolism
- Increased blood viscosity (myeloma)
- Septic emboli
- Vasculopathy
  - Infectious (VZV, aspergillosis)
  - Radiation (brain tumors)
- Arterial compression (GBM)

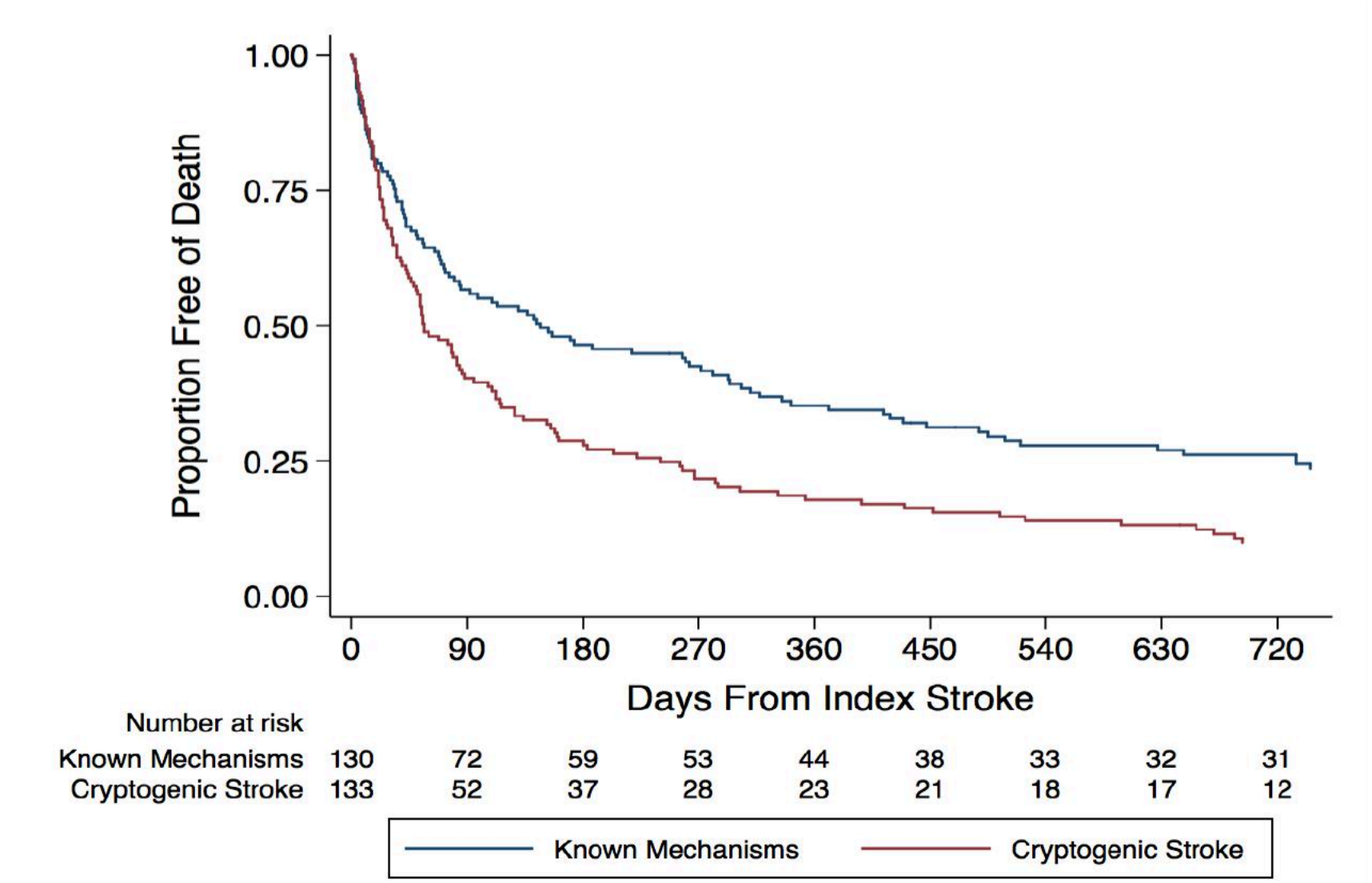
Navi BB, Iadecola C, Ann Neurol 2018.

Recurrent Stroke Risk

- Retrospective study of 263 patients with active systemic cancer and MRI-confirmed AIS at MSK from 2005-2010
- 90-day KM recurrent thromboembolism (RTE) rate 31%
  - 90-day KM recurrent stroke rate 13%
  - Adenocarcinoma predicted for RTE (OR 1.65)
- Similar RTE rates with AC versus APs (HR 1.19, 95% CI 0.72-1.97)
  - Confounding by indication bias?
- High recurrent stroke rate in cancer patients confirmed in several other populations
- D-dimer level associated with recurrent stroke risk, early neurological deterioration, and death in cancer-stroke patients

Navi BB et al, Neurology 2014; Kim JM et al, J Neurooncol 2013; Lau KK et al, PLOS One 2014;
Fujinami J et al, Cerebrovasc Dis 2018; Nam KW et al, Eur J Neurol 2017; Shin YW et al, J Neurooncol 2016.

Survival in Cancer-Associated Stroke



Navi BB et al, Stroke 2015.

Acute Stroke Recanalization Therapy

- Cancer patients generally excluded from trials, but not an absolute contraindication

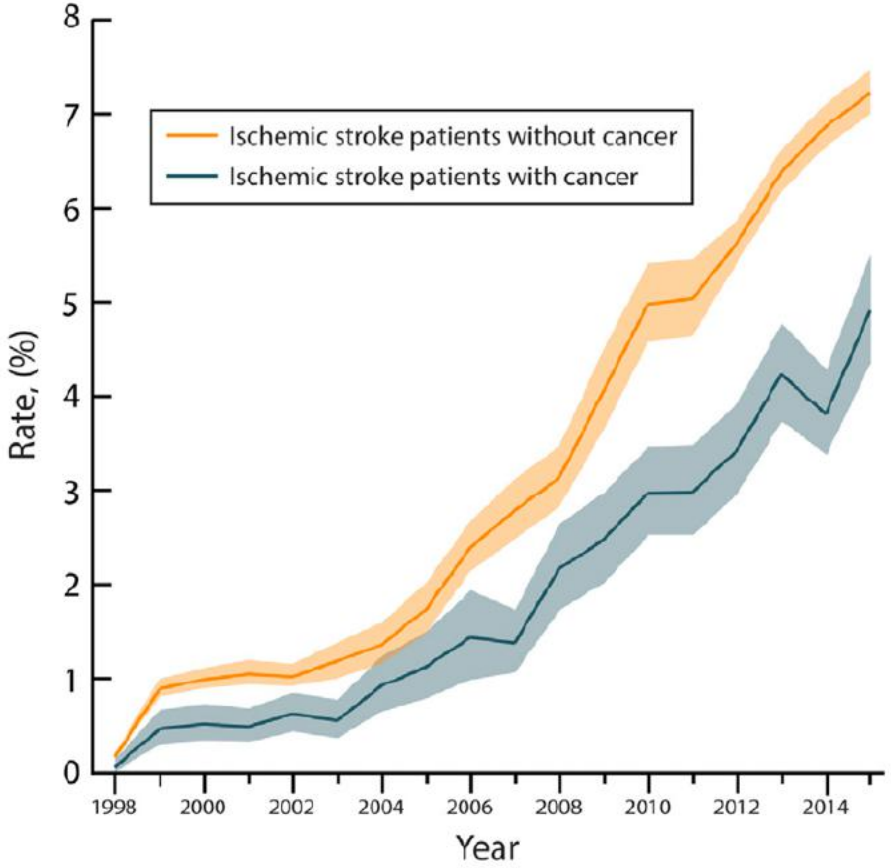
- Observational data suggests that IV TPA can be safe
  - 1/18 (6%) cancer patients treated with TPA for AIS had sICH
  - 4.1% ICH rate among 641 cancer-stroke patients treated with TPA in NIS
  - Different NIS study reported that comorbid cancer is associated with an increased odds of ICH from TPA for AIS

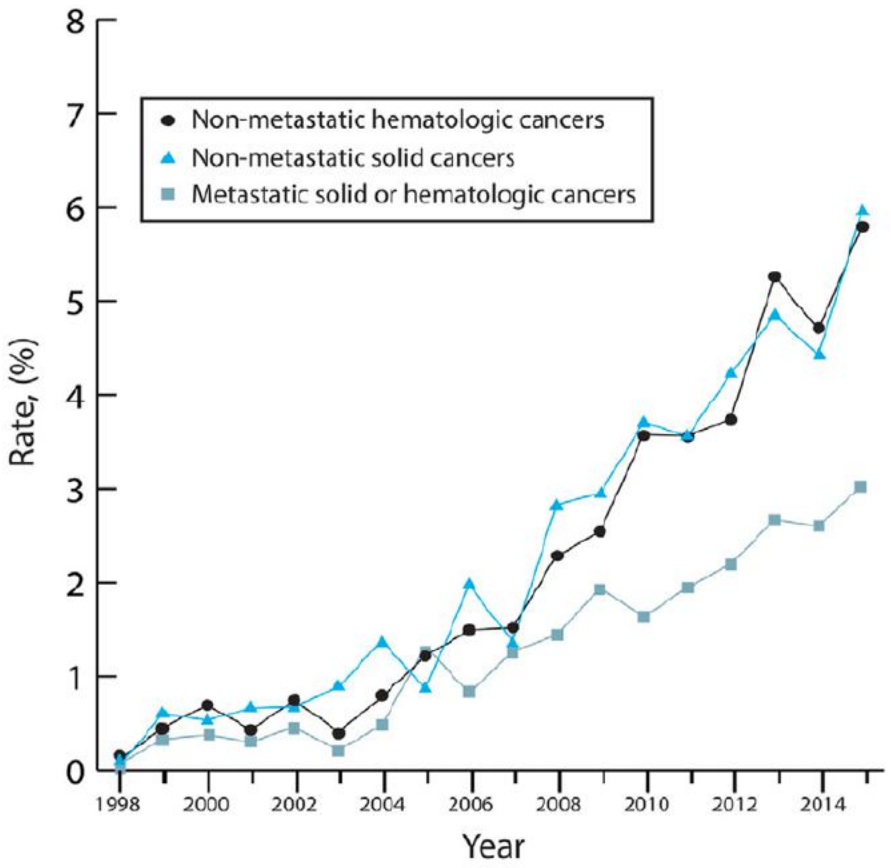
- Thrombolysis should be avoided in malignant brain tumor patients, though reports exist

- Endovascular therapy may be beneficial in select cases

Masrur S et al, J Stroke Cerebrovasc Dis 2011; Murthy SB et al, Stroke 2013; Weeda ER, Int J Stroke 2018; Murthy SB et al, J Clin Neuroscience 2015; Merkler AE et al, Neurohospitalist 2014.

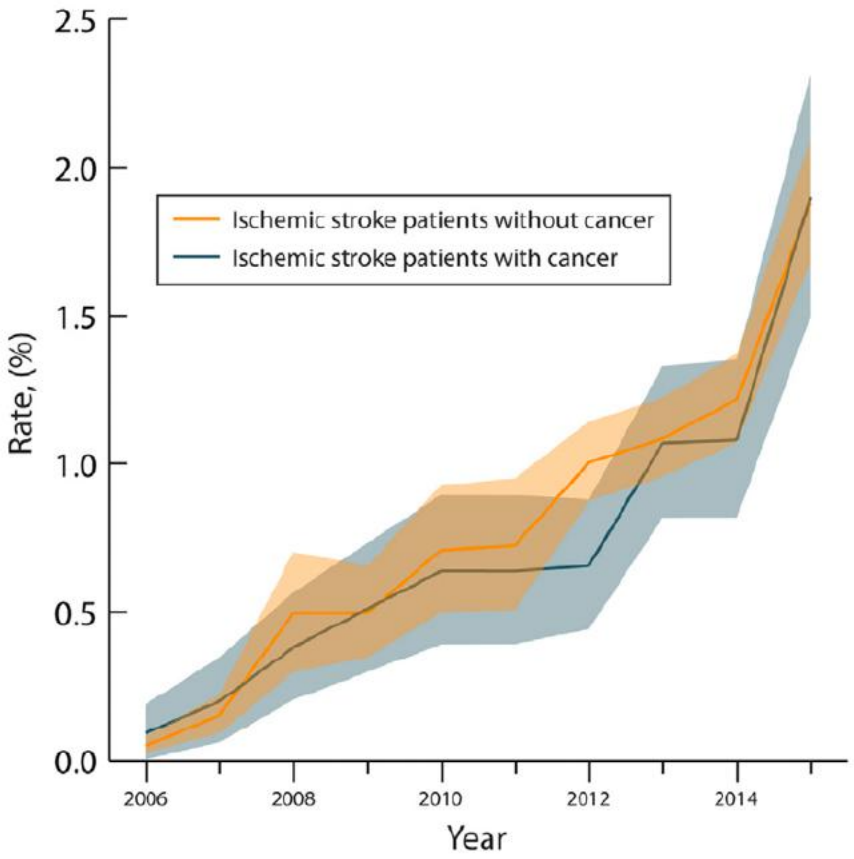
IV TPA Use for AIS in NIS

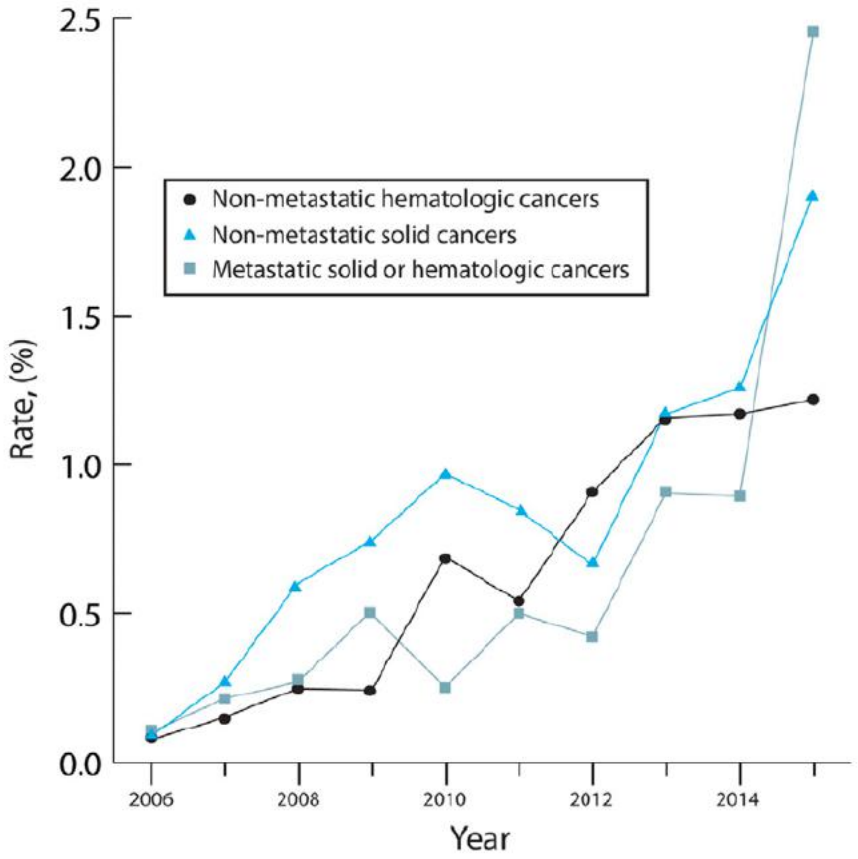




Chatterjee A et al, J Stroke Cerebrovasc Dis 2019

Mechanical Thrombectomy for AIS in NIS





Chatterjee A et al, J Stroke Cerebrovasc Dis 2019

Secondary Stroke Prevention

- Limited and inconclusive observational data
- No phase 3 randomized trials to guide therapy
- No AAN or AHA/ASA guidelines

Secondary Stroke Prevention

- Anticoagulation
  - Pros
    - May decrease D-dimer levels and TCD-MES
    - More directly addresses cancer-mediated hypercoagulability
    - LMWH, in particular, may have anti-neoplastic properties (CLOT/CATCH)
  - Cons
    - High bleeding risk, especially intracranially
    - Expensive, burdensome, difficult to administer
- Anti-platelets
  - Pros
    - Standard of care for most strokes (Level 1 evidence)
    - Excellent safety profile; easy to administer
    - May have direct anti-neoplastic properties
  - Cons
    - May not address cancer-mediated hypercoagulability

Seok JM et al, Ann Neurol 2010; Jang H et al, J Oncology 2015;
Lee AY et al, N Engl J Med 2003; Lee AY et al, JAMA 2015; Bath PM et al, Lancet 2001.

Histological Features of Intracranial Thrombi in Stroke Patients With Cancer

The histological features of thrombus in stroke patients with cancer are not well known. Using immunohistochemical staining of thrombi retrieved during mechanical thrombectomy in stroke patients, thrombus compositions were compared between 16 patients with active cancer, 16 patients with inactive cancer, and 16 patients without any history of cancer. The active cancer group showed higher platelet and lower erythrocyte fractions than the inactive cancer or the control group. Four patients with vegetation showed very high platelet and low erythrocyte fractions. Patients with cryptogenic etiology in the active cancer group showed a similar pattern to those with vegetation. These findings may aid the determination of treatment strategies in cancer-associated stroke.

ANN NEUROL 2019;86:143–149

Park H et al, Ann Neurol 2019

TEACh: Trial of Enoxaparin versus Aspirin in Cancer Patients with Stroke

- Pilot, multicenter, randomized clinical trial focused on feasibility
- Patients with active solid or hematological cancer and MRI-confirmed AIS within past 4 weeks at 3 academic centers
  - Clear indications for AC (DVT, AF) or AP (stent) exclusionary
- Randomized to 6 months of SQ enoxaparin (1 mg/kg BID) or PO ASA (81 mg QD) and followed for 1 year
- 49 eligible patients, 20 enrolled, 41% enrollment rate (95% CI, 27-55%)
- 0.31 enrollments per site per month (3.75 enrollments per site per year) suggesting that **a randomized trial of AC vs. AP therapy for cancer-associated stroke is likely feasible**
- **Top reason for enrollment failure was aversion to injections (n=11); enrollment could have been as high as 63% (95% CI, 48-77%) w/ DOAC**
- 40% of patients randomized to LMWH crossed-over to ASA because of discomfort with injections so **DOAC is preferred AC for future trials**
- No significant differences in secondary safety or efficacy endpoints

Navi BB et al, JAMA Neurol 2018; Raskob GE et al, N Engl J Med 2017; Young AM et al, J Clin Oncol 2018.

Table 1. Reasons Screened Patients were Ineligible for TEACH, n=420 Patients*

Exclusionary Criteria	**No. (%)***
Clear indication for anticoagulation	128 (30%)
No active cancer	83 (20%)
Inability to get brain MRI or no stroke seen on MRI	53 (13%)
Life expectancy <1 month or hospice care	32 (8%)
Primary brain tumor	31 (7%)
ICH within the past 3 months including intratumoral hemorrhage	31 (7%)
Platelet count ≤70,000/mm^3	27 (6%)
Age <18 or >85 years	24 (6%)
Hemoglobin <8 gm/dl	20 (5%)
Active or serious bleeding within past 2 weeks	17 (4%)
Stroke asymptomatic	16 (4%)
Patient unavailable for follow-up	15 (4%)
Clear indication for antiplatelet therapy	12 (3%)
Symptomatic, cervical internal carotid artery stenosis	11 (3%)
Patient condition associated with high risk of bleeding	10 (2%)
Active bleeding diathesis	8 (2%)
INR >1.6 or PTT >40 seconds	8 (2%)
Prior acute ischemic stroke‡	7 (2%)
Index stroke not within previous 4 weeks	6 (1%)
Aspirin allergy	4 (1%)
Brain metastasis‡	3 (1%)
AST or ALT >200 Units/L	3 (1%)
Serum creatinine >2 mg/dl	2 (1%)

Conclusions

- Short-term stroke risk markedly increased with new cancer diagnoses
- Up to 10% of AIS patients diagnosed with cancer in the following year, especially if ESUS, D-dimer high, and 3-territory sign present
- Stroke mechanisms in cancer patients often unique and related to properties of the neoplasm or its treatment
- Optimal antithrombotic treatment strategy for cancer-associated ESUS uncertain; randomized trials needed
- Long-term prognosis generally governed by the underlying cancer

Questions?

- CORNELL
  - ***Cos Iadecola, MD***
  - Hooman Kamel, MD, MS
  - Peter Okin, MD
  - Alex Merkler, MD
  - Natalie Cheng, MD
  - Jordan Reichmann, MD
  - Neal Parikh, MD, MS
  - Jackie Burch, MD
  - Ryna Mathias, MD
  - Carla Sherman, RN
  - **Scott Tagawa, MD, MS**
  - Ashish Saxena, MD, PhD
  - Allyson Ocean, MD
  - Abhinaba Chatterjee, BS

- COLUMBIA
  - ***Mitch Elkind, MD, MS***
  - Randy Marshall, MD, MS

- UC Davis
  - ***Frank Sharp, MD***
  - Boryana Stamova, MD

- MSKCC
  - ***Lisa DeAngelis, MD***
  - Kathy Panageas, PhD
  - Sam Singer, MD
  - Anne Reiner, MS
  - Jacqueline Stone, MD
  - Dylan Bobrow, MD
  - Julia Wolfe, BS
  - Ellinor Peerschke, PhD

- UAB/REGARDS
  - ***Paul Muntner, PhD***
  - George Howard, DrPH
  - Virginia Howard, PhD
  - Mary Cushman, MD, MSc
  - Hong Zhao, MSPH
  - Suzanne Judd, PhD
  - Susan Lakoski, MD
  - Elsayed Soliman, MD