Cancer and Stroke

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Objectives

- Define the epidemiological relationship between cancer and stroke
- Identify the common mechanisms of stroke in patients with cancer
- Evaluate different treatment strategies for patients with cancer and stroke
- Review the prognosis of cancer patients who develop stroke

Health Burden

- 1.6M cancers diagnosed each year in USA
- Estimated 40% lifetime incidence of cancer[1]
- 800K strokes each year in USA[2]
- Leading causes of death
- 15% of cancer patients have cerebrovascular disease at autopsy[3]

[1]SEER Cancer Statistics Review, http://seer.cancer.gov/csr/1975_2013/ ; [2]Furie KL et al, Stroke 2011; [3]Graus F et al, Medicine 1985.

Intertwined Diseases

- Shared risk factors
  - Age
  - Smoking
  - Obesity
  - Atrial fibrillation[1, 2]
- Cancer-mediated hypercoagulability
- Effects of cancer therapies

[1]Oneal WT et al, Am J Cardiol 2015; [2]Conen D et al, JAMA Cardiol 2016.

Cancer the Chronic Disease?

- Earlier detection and improved cancer treatments have prolonged cancer survival
  - In USA, two-thirds survive >5 years
- Further advances through targeted agents and immunotherapy will likely lead to more cancer survivors but also more patients at risk for cardiovascular events

[1]Henley SJ et al, MMWR 2015.

Themes

- Cancer is an independent risk factor for stroke
- Mechanisms of stroke in cancer are unique
- Treatment is often unorthodox and individualized (and not very evidence based)

Cancer is Common in Stroke Patients

- 10% of stroke patients have a cancer history[1,2]
- 4% of stroke patients are diagnosed with cancer after their stroke (mean follow-up 2.4 years)[1]
- Stroke independently predicts new cancer diagnoses (RR 1.10)[1]

[1]Lindvig K et al, Int J Epidemiol 1990; [2]Sanossian N et al, J Stroke Cerebrovasc Dis 2013.

Does Cancer Predict Stroke?

- Using SEER-Medicare database, identified elderly patients (n=327K) with a new diagnosis of lung, breast, prostate, colorectal, or pancreatic cancer from 2001 to 2008[1]
  - 4 most common cancers (51% of all cancer) and cancer most commonly linked to thrombosis
- Controls matched by age, sex, race, region, Charlson comorbidity index, and HTN/AF
- Patients with prior cerebrovascular disease diagnoses excluded
- Followed until death, stroke, or 2010
- Stroke identified through validated ICD-9 codes

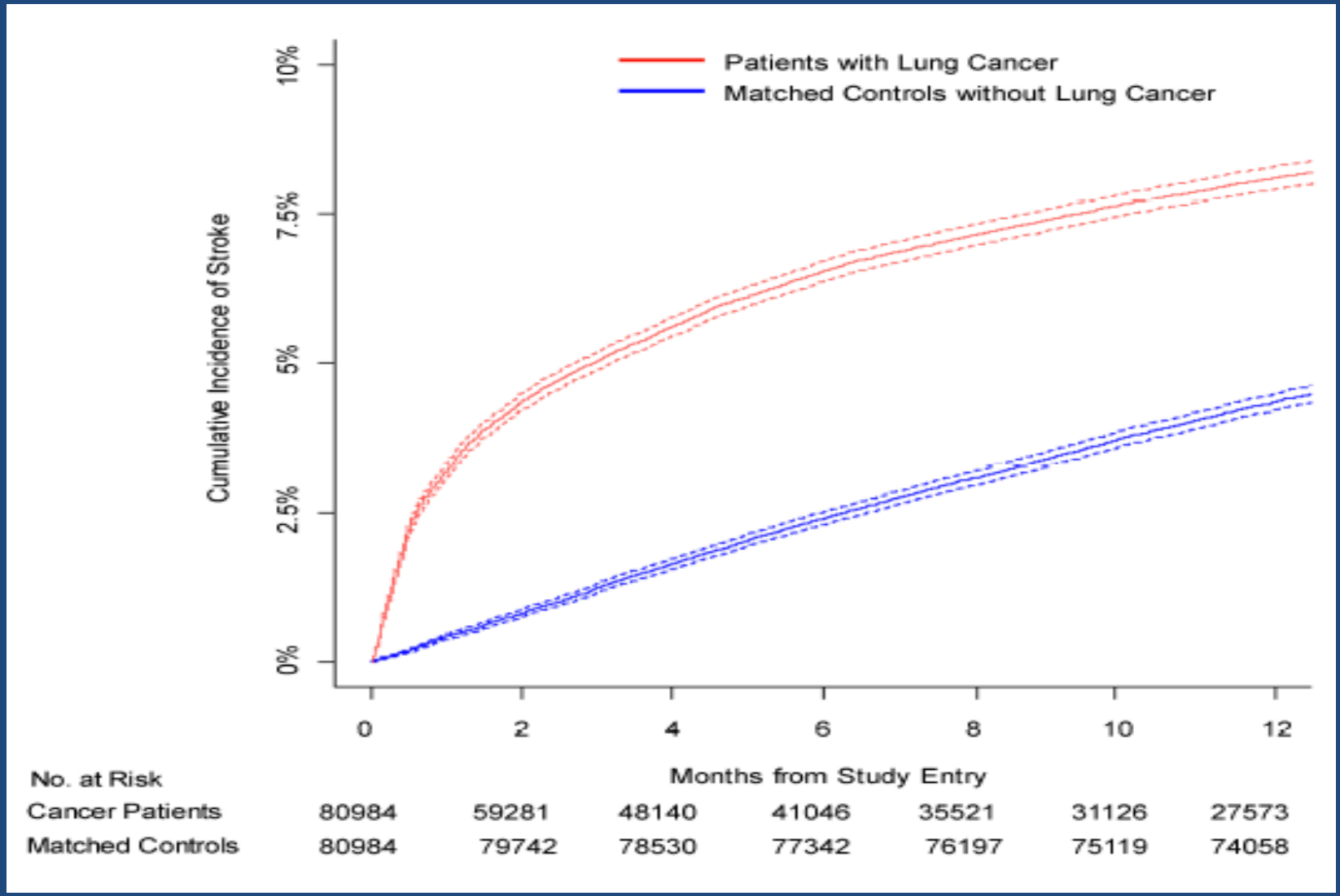
[1]Navi BB et al, Ann Neurol 2015.

Cumulative Incidence of Stroke

	3 Months	6 months	1 year
Prostate			
Cases	1.2 (1.1-1.3)	2.1 (2.0-2.2)	3.6 (3.5-3.8)
Controls	1.1 (1.0-1.2)	2.1 (2.0-2.2)	3.8 (3.6-3.9)
Lung			
Cases	5.1 (4.9-5.2)	6.6 (6.4-6.7)	8.1 (8.0-8.3)
Controls	1.2 (1.2-1.3)	2.4 (2.3-2.5)	4.4 (4.2-4.5)
Breast			
Cases	1.5 (1.4-1.6)	2.3 (2.2-2.4)	3.9 (3.8-4.1)
Controls	1.1 (1.0-1.2)	2.1 (2.0-2.2)	3.9 (3.7-4.0)
Colorectal			
Cases	3.3 (3.2-3.4)	4.7 (4.5-4.8)	6.2 (6.0-6.4)
Controls	1.3 (1.2-1.4)	2.4 (2.3-2.6)	4.6 (4.4-4.7)
Pancreas			
Cases	3.4 (3.1-3.6)	4.3 (4.0-4.6)	--
Controls	1.3 (1.2-1.4)	2.3 (2.1-2.6)	--

[1]Navi BB et al, Ann Neurol 2015.

Cumulative Incidence of Stroke—Lung Cohort



[1]Navi BB et al, Ann Neurol 2015.

Cumulative Incidence of Hemorrhagic Stroke

	3 Months	6 months	1 year
Prostate			
Cases	0.09 (0.07-0.10)	0.16 (0.14-0.19)	0.30 (0.26-0.33)
Controls	0.07 (0.06-0.09)	0.12 (0.11-0.15)	0.24 (0.21-0.27)
Lung			
Cases	0.51 (0.46-0.56)	0.66 (0.60-0.71)	0.86 (0.80-0.92)
Controls	0.07 (0.05-0.09)	0.13 (0.11-0.16)	0.25 (0.22-0.29)
Breast			
Cases	0.12 (0.10-0.15)	0.19 (0.16-0.22)	0.32 (0.28-0.37)
Controls	0.06 (0.04-0.08)	0.12 (0.10-0.16)	0.26 (0.22-0.30)
Colorectal			
Cases	0.17 (0.14-0.21)	0.28 (0.24-0.32)	0.43 (0.38-0.48)
Controls	0.09 (0.07-0.10)	0.16 (0.13-0.19)	0.27 (0.23-0.31)
Pancreas			
Cases	0.23 (0.16-0.30)	0.30 (0.20-0.40)	--
Controls	0.07 (0.03-0.10)	0.10 (0.05-0.20)	--

[1]Navi BB et al, Ann Neurol 2015.

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)

[1]Navi BB et al, Ann Neurol 2015.

SEER-Medicare Study Conclusions

- Incident cancer is associated with a markedly increased short-term risk of stroke[1]
- Risk is highest soon after cancer diagnosis and then attenuates over time
- Aggressiveness of underlying cancer correlates with degree of risk
- Risk increased for both ischemic and hemorrhagic stroke but persists longer for hemorrhagic type

[1]Navi BB et al, Ann Neurol 2015.

Cancer and Risk of Arterial Thromboembolism

- Using SEER-Medicare, study cohort expanded to 8 cancer types from 2002 through 2011, including breast, prostate, lung, colorectal, bladder, NHL, pancreatic, and gastric[1]
  - Represents 64% of all cancer in USA, 5 most common solid tumors, most common hematologic tumor, and 2 cancers with highest risk of VTE
- Identified controls matched by age, sex, race, geographic region, Charlson comorbidity index, and HTN/AF
- Patients with prior coronary and cerebrovascular disease excluded
- Followed until death, MI, ischemic stroke, or Dec 31, 2012
- Primary outcome was a composite of MI and ischemic stroke identified through validated ICD-9 codes
- Secondary outcomes included MI alone and ischemic stroke alone

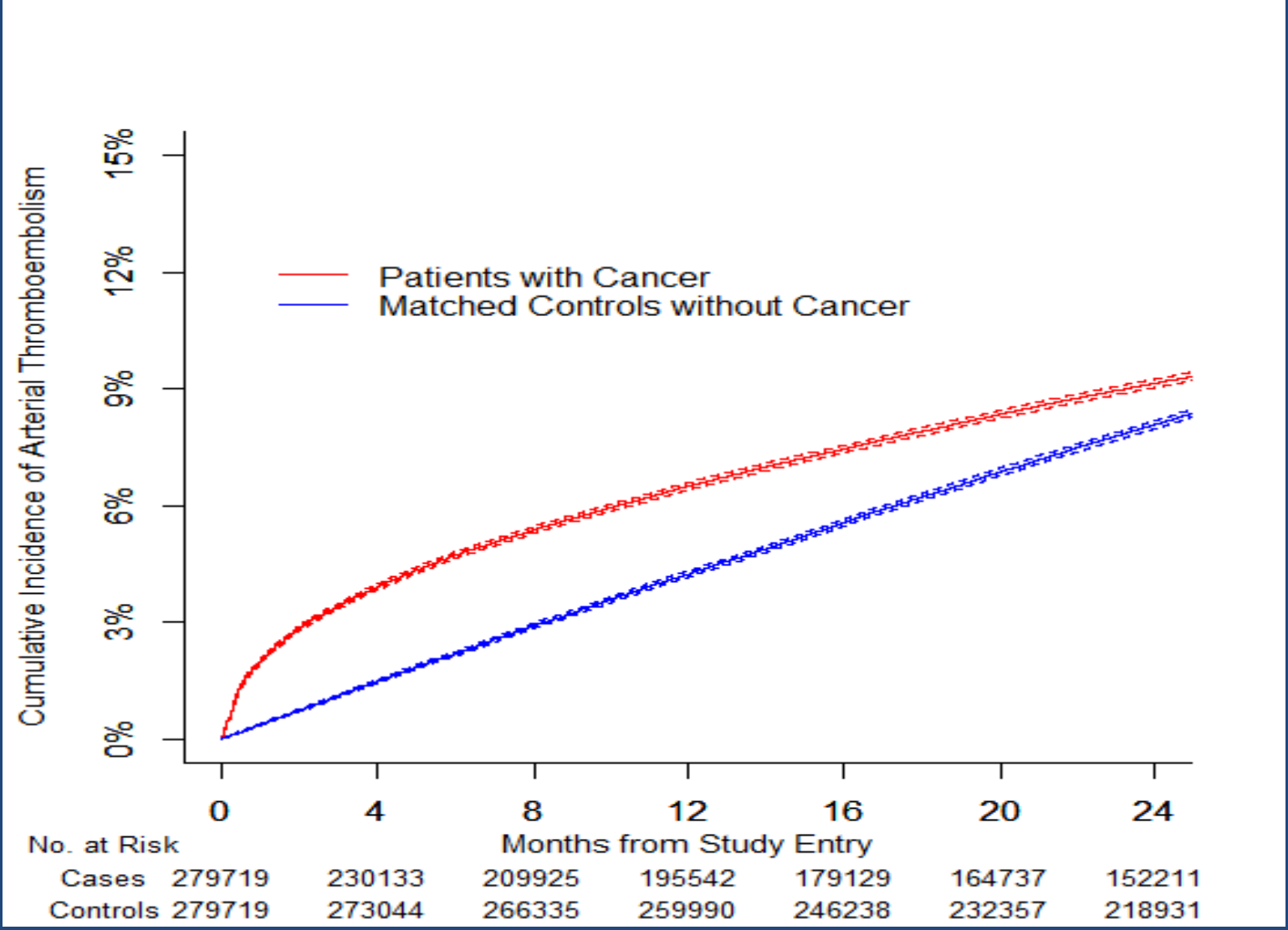
[1]Navi BB et al, submitted.

Baseline Characteristics

- 279,719 pairs of cancer patients and matched controls identified
- Median age 74 years, 48% men, 85% white
- Most had early stage disease (30% were stage 3 or 4 at diagnosis)
- Any Charlson comorbidity present in 25% and 61% had prior HTN or AF
- Median survival from time of cancer diagnosis was 5.2 years in cancer patients and not yet reached in matched controls

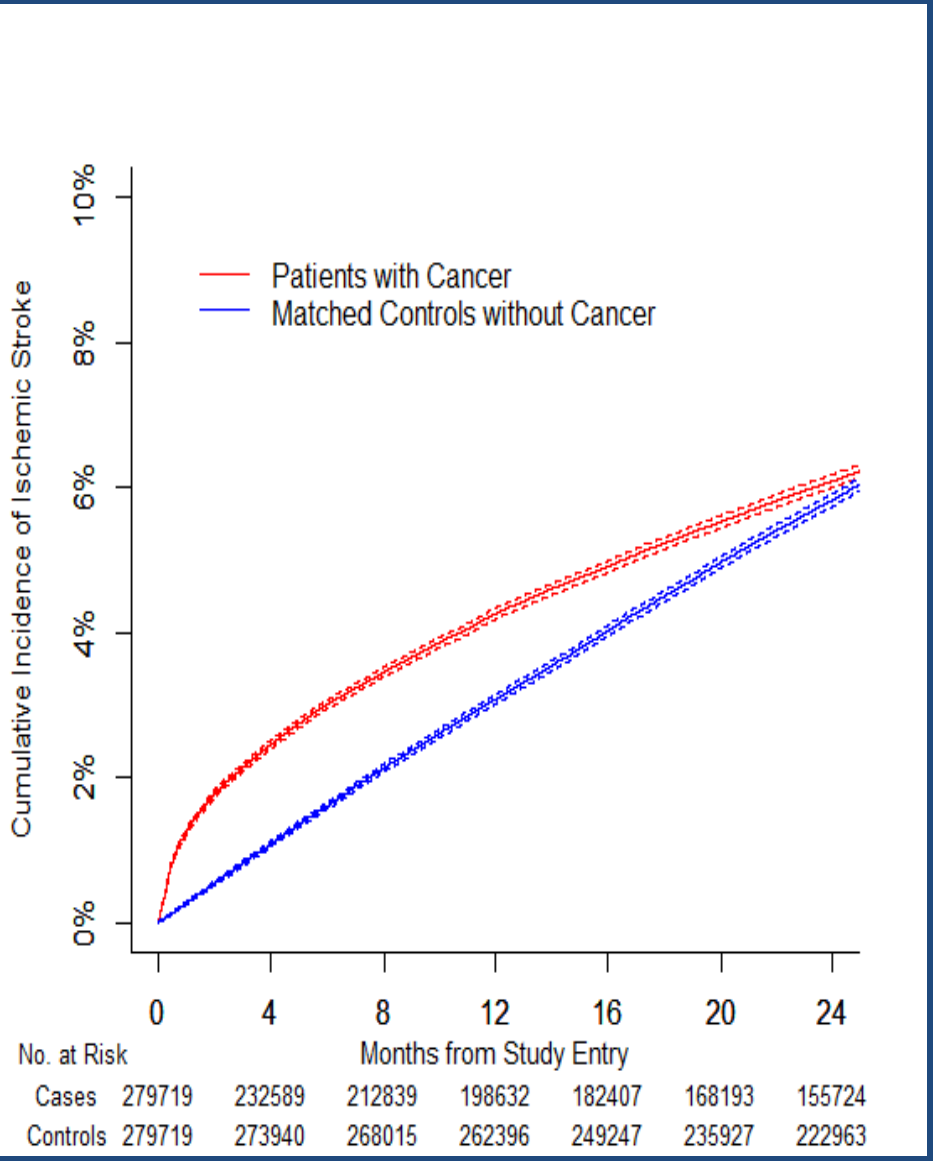
Navi BB et al, submitted.

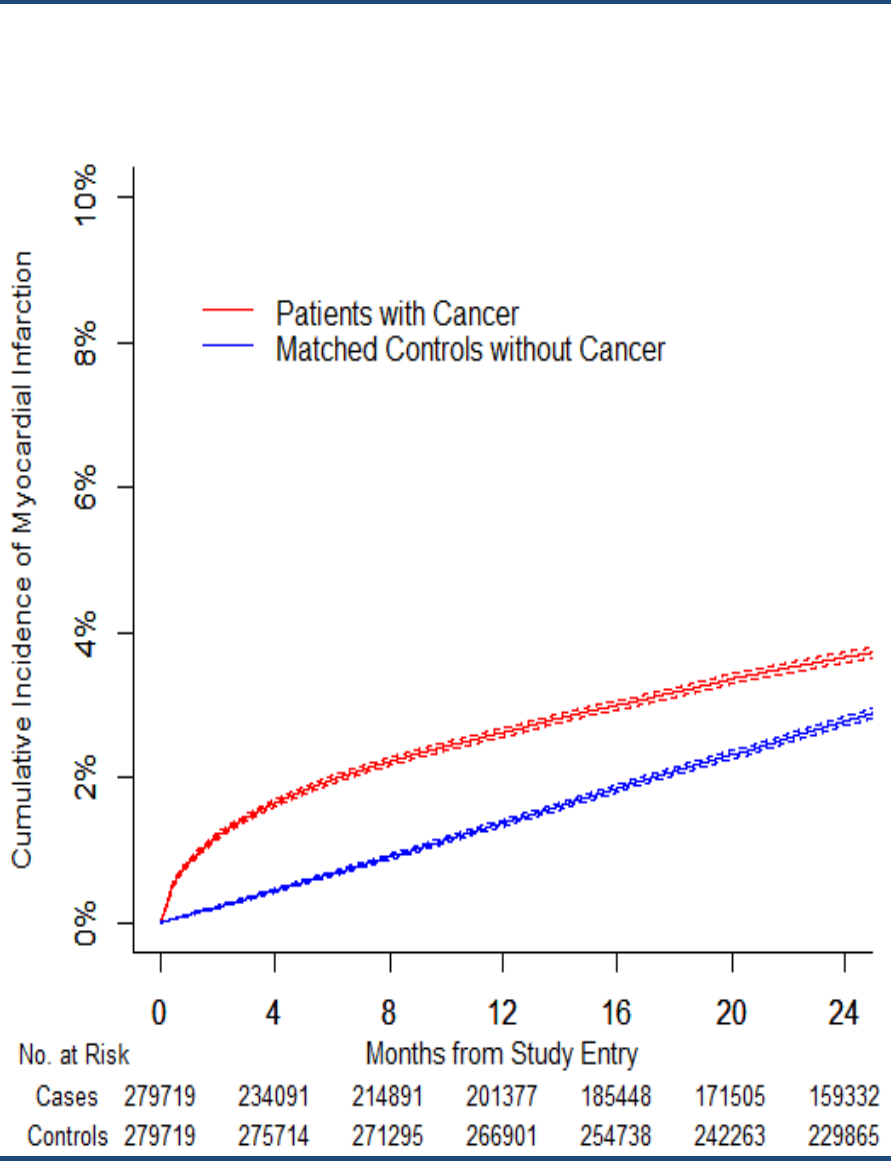
Cumulative Incidence of Arterial Thromboembolism in Cancer Patients and Matched Controls



Navi BB et al, submitted.

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





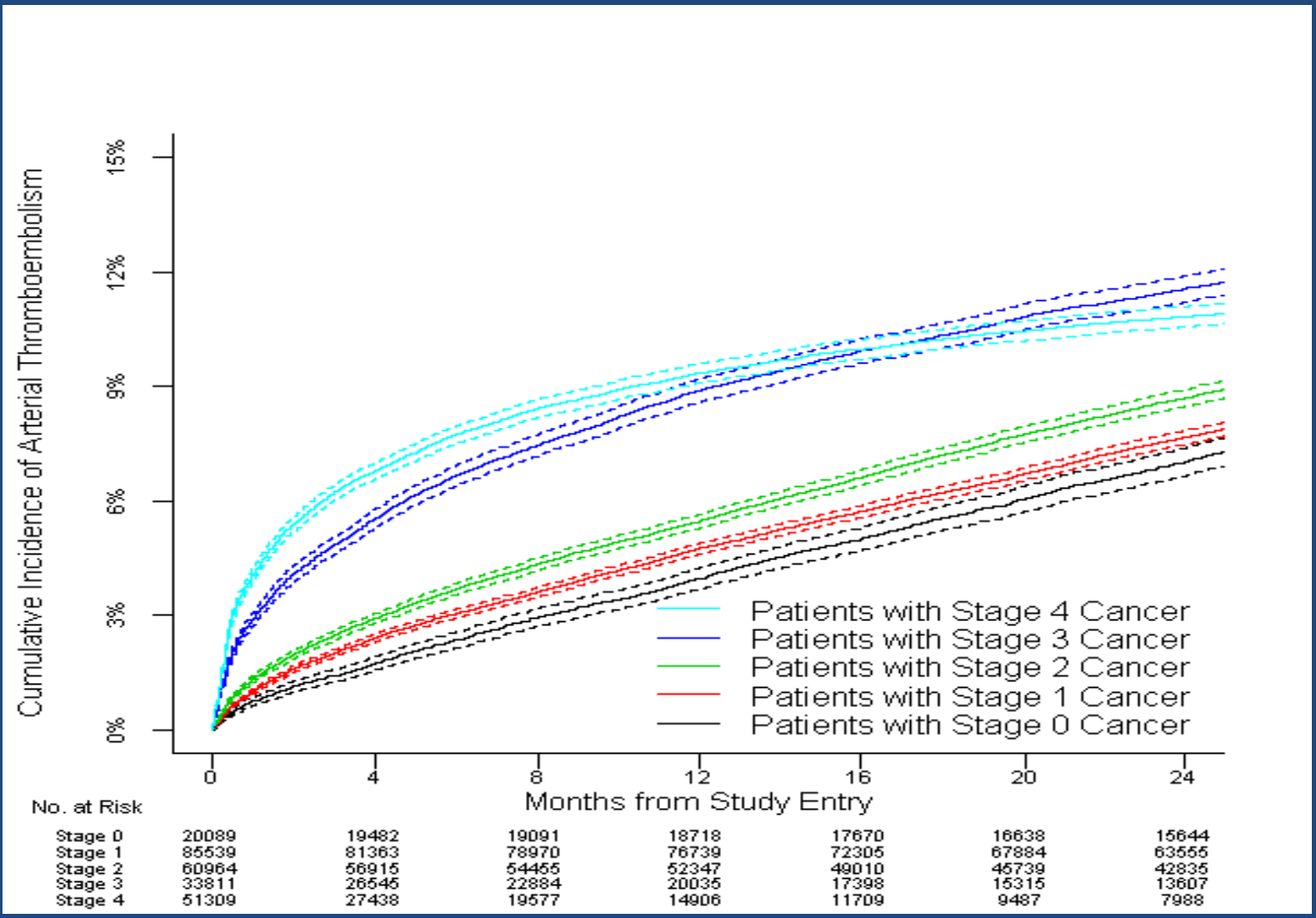
Navi BB et al, submitted.

Relative Hazards of Outcomes during Discrete Time Periods

	Time Periods After Cancer Diagnosis				
	0-1 Month	***1-3 Months***	***3-6 Months***	***6-9 Months***	***9-12 Months***
Arterial Thromboembolism	5.2 (4.9-5.6)	2.1 (2.0-2.2)	1.4 (1.3-1.5)	1.1 (1.1-1.2)	1.1 (1.0-1.1)
Myocardial Infarction	7.3 (6.5-8.2)	3.0 (2.7-3.3)	1.8 (1.6-1.9)	1.3 (1.2-1.4)	1.0 (1.0-1.1)
Ischemic Stroke	4.5 (4.1-4.8)	1.7 (1.6-1.8)	1.3 (1.2-1.3)	1.0 (1.0-1.1)	1.1 (1.0-1.2)

Navi BB et al, submitted.

Arterial Thromboembolism Incidence Stratified by Cancer Stage



No. at Risk

Stage 0	20089	19482	19091	18718	17670	16638	15644
Stage 1	85539	81363	78970	76739	72305	67884	63555
Stage 2	60964	56915	54455	52347	49010	45739	42835
Stage 3	33811	26545	22884	20035	17398	15315	13607
Stage 4	51309	27438	19577	14906	11709	9487	7988

Navi BB et al, submitted.

Limitations

- Retrospective studies that rely on administrative diagnostic codes for outcome assessments
- Lacked granular clinical data such as ECG and imaging findings, lab values, severity of outcomes, and medicines administered
- Excluded patients younger than 66 and those without Medicare insurance
- Unable to match on smoking or unmeasured factors so residual confounding possible

REGARDS

- REasons for Geographic and RAcial Differences in Stroke study[1]
- NIH-funded, nationwide, population-based prospective cohort study with adjudicated ascertainment of stroke
- Between 2003 and 2007, 30,239 participants 45 years or older enrolled
- After baseline study visit, participants followed every 6 months for clinical outcomes

[1]Howard VJ et al, Neuroepidemiology 2005.

Link between Cancer and Stroke in REGARDS

- Analyzed REGARDS participants 66 years or older with Medicare coverage
- Participants with history of cancer or stroke excluded
- Time-dependent exposure was a new diagnosis of malignant cancer, identified through Medicare claims algorithms
- Participants followed from baseline REGARDS visit through 2013 for primary outcome of a neurologist adjudicated stroke
- Multivariable Cox regression used to evaluate the association between incident cancer and subsequent stroke while adjusting for potential confounders such as smoking
- Follow-up time modeled in discrete time periods to fulfill the proportional hazard assumption

Navi BB et al, submitted.

Link between Cancer and Stroke in REGARDS

- 5,743 REGARDS participants met eligibility criteria
- 984 diagnosed with cancer during follow-up
- New cancer diagnosis strongly associated with subsequent stroke in the first month after cancer diagnosis (**HR 5.1, 95% CI 1.9-13.8**)
- Association even stronger after adjustment for demographics, region of residence, and vascular risk factors (**HR 6.9, 95% CI 2.5-18.5**)
- No significant association beyond one month; however, study underpowered and strong trends seen in 1 to 3 month period for high-risk cancer types, particularly lung, pancreatic, and colorectal cancers

Navi BB et al, submitted.

Risk Factors for Stroke in Cancer Patients

- Not cancer-mediated[1]
  - Male gender
  - Older age
  - Vascular comorbidities
- Cancer-mediated
  - Active cancer, particularly advanced stage
    - Rarely, stroke is initial manifestation of cancer
  - Recent chemotherapy
    - Platinum based therapy[2]
    - Anti-angiogenesis drugs[3]
    - Bisphosphonates and AF[4]
  - Prior radiation[5]

[1]Navi BB et al, Neurology 2014; [2]Li SH et al, Clin Neurol Neurosurg 2006; [3]Zuo PY et al, Plos One 2015; [4]Wilkinson GS et al, J Clin Oncol 2010; [5]De Bruin ML et al, J Natl Cancer Inst 2009.

Ischemic Stroke Mechanisms in Cancer Patients

- Often unconventional (51%)[1]
- Commonly related to properties of neoplasm or its treatment
- Frequently embolic appearing (54%)[2]

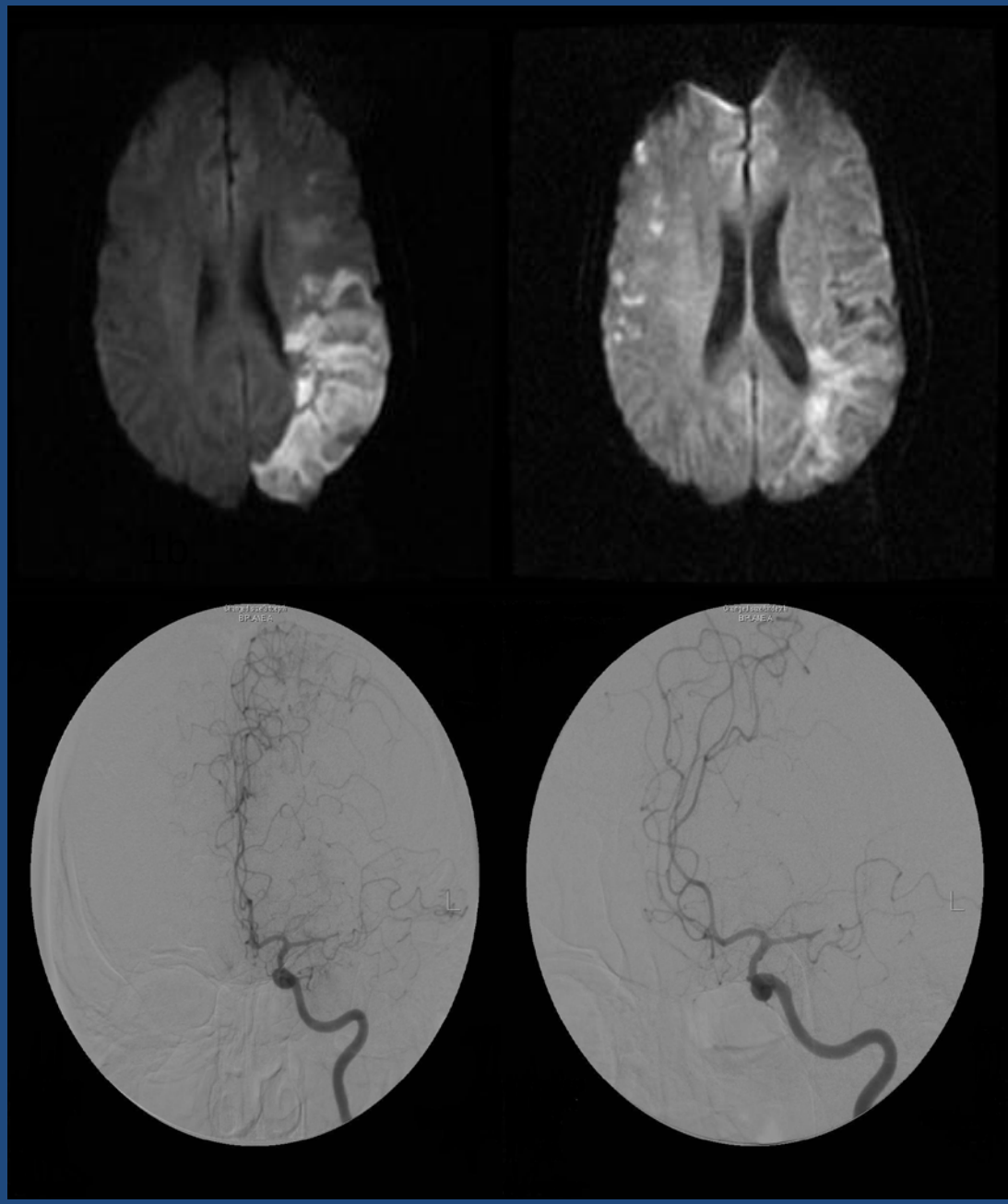
[1]Seok JM et al, Ann Neurol 2010; [2]Cestari DM, Neurology 2004.

TCD Microemboli Analysis

- Prospective TCD study of 74 active cancer patients with MCA distribution strokes[1]
- Microemboli observed in 46% of overall cohort and 58% of those with unconventional stroke mechanisms
- Microemboli associated with high D-dimer levels and adenocarcinomas
- D-dimer levels decreased dramatically after a few days of anticoagulation

[1]Seok JM et al, Ann Neurol 2010.

- 46 year old woman
- History of HTN, HL, smoking
- Presented w/ recurrent neurological symptoms over 1 month, some persistent
- Serial MRI showed recurrent, multifocal infarctions despite aggressive medical therapy
- NSTEMI also diagnosed
- Ultimately tissue obtained and diagnosis made



[1]Navi BB et al, J Neurooncol 2007.

Nonbacterial Thrombotic Endocarditis

- Leading cause of symptomatic ischemic stroke in patients with active cancer[1]
- Sterile, small platelet-fibrin vegetations on normal cardiac valves
- Lesions prone to embolization and typically present with embolic strokes (multiple vascular distributions)
- More common with advanced, metastatic disease but can herald cancer diagnosis
- Because of small size, very difficult to definitively diagnose with echo, though TEE superior to TTE[2]

[1]Graus F, et al, Medicine 1985; [2]Merkler AE, Navi BB et al, J Neurooncol 2015.

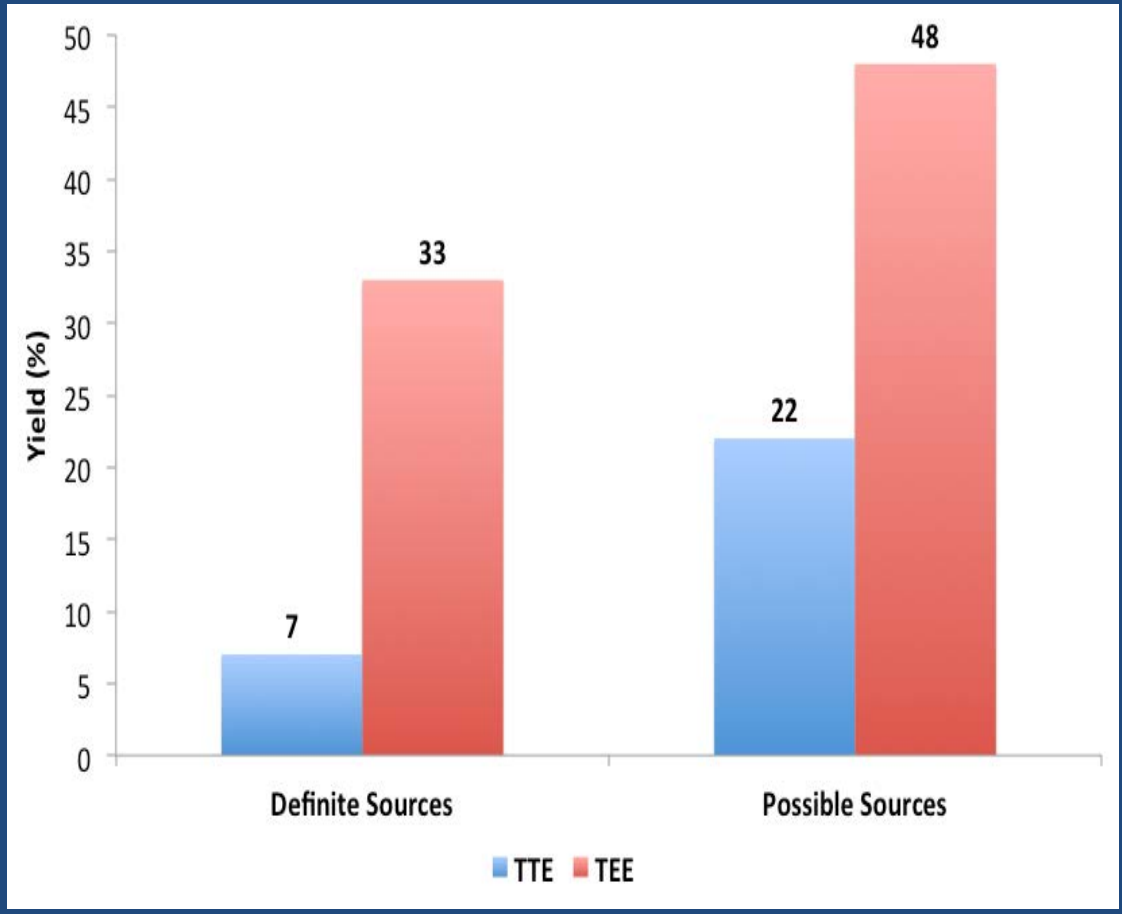
Pathogenesis of NBTE

- Multifactorial and incompletely understood
- Increased cytokines such as TNF and interleukin-1
- Excessive platelet and coagulation factor activity
- Increased circulating tissue factor and cancer microparticles
- Blood flow and shear forces likely contribute as well because vegetations generally form in high flow areas on valve leaflets

[1]El-Shami et al, The Oncologist 2007.

Echo Yield in Cancer Patients with AIS and Suspected Cardioembolism

- 220 patients with cancer and AIS evaluated by echo[1]
- 92 with suspected cardioembolism by neuroimaging had TTE and 21 had TEE
- 4 (4%) vegetations seen on TTE, all from NBTE
- 6 (29%) vegetations seen on TEE, 4 from NBTE, 2 infectious



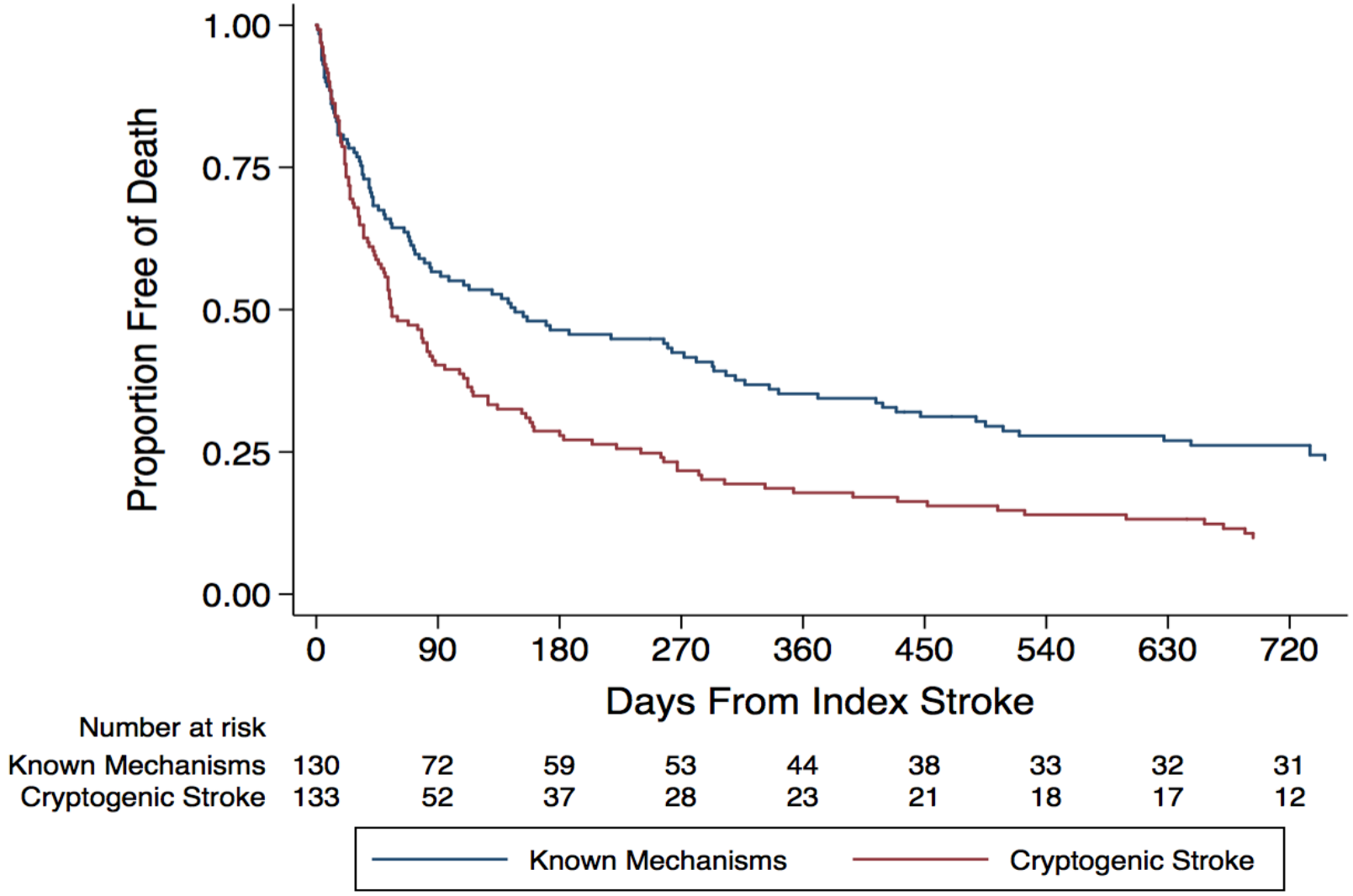
[1]Merkler AE, Navi BB et al, J Neurooncol 2015.

Cryptogenic Stroke in Cancer Patients

- 51% cryptogenic rate in largest clinical series[1]
- Metastatic disease, infarcts in multiple vascular distributions, and high D-dimer levels more common in cryptogenic group[2]
- **Conclusion:** many cryptogenic strokes likely from unconfirmed NBTE

[1]Navi BB et al, Stroke 2014; [2]Kim SG et al, Stroke 2010.

Survival in Cryptogenic Strokes



Navi BB et al, Stroke 2015.

Atherosclerosis

- 35% of ischemic strokes in patients with active cancer[1]
- Likely most common cause in those whose cancer is in remission
- Prior radiation accelerates disease[2,3]
  - ICA stenosis with head and neck cancers
  - Great vessel stenosis and cardiomyopathy with breast cancer and lymphoma
  - CNS vasculopathy with brain tumors

[1]Kim SG et al, Stroke 2010; [2]Plummer C et al, Stroke 2011; [3]De Bruin ML et al, J Natl Cancer Inst 2009.

Other Causes of Ischemic Stroke in Cancer Patients

- Venous infarction[1]
  - Hypercoagulability
  - Neoplastic compression (breast, meningioma)
- Paradoxical embolism
- Tumor embolism
- Increased blood viscosity (myeloma)
- Septic emboli
- Vasculopathy
  - Infectious (VZV, aspergillus)
  - Neoplastic (Hodgkin lymphoma)
  - Radiation (brain tumors)
- Arterial compression (GBM)

[1]Posner JB, DeAngelis LM. Neurologic complications of cancer. 2nd. Oxford 2009.

Recurrent Stroke Risk

- Retrospective cohort study of 263 patients with active systemic cancer and MRI-confirmed AIS at MSK from 2005 to 2010[1]
- Recurrent thromboembolism rate of 34% (117 in 90 patients) despite median survival of 84 days
  - 90-day KM RTE rate 31% (~15% w/ competing risk analysis)
  - 90-day KM stroke rate 13%
- No difference in RTE rates with AC as compared with AP therapy (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[2,3]

[1]Navi BB et al, Neurology 2014; [2]Kim JM et al, J Neurooncol 2013; [3]Lau KK et al, PLOS One 2014.

Predictors of RTE

- Multivariable logistic regression
- Several a priori selected clinical factors
- Predictors
  - ***Adenocarcinoma*** (OR 1.65, 95% CI 1.02-2.68)
  - Suspected or confirmed NBTE (OR 1.53, 95% CI 0.96-2.44)
  - Recent chemotherapy (OR 1.33, 95% CI 0.87-2.03)

Navi BB et al, Neurology 2014.

Treatment—Ischemic Stroke

- Often unconventional
- May depend on underlying stroke mechanism
- Very little evidence to guide decisions

Recanalization Therapy for AIS

- Cancer patients excluded from trials, but not an absolute contraindication
- Recent data suggests that IV tPA can be safe
  - 1/18 (6%) patients with active cancer treated with IV tPA for stroke had sICH; 61% had systemic metastases[1]
  - 4.1% ICH rate among 641 cancer patients treated with TPA for stroke in NIS[2]
- Thrombolysis should be avoided in malignant brain tumor patients, though reports exist[3]
- Endovascular therapy may be beneficial in select cases[4]

[1]Masrur S et al, J Stroke Cerebrovasc Dis 2011; [2]Murthy SB et al, Stroke 2013;
[3]Murthy SB et al, J Clin Neuroscience 2015; [4]Merkler AE et al, Navi BB, Neurohospitalist 2014.

Secondary Stroke Prevention

- Limited and inconclusive observational data
- No published specific trials to guide therapy
- No AAN or AHA/ASA guidelines
- Therapy often overshadowed by systemic illness

Secondary Stroke Prevention

- Anticoagulation with low-molecular weight heparin?
  - Pros
    - Anticoagulants, especially LMWH, decrease D-dimer levels and TCD-microemboli[1,2]
    - Extrapolation from CLOT/CATCH studies[3,4]; reduces risk of VTE
  - Cons
    - Increased risk of bleeding, which may outweigh any incremental AIS risk reduction (i.e., stroke trials in non-cancer patients)[5]
    - Expensive, burdensome, difficult to administer
- Anti-platelets?
  - Pros
    - Standard of care for most strokes (Level 1 evidence)
    - Excellent safety profile; easy to administer
  - Cons
    - May not address cancer-mediated hypercoagulability

[1]Seok JM et al, Ann Neurol 2010; [2]Jang H et al, J Oncology 2015;
[3]Lee AY et al, N Engl J Med 2003; [4]Lee AY et al, JAMA 2015; [5]Bath PM et al, Lancet 2001.

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

- Multi-center, open-label, pilot, feasibility and safety randomized trial[1]
- Patients with active systemic cancer and MRI-confirmed AIS within past 4 weeks at MSK, Cornell, and Columbia
- Randomized to 6 months of SQ enoxaparin or PO ASA
  - Stratified by adenocarcinoma histology
- Clinical visits at 1, 3, and 6 months, and blood work at 2 and 4 weeks
- Primary aims are to determine if a randomized trial comparing AC to AP therapy is feasible in patients with cancer and AIS and to obtain a preliminary safety profile for both treatments
- Enrolled target of 20 patients; follow-up phase will be completed this month

[1]http://clinicaltrials.gov/ct2/show/study/NCT01763606?term=cancer+and+stroke&rank=1.

Hemorrhagic Stroke in Cancer Patients

Mechanisms—Hemorrhagic Stroke

- Unique causes predominate; 33% multifactorial[1]
- Often direct result of tumor or its treatment
- Etiology is closely linked to tumor type

[1]Navi BB et al, Neurology 2010

ICH and SAH in Cancer Patients

- Retrospective cohort study of 208 patients with ICH or SAH from 2000 to 2008 at MSK
- 181 ICH and 46 SAH
- 41% had multiple foci of hemorrhage
- 68% had solid tumors, 16% primary brain tumors, and 16% hematopoietic tumors
- Presentation was comparable to community setting with headache, hemiparesis, and encephalopathy

Navi BB et al, Neurology 2010

Intratumoral Hemorrhage

- Most common cause of ICH in patients with cancer (61%)[1]
- Melanoma and lung cancer are the most common solid tumor offenders
  - High prevalence, frequent brain metastases, vascular lesions
- GBM and oligodendroglioma are the most common primary brain tumors to bleed
  - Retiform type capillaries[2]
- XRT can precipitate intratumoral hemorrhage[3]

[1]Navi BB et al, Neurology 2010; [2]Liwnicz BH et al, J Neurosurg 1987; [3]Anderson WS et al, Clin Neurol Neurosurg 2008

Coagulopathy

- 2nd most common cause of ICH or SAH in patients with cancer (46%)[1]
- Usually occurs with hematological cancers
- May be from platelet or clotting factor dysfunction or deficiency
- Often a result of chemotherapy and/or radiation
- Hemorrhages are often diffuse and in multiple intracranial compartments

[1]Navi BB et al, Neurology 2010

Hypertension

- Only accounts for 5-8% of ICH in cancer patients[1,2]
- Associated with VEGF inhibitors
- PRES may result from calcineurin inhibitors after transplantation

[1]Navi BB et al, Neurology 2010; [2]Graus F et al, Medicine 1985

Treatment—Hemorrhagic Stroke

- Should conform to standard guidelines[1,2]
- Correct any coagulopathy
  - Avoid recombinant factor VIIA[3]
- ICP management
- Blood pressure and glucose control
- Management of secondary complications

[1]Morganstern LB et al, Stroke 2010; [2]Bederson JB et al, Stroke 2009; [3]Mayer SA et al, N Engl J Med 2008

Treatment—Hemorrhagic Stroke

- Unique considerations[1]
  - Steroids for ITH
  - Consider resection and/or XRT for ITH
  - All-trans-retinoic acid for DIC from APML
  - Leukopharesis and chemo for leukostasis
  - Antibiotics for mycotic aneurysms; XRT or chemo for neoplastic aneurysms

[1]Posner JB, DeAngelis LM. Neurologic complications of cancer. 2nd. Oxford 2009.

Conclusions

- Short-term risk of stroke markedly increased with new cancer diagnoses
- Cancer and stroke intricately linked
- Stroke mechanisms in cancer patients are unique and often related to properties of the neoplasm or its treatment
- Treatment is often unorthodox and based on theory, not (great) evidence
- Long-term prognosis is governed by the underlying cancer

Questions?

- CORNELL
  - ***Cos Iadecola, MD***
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