

# ***Failure to Screen for Cancer***

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# Introduction

- Talk has little to do with your every-day experience as oncology nurses, but should shed light on a whole different area of oncology
- Speaker's experience in the medical-legal arena positions him to comment on this aspect of the litigation process and potential crisis



# Cancer and Medical Malpractice

- Historically the missed diagnosis of cancer amounts to a large percentage of medical malpractice claims; single biggest cause of lawsuits against doctors from 1985 to 1996
- Allegation of failure to diagnose cancer affects primary-care physicians and specialists
- Examples (breast cancer):
  - Failure to interpret mammogram correctly (radiologist) or...
  - Failure to act on abnormal mammogram report (PCP)
  - Assumption that normal mammogram excludes cancer (PCP)



# Further examples – lung cancer

- Failure to read chest xray correctly (radiologist) or....
- Failure to act on abnormal report, either by failing to see report before it is filed or by failing to realize significance of abnormal report (PCP)
- Failure to follow up pneumonia in adults to the point of radiographic clearing (PCP or pulmonologist)



# Another Example: Prostate Cancer

- Failure to notice abnormal PSA before put in chart
- Failure to act on elevated PSA



# New Wrinkle in Problem

- Information about cancer screening has been widely promulgated to general population
- People have expectations about what is appropriate level of concern on the part of their PCP
- New litigation paradigm ensues: failure to screen for cancer





# Objectives

- Elucidate the issue: failure to screen for cancer given contemporary guidelines
- Discuss the evidence behind efficacy of screening to improve outcome in colorectal and prostate cancer
- Analyze two cases from the perspective of litigation: where biology of cancer meets the courtroom



# Failure to screen for cancer in asymptomatic individuals: two cases

## ■ Example #1:

- 58 y.o. man enters the hospital via the ED with crampy abdominal pain
- Anemic: H/H 8/30 MCV 72 platelets 585,000
  - Ferritin 8; Fe/TIBC 15/400
  - Stool hemoccult positive
- Picture of bowel obstruction on x-rays
- Further work-up reveals obstructing cancer of hepatic flexure
- Semi-urgent cecostomy performed to decompress bowel
- Several days later definitive surgery done...





# Example #1, continued

- At laporotomy large cancer of hepatic flexure is encountered with impending perforation
- Numerous metastatic lesions in liver and omentum discovered; largest is 3 cm
- Palliative resection performed
- Post-operatively patient started on chemotherapy; lives for 22 months, dies of metastatic disease
- **Before death, patient sues PCP for failing to initiate colorectal screening at age 50; estate carries on with suit after his death**



# The Lawsuit

- Claim states that if screening had been initiated at age 50 tumor would have been found while it was still polyp or at a stage when much smaller cancer and metastases would have been prevented
- Issues to discuss in analyzing physician's potential negligence and whether earlier diagnosis would have made a difference (proximate cause):
  - Frequency of screening of asymptomatic individuals in general population (i.e., does failure to screen constitute negligence?)
  - Likelihood of finding lesion even if appropriate guidelines had been followed
  - Value of the early detection of colorectal cancer in the prevention of excess mortality in this case and in general

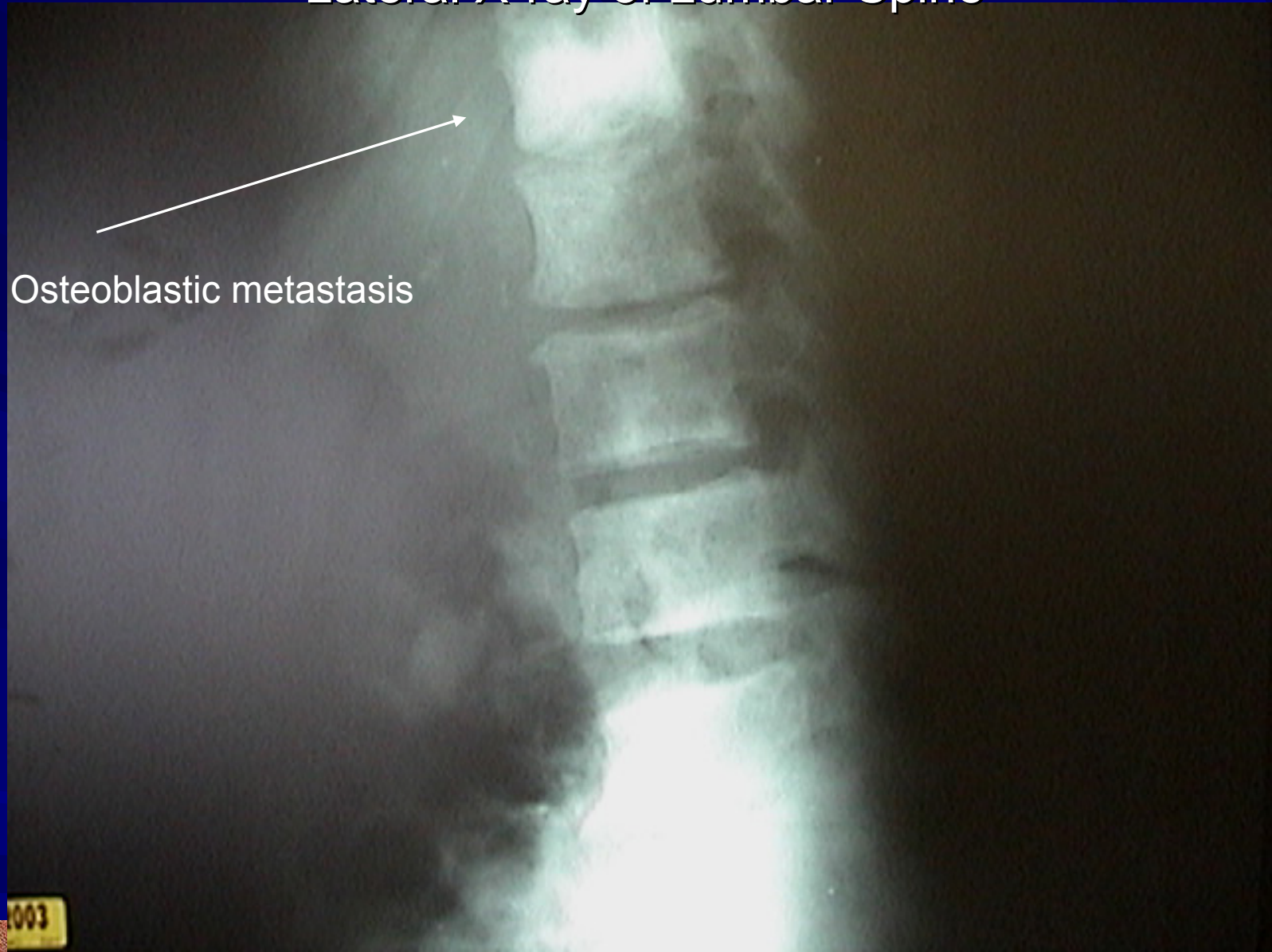


# Example # 2

- 62 year old man goes to PCP complaining of back pain
- Examination: enlarged nodular prostate
- PSA 52
- Bone scan diffusely positive; plain films done...

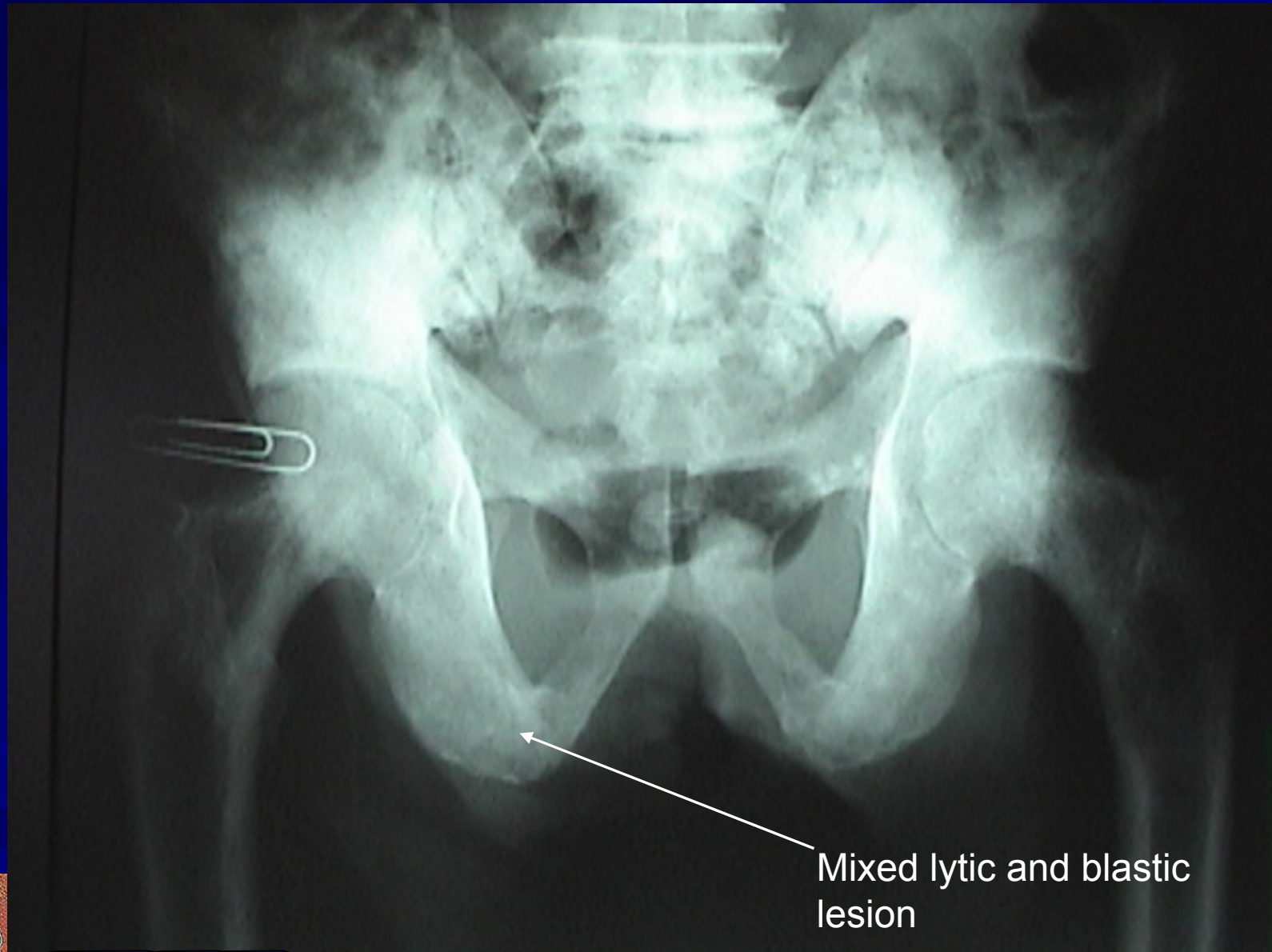


# Lateral X-ray of Lumbar Spine





# AP view of the Pelvis



Mixed lytic and blastic  
lesion



# Example #2, continued

- Prostate biopsy + in all quadrants for poorly differentiated adenocarcinoma
  - Gleason's score  $4+5=9$  in worst biopsy
  - Most biopsies  $3+4=7$
- Started on depo-lupron with prompt relief of back ache, reduction of PSA to 0.5; remission lasts fifteen months; then pain returns, PSA increases; dies ten months later
- Initiates lawsuit against PCP for failing to obtain annual prostate cancer screening (PSA and digital rectal examination) starting at age 50





# Issues in evaluating physician's responsibility and relation of delay to outcome

- Assess frequency of PSA screening in general population at risk (men over 50)
- Evaluate evidence that PSA screening saves lives
- Try to estimate what PSA would have been years earlier (e.g., when he was 50)
- Incorporate his unfavorable Gleason's score into overall prognosis
- Try to assess impact on outcome of earlier diagnosis



# Basics of cancer screening

- Disease must be common
- Patient must be asymptomatic for disease being screened or event is not true “screening”
- Screening test must be safe, cost-effective (defined in societal terms: cost/life saved; what society will bear as burden) and have high sensitivity (few false negatives; false positive rate may increase with enhanced sensitivity)
- Outcome of disease screened must be altered by early detection



# Screening basics, cont.

- Above considerations rule out screening for such things as ca pancreas, brain tumors and, probably, ca lung
- With colon cancer, slow growth rate and long premalignant (i.e., adenomatous polyp) phase make argument for screening most compelling among all diseases commonly screened (along with cancer of cervix)



# Guidelines for Colorectal Screening

- Everyone over the age of 50
- People at high risk should be started at earlier age (e.g., familial syndromes)
- Screening itself involves *at least*:
  - Episodic flexible sigmoidoscopy
  - Annual stool hemoccults X 3 on meat-free high residue diet
  - Guidelines do vary a bit among various bodies that set the standards (e.g., American College of Surgeons vs. American Cancer Society vs. American College of Physicians)



# Current ACS guidelines: probably represent minimum

- fecal occult blood test (FOBT) every year\*, or
- flexible sigmoidoscopy every 5 years, or a fecal occult blood test every year plus flexible sigmoidoscopy every 5 years, or
- double-contrast barium enema every 5 years, or colonoscopy every 10 years

If this isn't confusing....??

\*For FOBT, the take-home multiple sample method should be used





Best recent data on compliance: attempt to answer question regarding frequency of screening

- Very large study from 1340 PCP's in managed care plan in California
- Looked at practice patterns in 1999-2000
- Utilized detailed questionnaires in retrospective look at practice patterns among average risk patients > 50 y.o.
- High return rate on questionnaires
- Results.....





# Compliance\* for various colorectal screening tests (based on physician's recall)

Test type	Median (IQR)		
	% of patients to whom test was recommended	% of patients who followed screening recommendation	Most commonly recommended screening interval (yrs)
FOBT	90 (50–100)	70 (50–80)	1 (1–1)
FS	70 (30–90)	50 (30–75)	5 (3–5)
Barium enema	5 (0–20)	50 (10–80)	5 (5–5)
Colonoscopy	8 (0–30)	50 (10–90)	5 (5–10)

IQR: interquartile range; FOBT: fecal occult blood testing; FS: flexible sigmoidoscopy.

**\*i.e., 50<sup>th</sup> percentile physician recommended 90% of time**

**Therefore overall compliance is 63%**



# Colorectal screening recommendations summarized

- PCP should articulate in the chart plan for CRS when patient becomes eligible
- If patient declines to participate this should be explicitly documented
- Despite California data, overall compliance rate in US is probably lower (35-55%, including people with no regular physician) based on other published information



## Evidence to Support CRC Screening: Attempt to answer question on value of screening

- Fecal occult blood testing: Three large studies show altered outcome for patients screened versus general population
  - The Göteborg Study
  - The English FOB trial
  - The Mandel US trial – best data, longest follow-up...



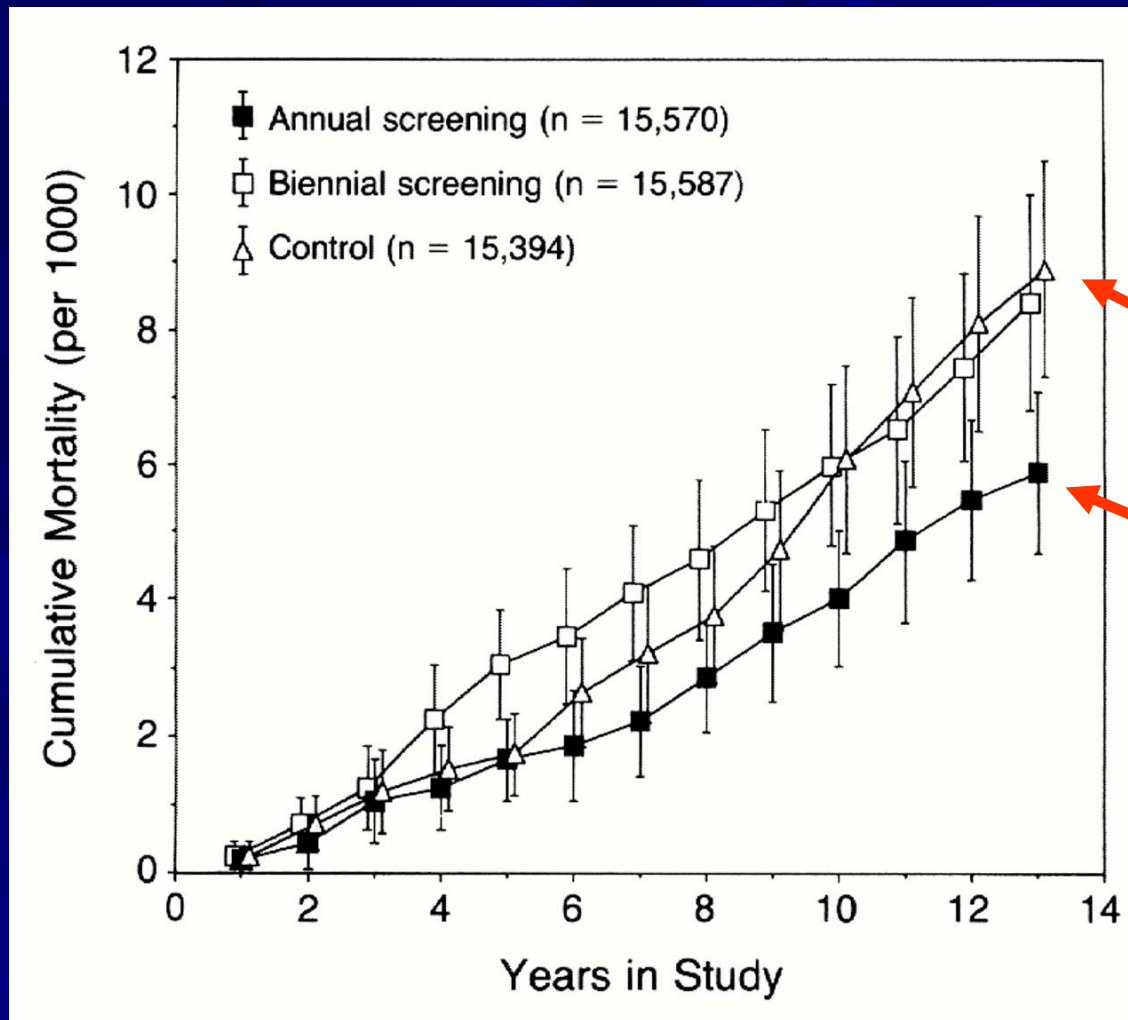
# Mortality reduction from FOB screening

- Mandel study in *NEJM* shows dramatic reduction in mortality as a result of FOB testing
- 46,551 participants
- Screenings annual, or once every two years, or no screening
- Long follow-up.....





## Cumulative Mortality from Colorectal Cancer, According to Study Group

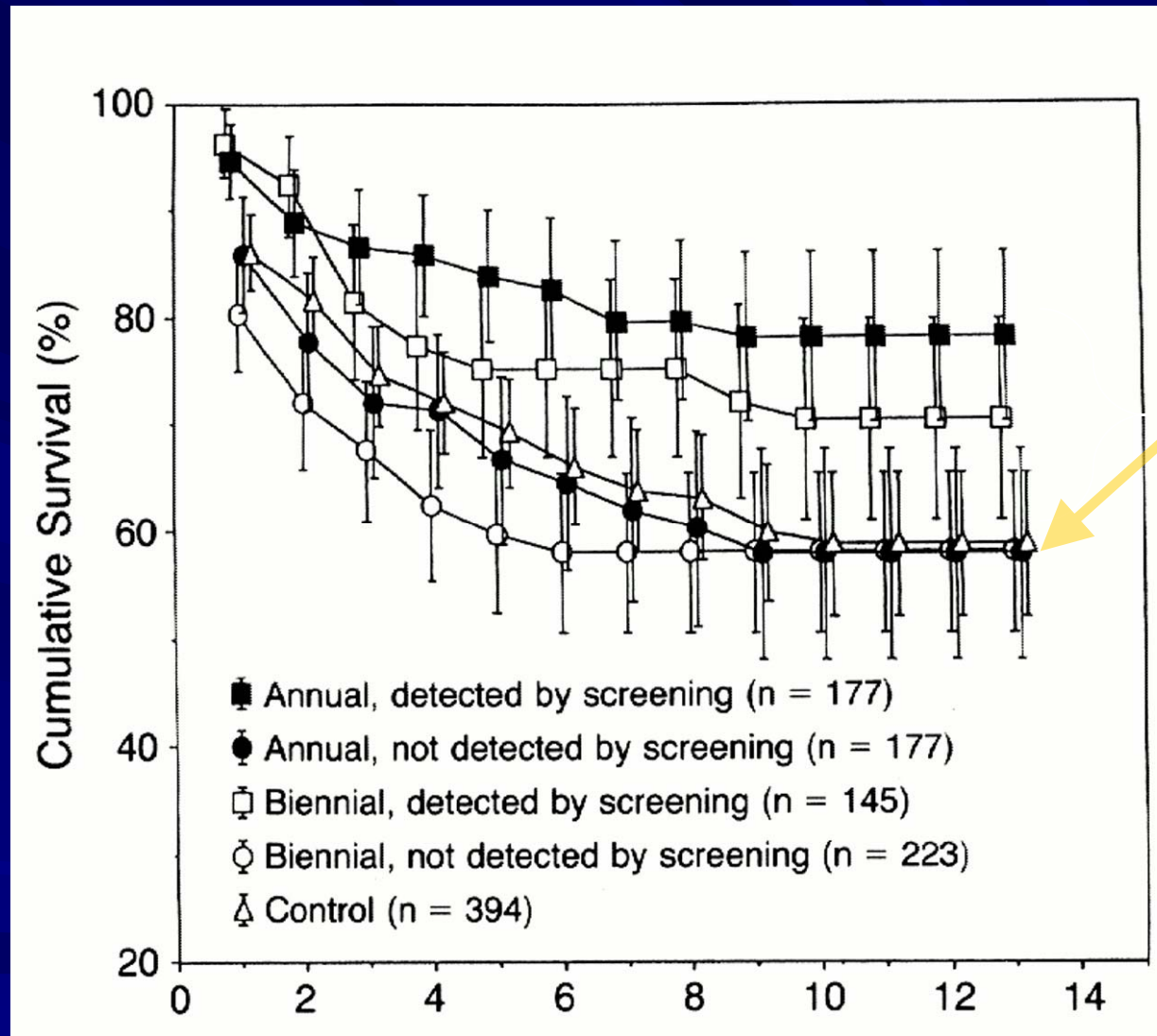


Big difference between annual screening and none

Mandel, J. S. et. al. N Engl J Med 1993;328:1365-1371



## Cumulative Survival of Participants with Colorectal Cancer, According to Method of Detection and Study Group



Mandel, J. S. et. al.





# CRC Screening: flexible sigmoidoscopy (SS)

- Best data from case-control study\*
  - Not true randomization; compares screening in affected group vs. general population
- Looked at records of 261 Kaiser Permanente Medical Care Program enrollees in SF Bay area who died of colon cancer between 1971 and 1988
- 8.8% of the 261 had undergone SS in 10 years prior to diagnosis of cancer
- 868 age- and sex-matched non-cancer controls selected from their database (didn't use cancer survivors (!))
- 24.2% of Kaiser control enrollees had undergone SS in same period of time



\*Selby *NEJM* 323: 653, 1992



# Kaiser, continued

- Next looked at 268 patients dead of CRC with tumors beyond reach of SS
- Looked at 268 controls from Kaiser database
- No difference in frequency of SS between groups
- Conclusion: SS reduces mortality from CRC in that portion of colon seen with scope ( $p < 0.0001$ ); absence of change in mortality in proximal colon validates model



# Role of Colonoscopy in CRC screening

- As screening test poorly defined; no randomized trials; theoretically should be best; question is how much gain of information versus cost/morbidity
- VA Study\* studied 17,732 patients; 97% men
- 3121 agreed to colonoscopy
- 37.5% had some sort of neoplasm – often tiny polyp
- Significant polyps in 9.5%
- Invasive cancer in 1%
- 1765 had negative exams as far as flex sig would have reached
  - 2.7 % of these had large polyps or cancer more proximally
  - 52% of patients with proximal lesions had no distal lesions
- Authors concluded that colonoscopy added value above and beyond flexible sigmoidoscopy

Key finding



# The Imperiale Study

- Looked at value of adding colonoscopy to screening sigmoidoscopy
- Screened 1994 asymptomatic adults (>50 y.o.) 1995-98 as part of elective screening program offered by single employer
- 97% success rate in getting to cecum
- Detailed results....



Imperiale, T. F. et al. N Engl J Med 2000;343:169-174



## Prevalence of Advanced Proximal Neoplasms According to the Distal Findings

DISTAL FINDING	TOTAL no. of patients (%)	ADVANCED PROXIMAL NEOPLASM		ADJUSTED RELATIVE RISK (95% CI)†
		no. of patients	% (95% CI)	
No polyp	1564 (78.4)	23	1.5 (0.9–2.1)	1.0
Hyperplastic polyp	201 (10.1)	8	4.0 (1.3–6.7)	2.6 (1.1–5.9)
Tubular adenoma	168 (8.4)	12	7.1 (3.3–11.0)	4.0 (1.9–8.3)
Advanced neoplasm	61 (3.1)	7	11.5 (3.4–19.5)	6.7 (3.2–16.6)

\*An advanced neoplasm was defined as a polyp or polypoid lesion with villous features, a polyp or polypoid lesion with high-grade dysplasia, or cancer. CI denotes confidence interval.

†The relative risk was adjusted for age and sex. The group of patients with no distal polyps was the reference group.

Imperiale, T. F. et al. N Engl J Med 2000;343:169-174

?Magnitude of benefit of adding colonoscopy to negative flex sig



Intro Cas Cas Screening





# Accuracy of Colonoscopy

- Previously thought to be Gold Standard
- Latest studies show 4-10% chance of missing polyp  $\geq 5$  mm; higher for smaller lesions
- Sites most likely missed are on proximal side of colonic fold and in the distal rectum
- Virtual colonoscopy has given us new tool to analyze accuracy of traditional colonoscopy
  - Virtual colonoscopy misses 10-12% of polyps, but different polyps from the ones missed by regular colonoscopy
- “Gold Standard” called into question

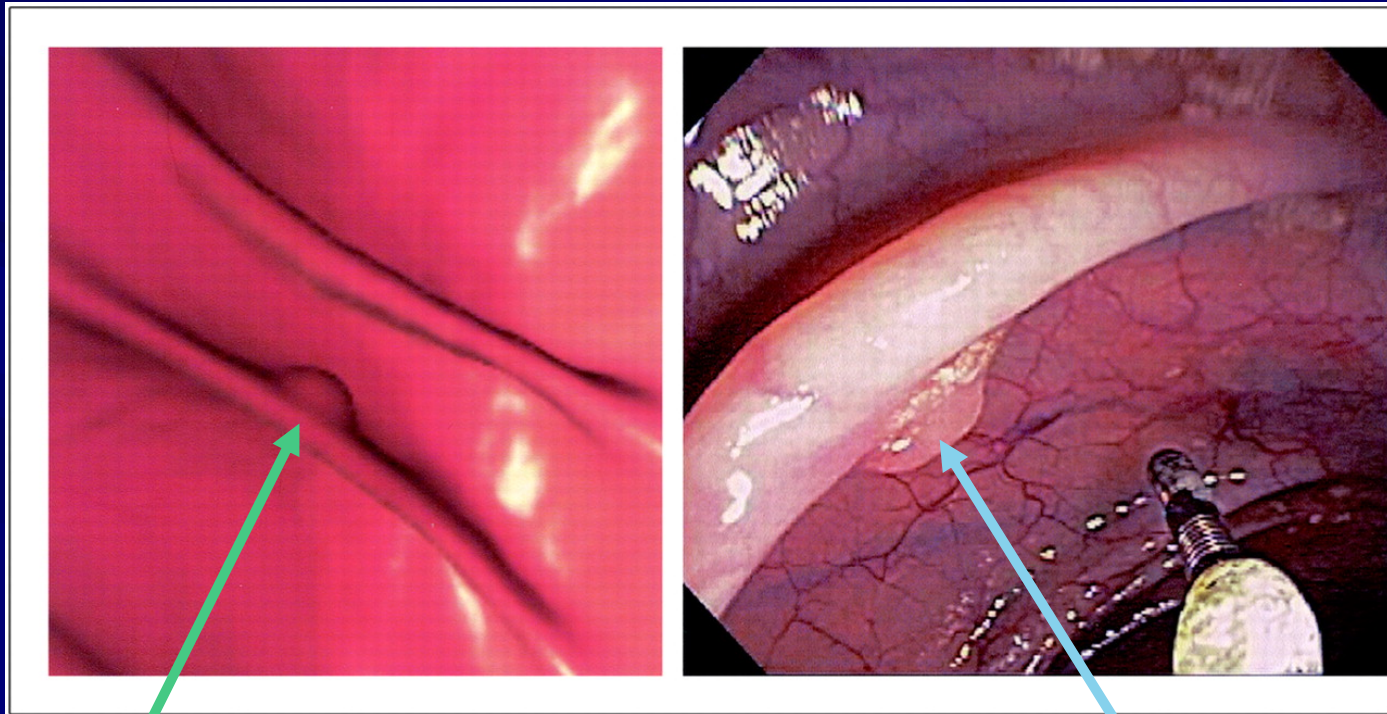


Pickhardt *Ann. Int. Med* 141:352-9, 2004





## 6-mm tubular adenoma located on the proximal aspect of a fold at the hepatic flexure missed on initial colonoscopy

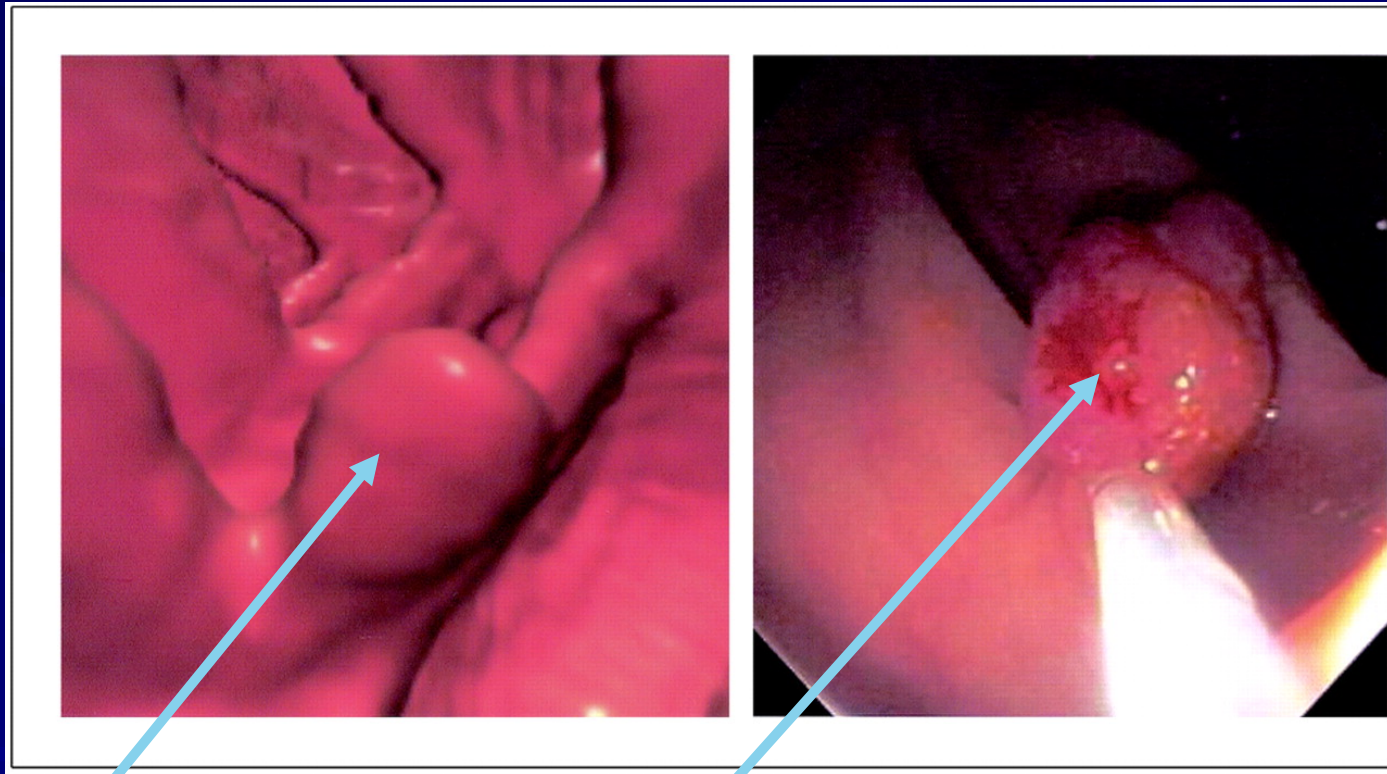


Polyp seen at virtual colonoscopy

"second-look"  
colonoscopy of same  
lesion



**11-mm malignant polyp located near the hepatic flexure missed on initial colonoscopy and missed again even after endoscopist knew to look for it**



Large malignant polyp seen initially only by virtual colonoscopy

Lesion seen only after several attempts at the time of second colonoscopy; location made visualization difficult

Pickhardt, P. J. et. al.



Intr Case Cas Screening



# Summary of Colonoscopy Studies

- Studies show a likelihood of  $<3\%$  that a colonoscopy will show significant pathology in the face of a negative flexible sigmoidoscopy
- Colonoscopy is not the Gold Standard previously assumed; 10% error rate for small polyps surprising and disturbing
- Error rate creates some confusion about value of procedure
- Whether, all things considered, data are compelling enough to support colonoscopy as screening test is unclear
- Colonoscopy probably not yet “standard of care” for colorectal cancer screening in the average-risk adult





# Colorectal screening: conclusions

- Recommendations still call for all patients over age 50 to be screened
  - Data strongly support role of FOB testing
  - Sigmoidoscopy data less compelling but still positive
  - Colonoscopy data in evolution; makes sense but little cost-benefit outcomes data to support routine use
  - “Gold Standard” only 90% accurate
  - Current guidelines support use of FOB plus endoscopy of some sort
- Physicians should have a plan of care for all patients in practice > 50 y.o.



# What about our patient?

- In case #1 based on data presented it is conceivable (based on compliance data) to construct a defense that screening is not the *de facto* standard of care but impossible to show that it does not affect the outcome
- Data on outcome with screening make argument for screening compelling
- Remaining questions for *this* malpractice claim: how long had cancer been present and diagnosable; did he have metastatic disease when cancer could have been found?





# Growth Rate of Primary Colon Cancer: What is Known

- Slowest growing common adult malignancy
- Studies looking back at previous barium enemas (where cancer was missed!) suggest doubling in volume of tumor every one to two years
- Polyps probably present for many years before they undergo malignant degeneration and probably grow even more slowly than the tumor into which they evolve
- Eight-fold increase in volume (three doublings) required for only two-fold increase in diameter ( $V = \frac{4}{3} \pi r^3$ )
- Therefore any cancer diagnosed by endoscopy or barium enema has probably been there and visible for many years, including period during which cancer was only a polyp



# Growth Rate of Metastases: What is Known

- What is known: Havelaar and Finley studies
- At the time of diagnosis of metastasis “doubling time” of metastases in untreated patients is between 40 and 150 days



Case # 1

Havelaar IJ et al *CANCER* 54: 163-171, 1984

Finley IG et al *Br. J. Surg* 75: 641-44, 1988



# Making a long story short...

- Based on established mathematical models (available if desired to the numerologists in the group) there is no way that the 3 cm omental metastasis was present at the time that screening for colorectal cancer should have been started



# Conclusions regarding Case # 1

- Based on very slow growth rate of primary colon cancer and even slower growth rate of adenomatous polyp, diagnosable abnormality was likely present for many years
- Based on model of growth kinetics and literature on growth rate of metastases in colorectal cancer 3 cm (largest) metastasis had been present for between one and four years – probably not long enough for the defendant to prevail on argument of proximate cause



# Case # 2: Issues in Diagnosis and Treatment of Prostate Cancer

## ■ Recall:

- 62 y.o. man with widespread metastatic prostate cancer
- Is PSA screening now the standard of care?
- Would PSA screening initiated 12 years earlier have made a difference to his outcome?





# Performance of PSA screening by age of patient and medical specialty:

## What is the real-world standard of care? How does this relate to our patient?

PCP's perform PSA (%)	<i>age range of patients</i>				
	50-59	60-69	70-74	75-79	80+
Almost always	55	66	65	58	53
> 1/2 time	16	14	11	14	13
≤ 1/2 time	29	20	24	28	34

### Urologists recommend PSA

Yes	97	98	88	50	25
No	3	2	12	50	75



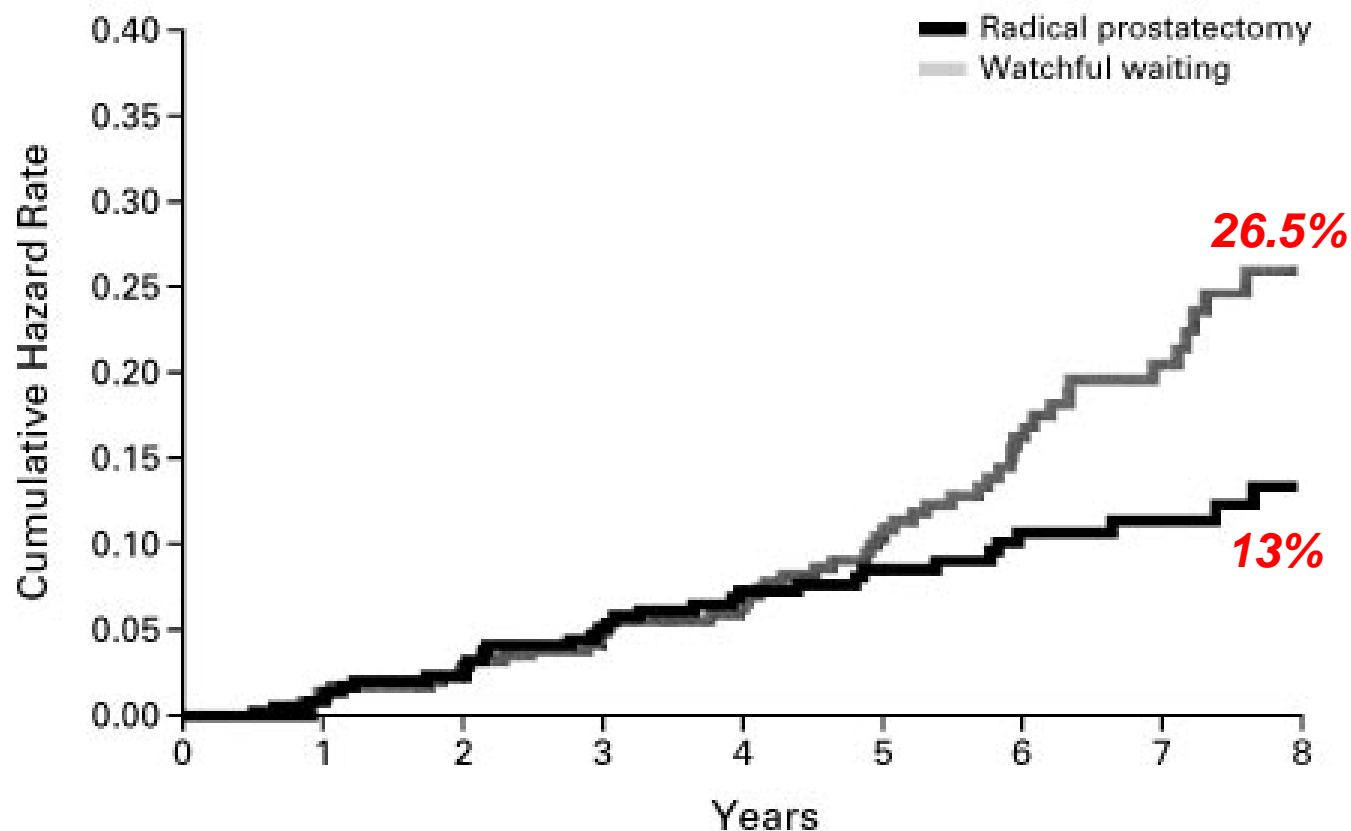
# Do screening and early intervention matter?

## The Scandinavian Prostatic Cancer Group Study Number 4

- Only truly prospective randomized trial; all other studies were retrospective analyses and are tainted by heavy selection bias
- 695 men with newly diagnosed CaP randomized to radical prostatectomy vs. watchful waiting
- All had T1b, T1c or T2 tumors
- Some in each group (about 6%) wound up with the other treatment
- Median follow-up 6.2 years...



# Cumulative Hazard of Development of Distant Metastasis



No. AT Risk

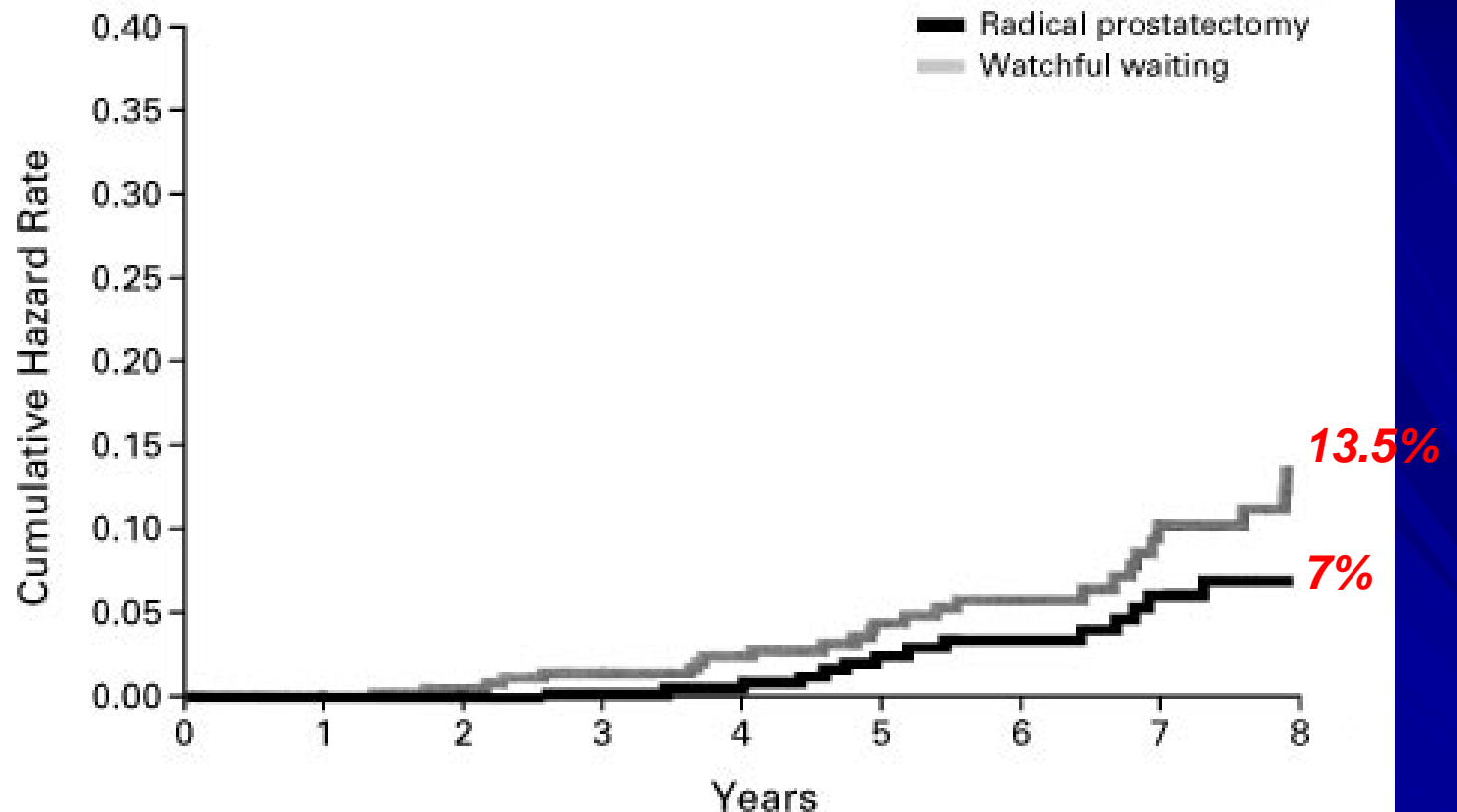
Radical prostatectomy	347	340	331	294	263	220	172	126	82
Watchful waiting	348	341	329	291	262	216	167	106	69

Holmberg, L. et. al. N Engl J Med 2002;347:781-789

Case # 2



# Cumulative Hazard of Death from Prostate Cancer



No. AT RISK

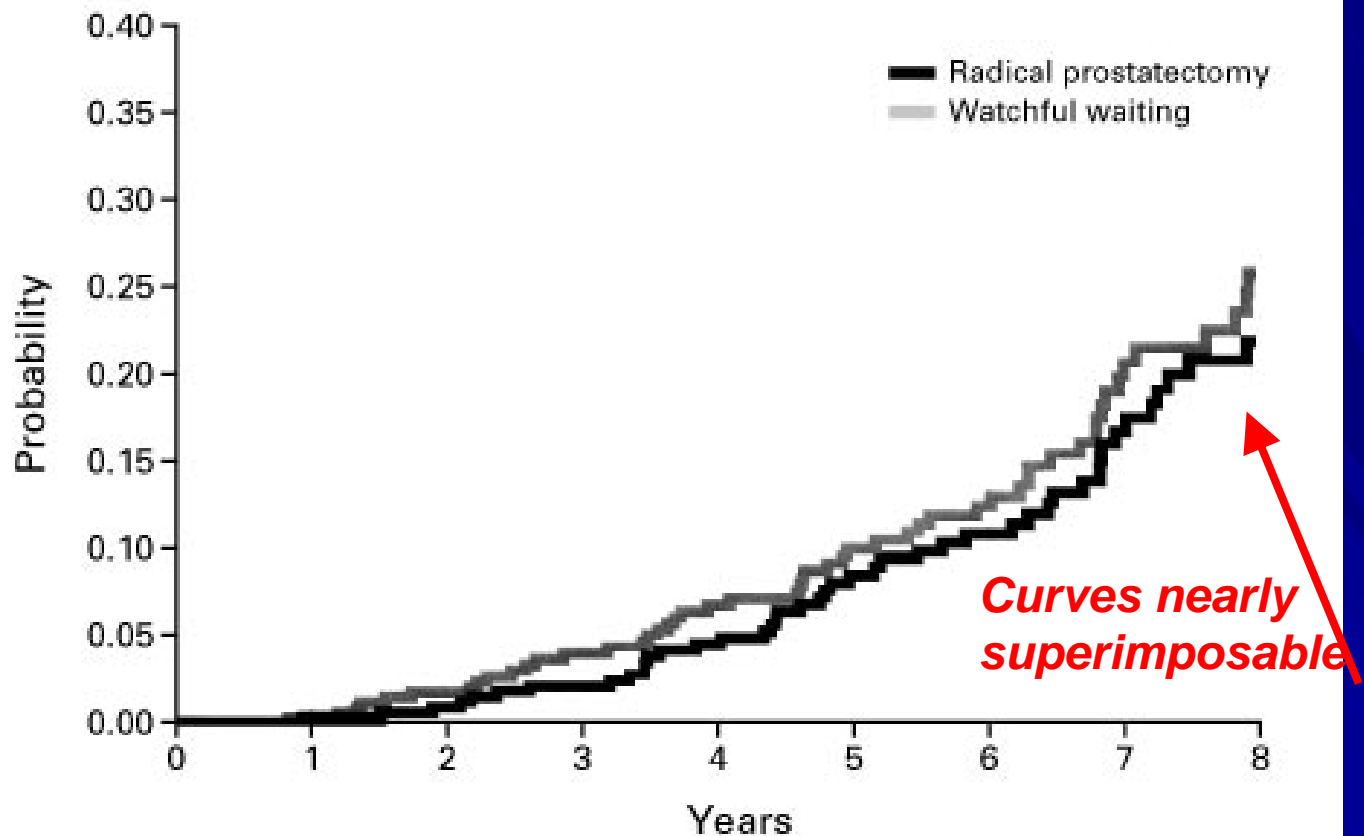
Radical prostatectomy	347	343	339	308	281	233	185	134	89
Watchful waiting	348	346	337	302	275	231	185	121	82

Holmberg, L. et. al. N Engl J Med 2002;347:781-789

Case # 2



# Cumulative Probability of Death



No. AT RISK

Radical prostatectomy	347	343	339	308	281	233	185	134	89
Watchful waiting	348	346	337	302	275	231	185	121	82

Holmberg, L. et. al.

Case # 2





# Causes of Death in Treatment and Observation Groups

CAUSE OF DEATH	WATCHFUL WAITING (N=348)	RADICAL PROSTATECTOMY (N=347)
	number	
Prostate cancer	31	16
Other causes	31	37
Other main cause with metastases	3*	1†
Other main cause without metastases but with local progression or recurrence	8*	6†
Other main cause with no evidence of metastases or local progression or recurrence	19‡	29§
Other main cause within first mo after randomization	1	1
All causes	62	53

\*Of these 11 men, 3 died from another cancer.

†Of these 7 men, 3 died from another cancer.

‡Of these 19 men, 5 died from another cancer.

§Of these 29 men, 12 died from another cancer.

Seemingly  
negates  
value of  
surgery



# Prostate Cancer, continued

- Scandinavian study is best study thus far regarding value of intervention but results show modest improvement and have not been corroborated
- These study results create problems for totally nihilistic approach to screening; data are unique for prostate cancer
- Nonetheless the American College of Physicians (the honor society for internists) still refuses to endorse screening because of relative paucity of data
- The screening/litigation dilemma for prostate cancer:
  - Fear of litigation is pushing more doctors into screening
  - The Standard of Care is thus tilting in direction of screening because more and more doctors are doing it with only marginal data to support altered outcomes
  - Litigation thus drives the standard rather than the reverse!



# Back to our patient:

## Issue of PSA rate of increase

- Had the man in case #2 been screened starting at age 50 when would his PSA have become abnormal?
- Data such as it is suggests a PSA doubling time on the average of about 4 years for the several years prior to the diagnosis of cancer
- What does this mean in practical terms?



# Looking backward on PSA:

- Using 4 years as average DT of PSA over life of cancer, PSA was:
- 26 when he was 58
- 13 when he was 54
- 6.5 when he was 50 (when screening arguably should have been initiated)
- Likelihood of + biopsy in 50 y.o. with PSA > 4 substantial but not a given; however, with serial follow-up *at some point in the near future* diagnosis would have been made
- By this analysis his outlook would have been much better when he was 50, at a time when screening could have been started



# What about Gleason's score?

- Score of worst biopsy at time of diagnosis was 9; associated with bad outcome no matter what PSA is at time of diagnosis
- Did Gleason's score worsen over time, i.e., does prostate cancer de-differentiate over time?
- If so, then defendant is in even worse trouble, for PSA at age 50 would have been 6.5 and Gleason's score would have been more favorable – leading to a high probability of survival





# Does Gleason's score worsen over time?

- Answer requires serial prostate biopsies over time; only two studies done
- Results are in conflict; one suggests random Gleason drift; the other suggests a worsening over time
- Situation as to impact of delay on Gleason's score (and implied prognosis) unresolved to date



# Conclusions about case # 2

- Standard of care is to screen men over the age of 50; compliance  $> 50\%$  among PCP's
- Based on what is known about average PSA increases over time, PSA at age 50 would have been  $< 10$  (favorable)
- ? Of Gleason's drift over time unresolved
- Difficult case to defend because of long delay



# Conclusions

- Data for value of colorectal screening are solid; clearly lives are saved
- Data for altered outcome with prostate screening are much less compelling
- Models for tumor growth can be used to help analyze impact of alleged delay on outcome
- Failure to screen will become an important battleground in oncology litigation in the coming years



For more enlightenment, visit:  
[www.StarkOncology.com](http://www.StarkOncology.com)

