

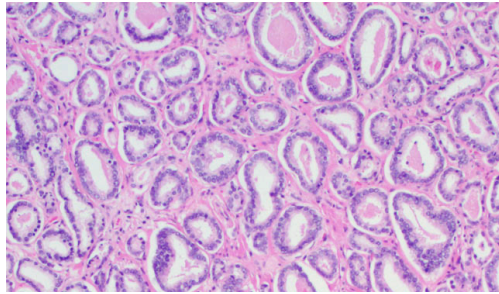
Renaming Grade Group 1 is a Public Health Priority

Removing the designation of cancer from pattern 3 prostate disease will do more good than harm

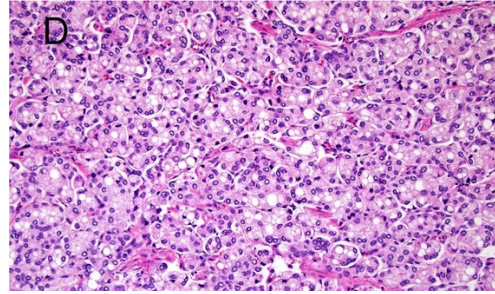
Andrew Vickers

Memorial Sloan Kettering Cancer Center

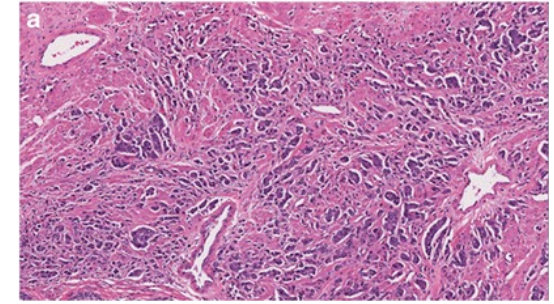
Quick recap on Gleason



Pattern 3



Pattern 4



Pattern 5

More	Less	Gleason score	Grade group
3	3	3+3	1
3	4	3+4	2
4	3	4+3	3
4	4	4+4	4
Some 5		5+? or ?+5	5

Low-Grade Prostate Cancer: Time to Stop Calling It Cancer

Scott E. Eggener, MD¹; Alejandro Berlin, MD²; Andrew J. Vickers, PhD³; Gladell P. Paner, MD⁴; Howard Wolinsky⁵; and Matthew R. Cooperberg, MD⁶

Introduction

Prostate-specific antigen (PSA) screening for prostate cancer (PCa) remains highly controversial, largely because it is unclear whether the primary benefits of reducing rates of metastases and cancer mortality are worth the risks of overdiagnosis, overtreatment, and potential treatment-related morbidity. A major contributing factor to overdiagnosis and overtreatment is the designation of a particular pattern of low-grade cellular changes in the prostate as cancer, which, in our view, should not be called cancer. A simple terminology change for these lesions and removal of the cancer label would dramatically reduce overdiagnosis and overtreatment and markedly change the cost-

PCa.³ GS6 is largely a natural, age-related histologic observation defined artefactually as a disease, not known to cause symptoms or metastases,⁶ but paradoxically leads to invasive monitoring or treatment. These concerns were a primary factor contributing to the US Preventive Services Task Force categorically discouraging PCa screening in 2012, specifically noting the common diagnosis and treatment of “microscopic, well-differentiated lesions...unlikely to be clinically important.”⁷

Low-Grade Prostate Cancer Behaves Clinically Like Precancer Rather Than Cancer

A common definition of cancer is a “malignant tumor

Research as well as rhetoric

The image shows the header of a journal article from Urology. The journal title 'UROLOGY' is in large white letters on a dark brown background. To the right is a 'Log in' link. Below the title bar, the text 'ONCOLOGY | VOLUME 170, P154-160, DECEMBER 2022' is followed by a 'Download Full Issue' button. The article title 'Blood Prostate-specific Antigen by Volume of Benign, Gleason Pattern 3 and 4 Prostate Tissue' is displayed in white. Below the title are the authors: 'Ciro Andolfi # • Andrew J. Vickers 人 信 • Matthew R. Cooperberg • ... Brian T. Helfand • Stanley L. Liauw • Scott E. Eggener • Show all authors • Show footnotes'. At the bottom, it says 'Published: August 16, 2022 • DOI: https://doi.org/10.1016/j.urology.2022.08.014 • Check for updates' with a circular icon.

PSA levels in ng/ml:
0.04 / cc of benign
0.07 /cc of pattern 3
0.56 / cc of pattern 4

Abstract

Objective

To evaluate how blood levels of prostate-specific antigen (PSA) relate to prostate volume of benign tissue, Gleason pattern 3 (GP3) and Gleason pattern 4 (GP4) cancer.



The diagnosis and management of Gleason pattern 3 prostate disease should be based on best evidence and established principles of good medical practice rather than be influenced by the highly emotive word “cancer”.

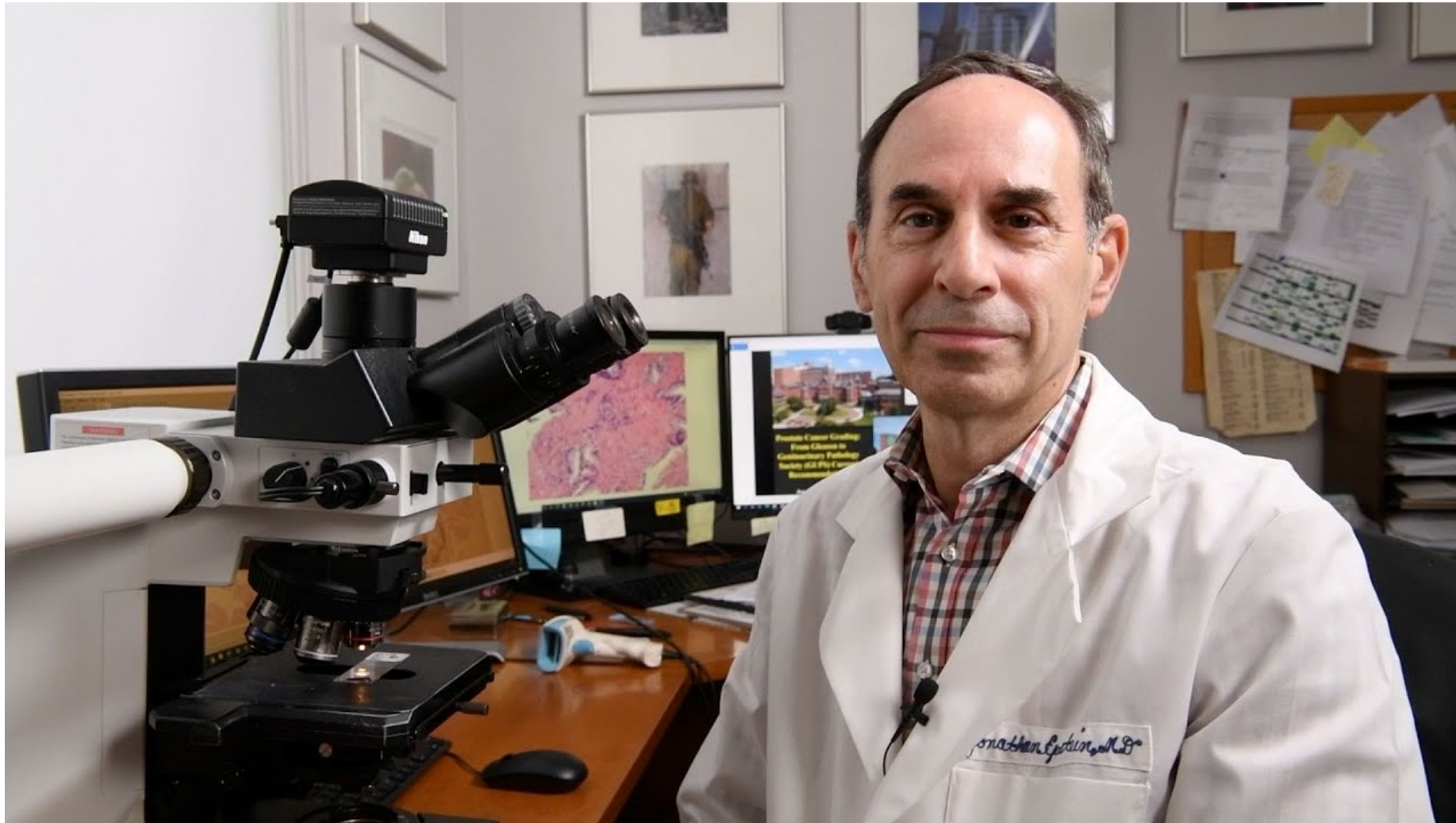
Overview

- Is redesignation even an option or it is: cancer is cancer?
- Public health benefits of redesignation
- Effects of redesignation on your practice

Overview

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“Morphologically and genetically, Gleason score 6 is cancer”



“Our duty as caregiver to fully and transparently inform patients”
“Hiding from patients with a Gleason score 6 ... the fact that they have prostate cancer would have important ramifications”

Don't worry, this isn't
an injection



Descriptions of cancer predate modern pathology by centuries

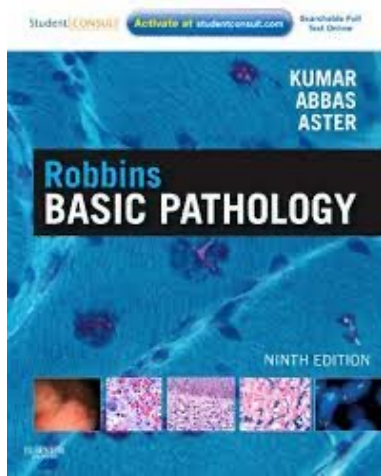
1500 BC



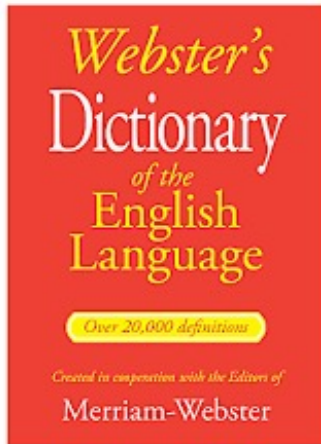
mid 1800's



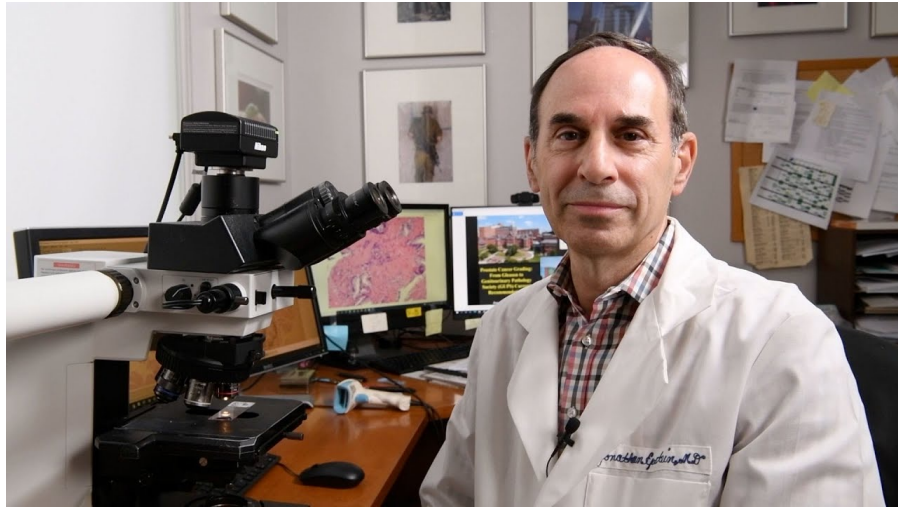
Definitions of cancer do not mention the basement membrane



- A malignant tumor (which) can invade and destroy adjacent structures and spread to distant sites



- A malignant tumor of potentially unlimited growth that expands locally by invasion and systemically by metastasis.



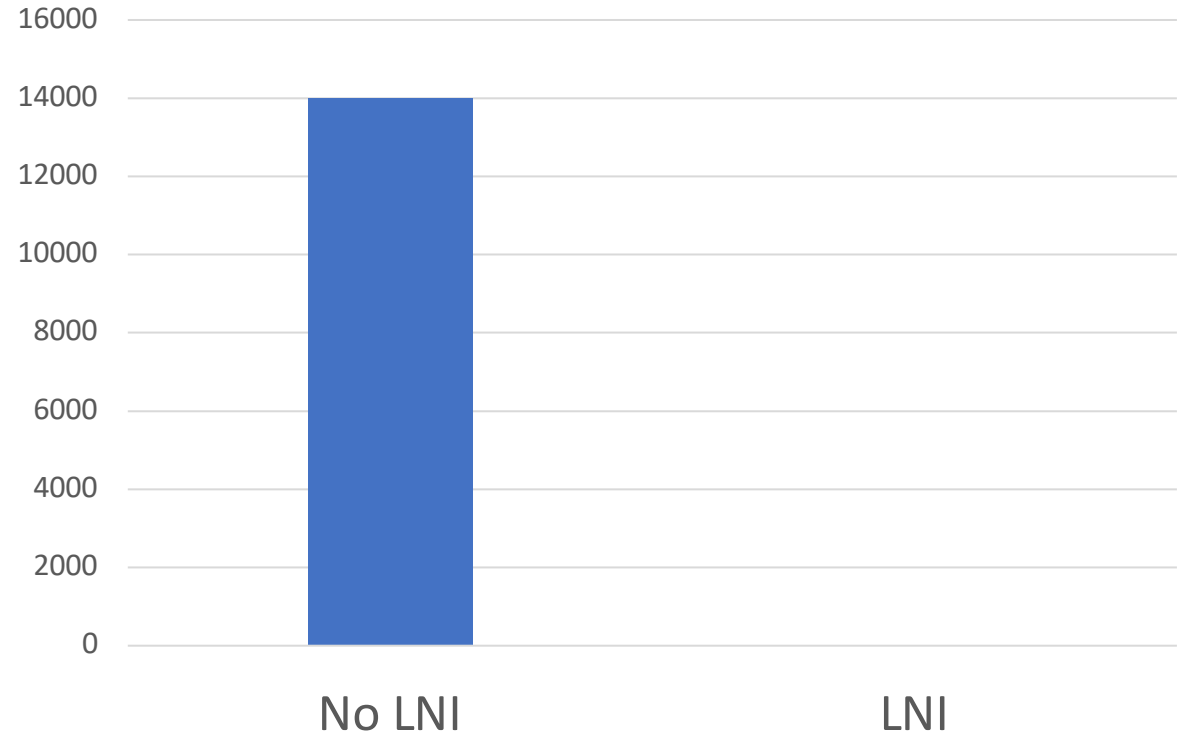
Published in final edited form as:

Am J Surg Pathol. 2012 September ; 36(9): 1346–1352. doi:10.1097/PAS.0b013e3182556dcd.

DO ADENOCARCINOMAS OF THE PROSTATE WITH GLEASON SCORE (GS) ≤ 6 HAVE THE POTENTIAL TO METASTASIZE TO LYMPH NODES?

Abstract

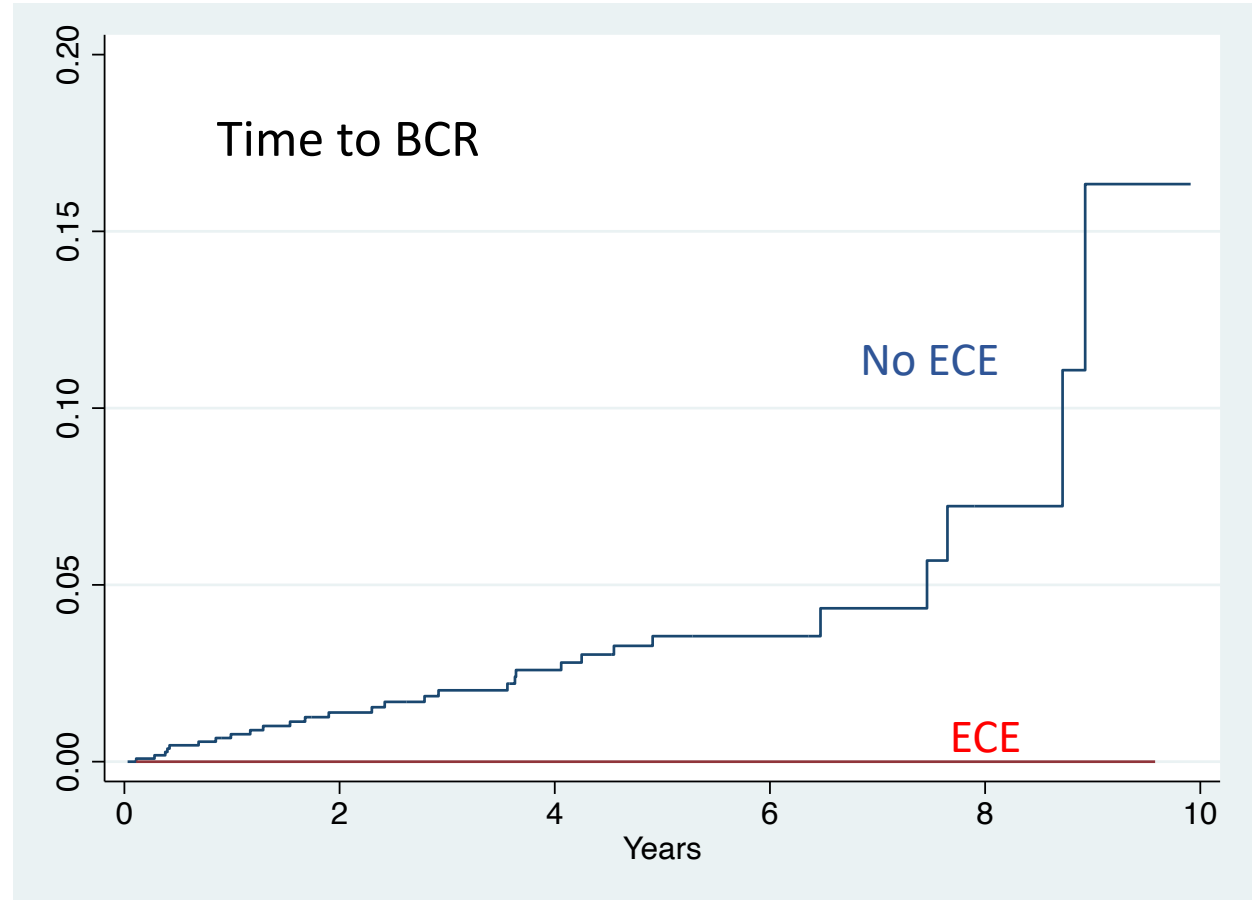
Although rare, there are cases within reported series of men with $GS \leq 6$ in radical prostatectomies that have pelvic lymph node (LN) metastases. However, there are no studies as to whether pelvic LN metastases occur in tumors $GS \leq 6$ using the International Society of Urological Pathology (ISUP) updated Gleason scoring system. We performed a search of the radical prostatectomy databases at 4 large academic centers for cases of $GS \leq 6$. Only prostatectomies submitted and embedded in entirety with pelvic lymph node dissections were included. A combined total of 14 123 cases were identified out of which 22 cases had a positive LN. Histopathology review of



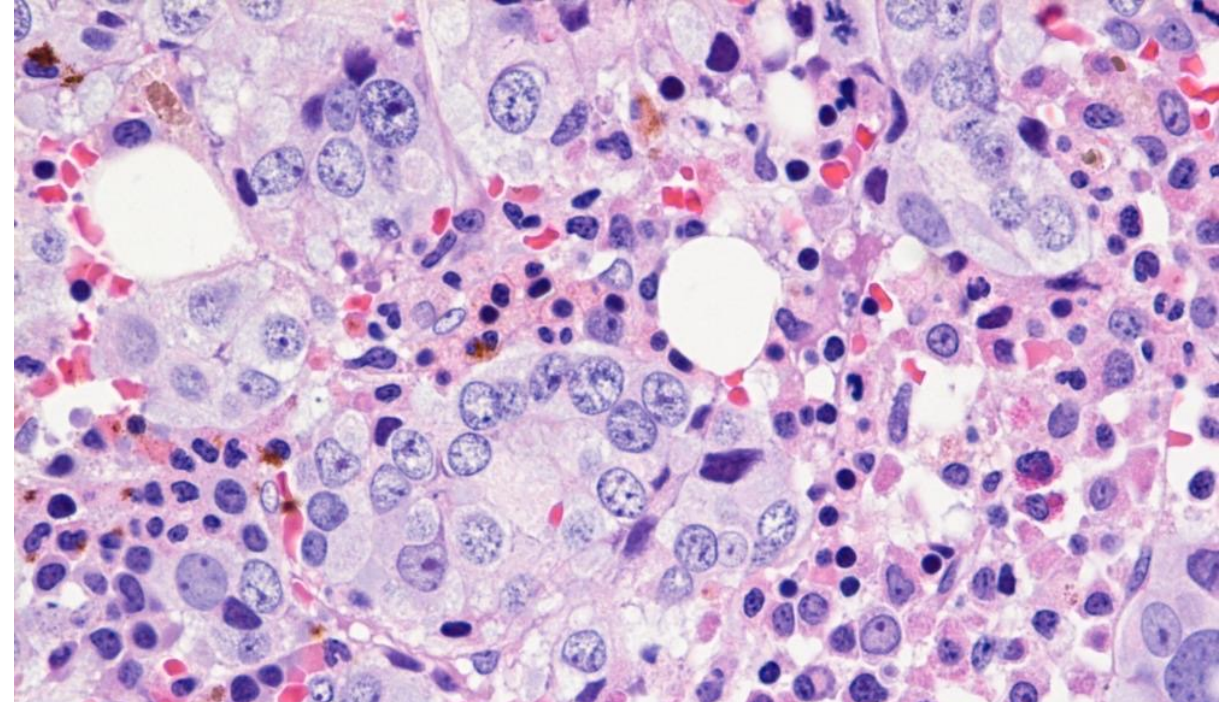
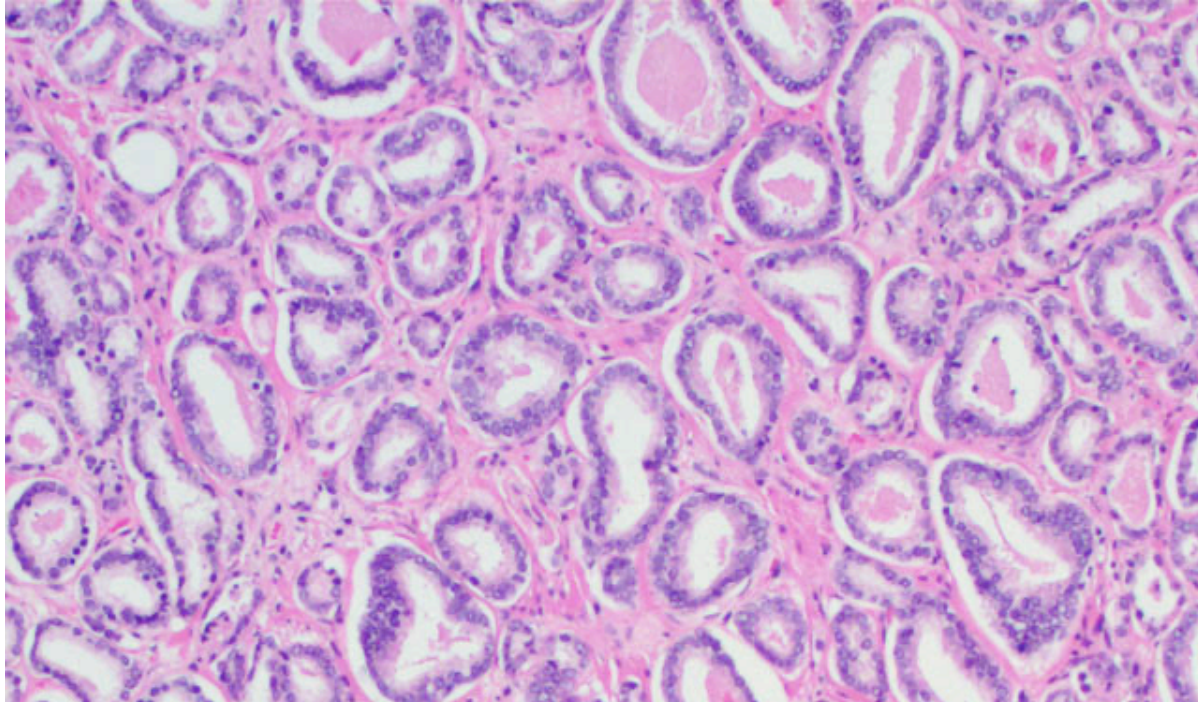
“Patterns 4 or 5 required for metastatic disease”

MSKCC: no local extension in pattern 3

- N=1325 with grade group 1
- 1 SVI, 1 LNI (error / artifact)
- 87 ECE (6.6%)
- ECE did not increase BCR



“Pattern 3 has the molecular hallmarks of cancer”



Burning cigarette has molecular hallmarks of combustion



“Genetically, Pattern 3 is cancer”

One of the strongest rationales for retaining the designation of cancer for GG1 tumors is the fact that Gleason pattern 3 cancer shares many morphologic and canonical molecular alterations associated with higher-grade prostate adenocarcinoma [16], [17]. These include nuclear and nucleolar features, lack of basal cells, invasion beyond the confines of the prostate gland proper, overexpression of AMACR, loss of PTEN, GSTP1 downregulation, and *TMPRSS2-ERG* gene fusions [18], [19].

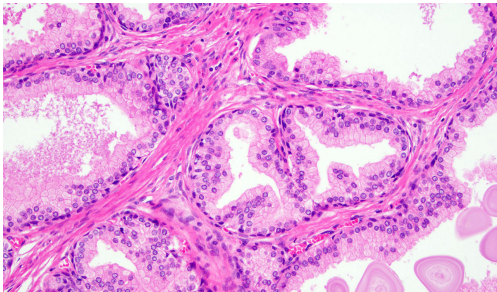
Therefore a trumpet is a type of car



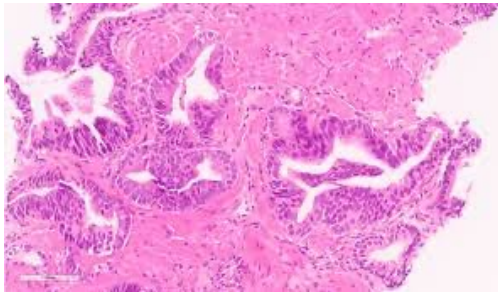
All molecular alterations in high grade cancer also in HGPIN or BPH

Alteration	Benign or HGPIN	Pattern 3 and pattern 4
ERG translocations (mainly TMPRSS2-ERG) [1,3,4,7,11,14,15]	+	+
TMPRSS2 expression [13]	+	+
PTEN loss [1,5–7]	+	+
p27 expression [11]	+	+
p53 (mutation and expression) [8,9]	+	+
CD44 expression [8]	+	+
CD10 expression [11]	+	+
c-Myc expression [10]	+	+
AMACR expression [11,12]	+	+
EZH2 expression [14]	+	+
NKX3.1 expression [14]	+	+
SPINK-1 expression [14,16]	+	+

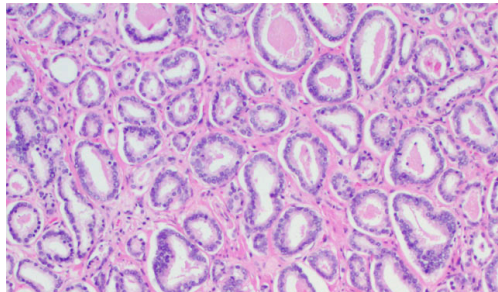
“Pattern 3 / HGPIN / BPH shares many of morphologic and canonical molecular alterations associated with higher-grade prostate adenocarcinoma”



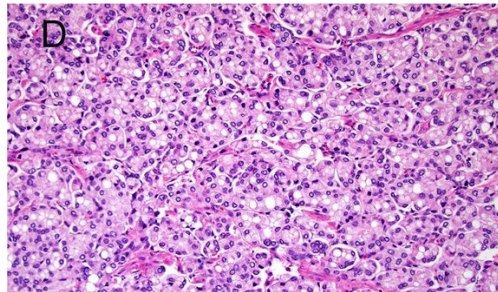
BPH



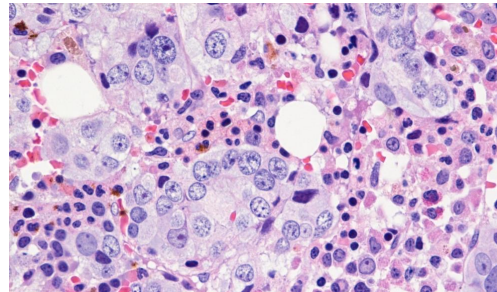
HGPIN



GG1

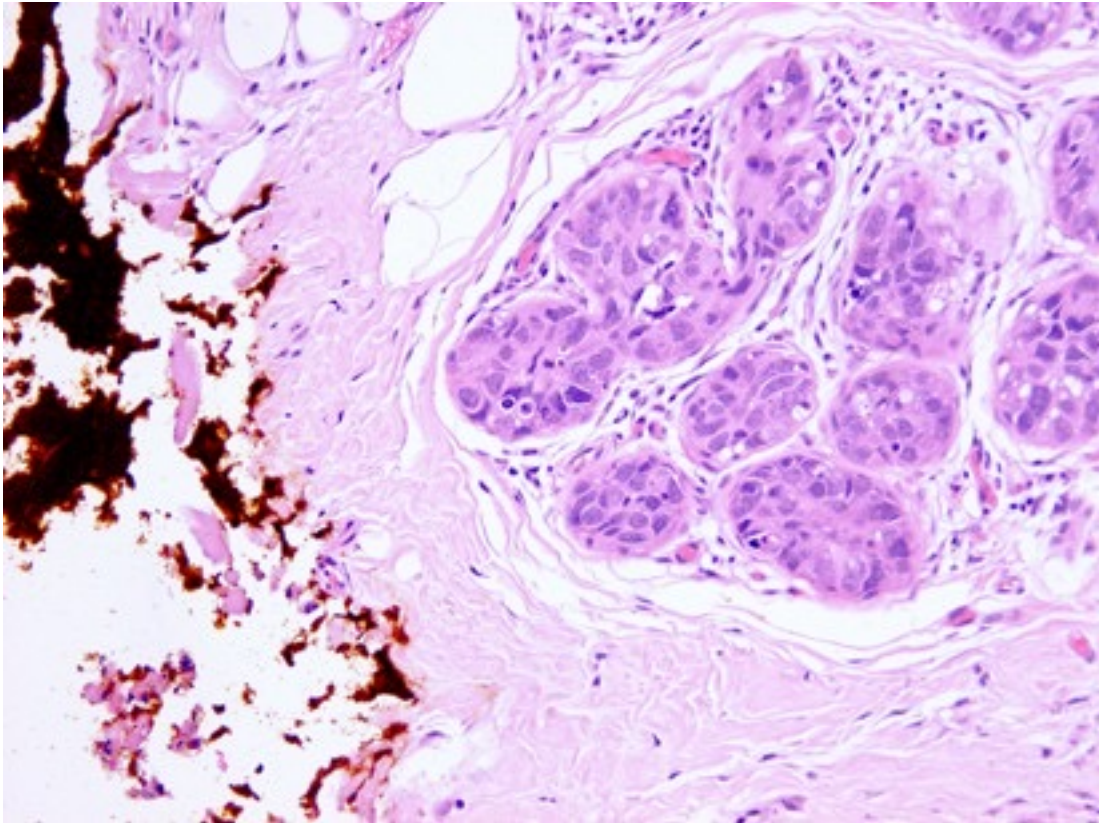


GG4



Mets

Involvement of basement membrane is NOT
synonymous with cancer



Ductal carcinoma in situ

Support for retaining cancer for GG1 not universal amongst pathologists

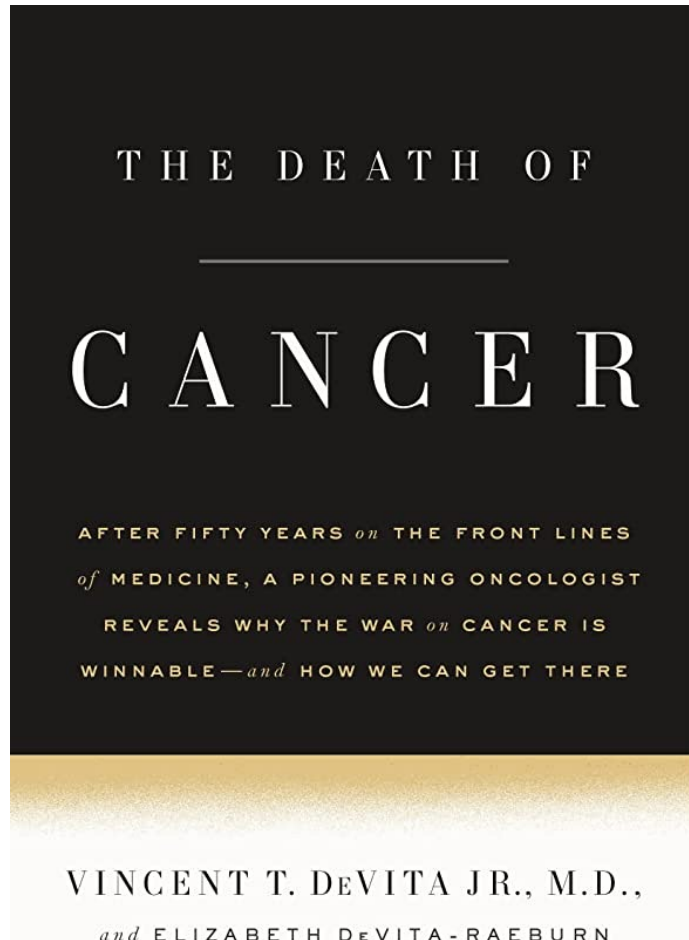
Opinion regarding the reclassification of the term
'cancer' for GG1 disease

	Support	Uncertain	Oppose
Urology (n=594)	282 (48%)	165 (27%)	147 (25%)
Pathology (n=260)	38 (15%)	64 (24%)	158 (61%)
Radiation oncology (n=197)	88 (45%)	76 (38%)	33 (17%)
Medical oncology (n=29)	13 (45%)	14 (48%)	2 (7%)

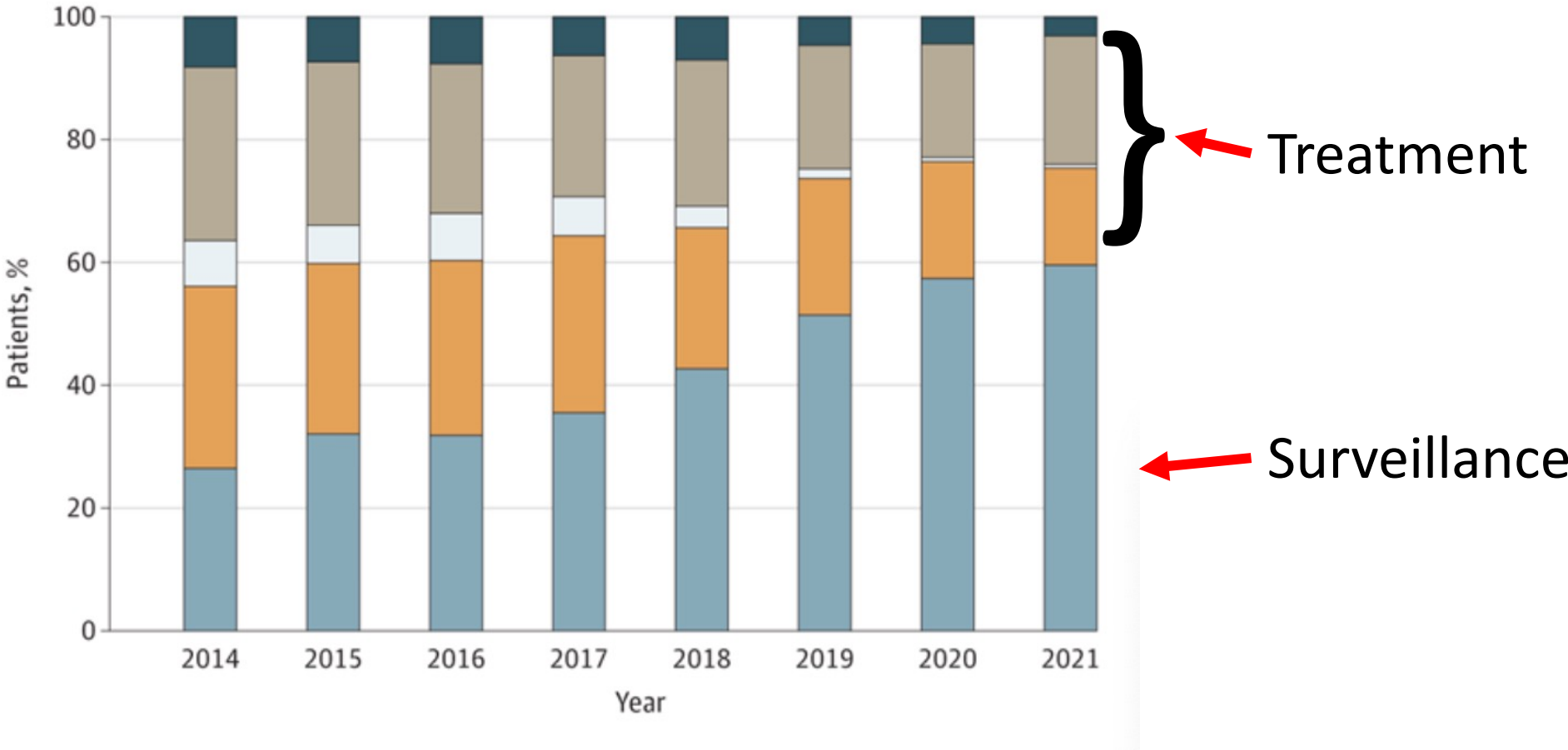
Overview

- Is redesignation even an option or it is: cancer is cancer?
- **Public health benefits of redesignation**
- Effects of redesignation on your practice

“Hearing I had prostate cancer was the worst day of my life”





Overtreatment remains rife, for low-risk



The term “cancer” causal for overtreatment

Patient reported factors influencing the decision-making process of men with localised prostate cancer when considering Active Surveillance—A systematic review and thematic synthesis

Maggie Cunningham¹  | Mike Murphy¹ | Paul Sweeney² | Helen L. Richards² 

¹School of Applied Psychology, University College Cork, Cork, Ireland

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Funding information

Open access funding provided by IReL

Abstract

Objectives: Outcomes for men with localised prostate cancer managed with Active Surveillance (AS) are similar to outcomes for men who have received Active Treatment. This review explore men's perceptions of the factors that influence their decision-making process when considering AS.

Method: A systematic review of studies was conducted up to May 2021, including qualitative studies which explored the decision making of men with localised prostate cancer when considering AS. Evidence was analysed using thematic synthesis.

Results: Thirteen papers, including 426 men, met inclusion criteria and were analysed in the review. Approximately half of the men had chosen AS and half had chosen Active Treatment. The choice of AS was not a one-off decision but rather an ongoing behaviour. Four themes were identified and considered within a temporal model: pre-diagnosis representations of cancer and treatment; experience of testing and diagnosis; patient decision making; and emotional adjustment to AS. Key barriers and facilitators to men choosing AS were identified. In deciding whether or not to choose AS, men balanced a desire for quality of life against fear of cancer progression.

Conclusions: Both cognitive representations and emotional arousal influence how

Stress of prostate diagnosis extends to suicide



Available at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.ejcancer.info



Risk of suicide in men with low-risk prostate cancer

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^d Clinical Epidemiology Unit, Örebro University Hospital and Örebro University, Örebro, Sweden

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^f CLINTEC Department, Karolinska Institute, Sweden

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^h Department of Surgical Sciences, Uppsala University, Uppsala, Sweden

Available online 19 January 2013

KEYWORDS

Prostatic neoplasms
Suicide

Abstract Purpose: Risk of suicide is increased among men with prostate cancer. We investigated this association among men with low-risk cancer, usually detected by prostate specific antigen (PSA)-testing.

Conclusion: Although the increase in absolute risk of suicide was modest, our findings reflect the severe psychological stress that prostate cancer patients may experience after diagnosis. The increased risk of suicide observed in men with prostate cancer, including low-risk, calls for increased awareness.

A diagnosis of cancer has unavoidable social implications

review articles

SPECIAL SERIES: ECONOMIC ISSUES IN CANCER CARE

Impact

Victoria S. Blinder, MI

INTRODUCTION

Employment provides financial benefits and health care for cancer survivors, ongoing economic distress is emotionally challenging and correlated with breast cancer distress among cancer survivors, which results from spending after a cancer diagnosis, a symptom burden that has increased quality of life. Advanced financial distress is associated with nearly double the odds of cancer survivors (odds ratio

This article describes cancer survivors; and socioeconomic status affects cancer outcomes, and possible approaches to improving work outcomes, including policy and patient-facing interventions. Much of the work on cancer outcomes literature emanates from outside of the United States, although the US literature is growing. The

Life Insurance: Coming to a Cancer Survivor Near You

Life insurers are putting their money where cancer researchers' mouths have been for some time.

Over the past several years, life insurance companies have begun to examine how much longer patients with breast and prostate cancer are living. Largely on the basis of data collected by cancer researchers, a few companies have lowered the price of policies for cancer survivors who were once considered risky.

"What you are looking at is a population that would have an extraordinarily intense appreciation for the value of life insurance," said Steven N. Weisbart, Ph.D., an economist with the Insurance Information Institute in New York City. "To the degree that one can safely underwrite an insurance policy for these people, this is a good thing both for the insurance company and the people who need and want the life insurance."

For cancer survivors, life insurance is a possible approach to improving work outcomes, including policy and patient-facing interventions. Much of the work on cancer outcomes literature emanates from outside of the United States, although the US literature is growing. The

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NEWS

Patient Education and Counseling 96 (2014) 120–127

Contents lists available at ScienceDirect



ELSEVIER

journal homepage: www.elsevier.com

Patient Education and Counseling

Coping with Cancer

Cross-sectional relationships between depression, and relationship satisfaction in cancer and their spouses

Tim W. Regan^{a,*}, Sylvie D. Lambert^b, Brian Kelly^c, Karen Kayser^f, Jane Turner^g

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^b Ingram School of Nursing, McGill University, Montreal, Canada
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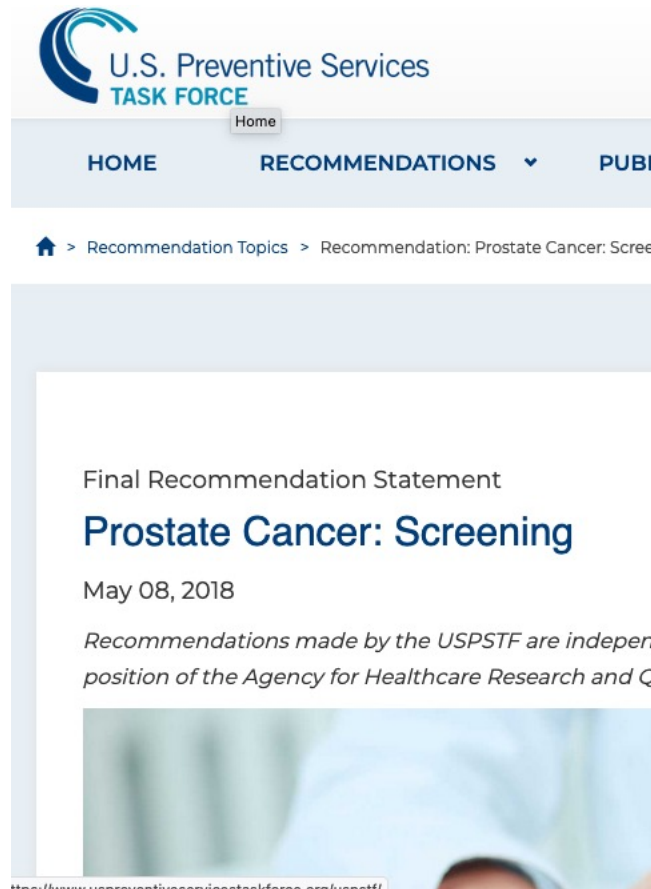
Keywords:
Dyadic coping
Couples
Prostate cancer
Distress
Relationships

ABSTRACT

Objective: Dyadic coping has limited evidence regarding cancer. The objective of this study was to examine dyadic coping, anxiety, depression, and relationship satisfaction in cancer survivors and their spouses completed measures of dyadic coping, anxiety, depression, and relationship satisfaction. Results: Relationship satisfaction and negative dyadic coping were associated with dyadic coping of supportive dyadic coping.



Overdiagnosis major reason for no population-based screening



U.S. Preventive Services
TASK FORCE

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HOME RECOMMENDATIONS PUBLICATIONS


Home > Recommendation Topics > Recommendation: Prostate Cancer: Screening

Final Recommendation Statement

Prostate Cancer: Screening

May 08, 2018

Recommendations made by the USPSTF are independent of the Agency for Healthcare Research and Quality.



Search the USPSTF Site



Shared Decision Making – prostate specific antigen

Next clinical review date March 2018

Deciding whether to have a prostate specific antigen (PSA) test

This short decision aid is for men who are considering having a test to find out more about their risk of having prostate cancer. The decision aid is not for people who have symptoms of prostate cancer and need a test to diagnose cancer.

The prostate specific antigen (PSA) test can tell you if you have a raised chance of prostate cancer. The PSA test cannot tell you for certain whether you have prostate cancer. If you decide to have a PSA test you can discuss this with your GP, who can arrange for you to have a test.

Whether you decide to have a test will depend on many things, including whether there is a history of prostate cancer in your family, whether you want to know about

Platinum Opinion

Prostate Adenocarcinoma Grade Group 1: Rationale for Retaining a Cancer Label in the 2022 World Health Organization Classification

George J. Netto^{a,*}, Mahul B. Amin^{b,c}, Eva M. Compérat^d, Anthony J. Gill^{e,f,g,†}, Arndt Hartmann^h, Holger Moch^{i,‡}, Santosh Menon^j, Maria R. Raspollini^k, Mark A. Rubin^l, John R. Srigley^{m,‡}, Puay Hoon Tan^{n,‡}, Satish K. Tickoo^o, Toyonori Tsuzuki^{p,‡}, Samra Turajlic^q, Ian Cree^{r,‡}, Daniel M. Berney^s

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The Gleason system forms the basis for prostate cancer grading worldwide. It has been modified on several occa-

in National Comprehensive Cancer Network [NCCN]) to active surveillance (AS) [8,9], a designation of GG1 of 5

Counter-arguments to redesignation are largely speculative

Speculation, speculation, speculation

- “If one were to drop the cancer label ... adherence to intensive monitoring and the option to choose definitive therapy could be jeopardized”.
- “[Redesignation] may raise legal risks related to potential grading disagreements”
- “One can anticipate a significant increase in the proportion of cases for which repeat biopsy is needed because of equivocal diagnoses ... reported by concerned pathologists.”
- To solve overtreatment we just need “education for surgeons and patients [about] the vital role of AS”

The sampling argument

- Yes, true pattern 3 cannot metastasize, but that is based on sampling the whole prostate. If you are diagnosed with pattern 3, you can't be sure you don't have higher grade.

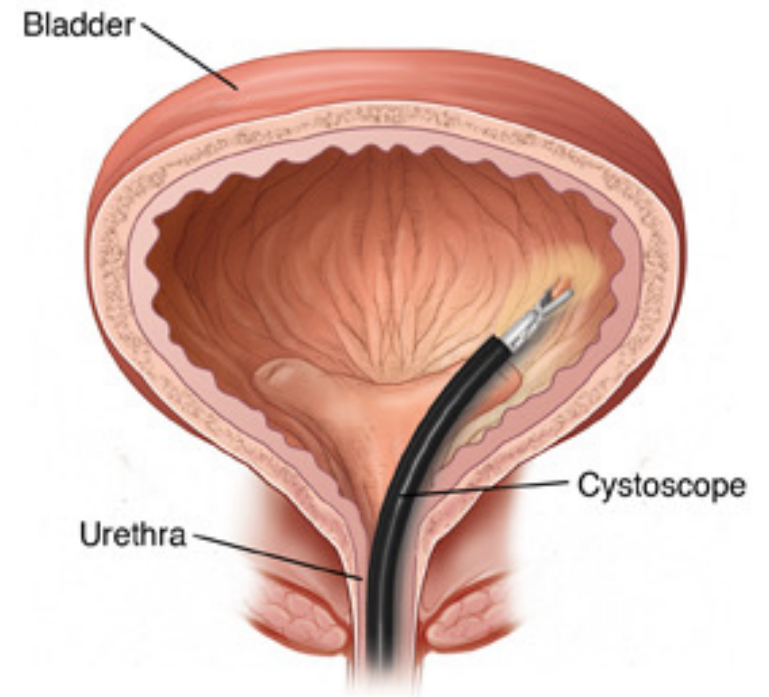


“Designation of tumor benignity or malignancy should not be based on the shortcomings of a diagnostic procedure and sampling errors.”



We are going to diagnose you with something even if we don't have evidence you have it, just in case you do have it.

		Disease:		
		Sick	Healthy	
Test result:	Positive	True positive (TP)	False positive (FP)	→ PPV
	Negative	False negative (FN)	True negative (TN)	→ NPV
		↓ Sensitivity	↓ Specificity	



Take any argument against redesignation and exchange the word “benign” for “pattern 3”

- “We have to call pattern 3 “cancer” because many men with only pattern 3 on biopsy would have pattern 4 on radical prostatectomy”
- “We have to call benign findings “cancer” because many men with only benign findings on biopsy would have pattern 4 on radical prostatectomy”

Take any argument against redesignation and exchange the word “benign” for “pattern 3”

- “We have to call pattern 3 “cancer” because otherwise men won’t comply with subsequent monitoring”
- “We have to call benign findings “cancer” because otherwise men won’t comply with subsequent monitoring”

Take any argument against redesignation and exchange the word “benign” for “pattern 3”

- “We have to call pattern 3 “cancer” because otherwise men will be confused if a subsequent biopsy shows pattern 4”
- “We have to call benign findings “cancer” because otherwise men will be confused if a subsequent biopsy shows cancer”

Try to avoid finding something it is important to worry about?

- “We have to call pattern 3 “cancer” because otherwise men won’t comply with subsequent monitoring”
- Also:
- “In my practice, I go out of my way not to diagnose pattern 3”

We go out of our way *not* to diagnose pattern 3. So why call it cancer?

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MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis

V. Kasivisvanathan, A.S. Rannikko, M. Borghi, V. Panebianco, L.A. Mynderse, M.H. Vaarala, A. Briganti, L. Budäus, G. Hellawell, R.G. Hindley, M.J. Roobol, S. Eggener, M. Ghei, A. Villers, F. Bladou, G.M. Villeirs, J. Viridi, S. Boxler, G. Robert, P.B. Singh, W. Venderink, B.A. Hadaschik, A. Ruffion, J.C. Hu, D. Margolis, S. Crouzet, L. Klotz, S.S. Taneja, P. Pinto, I. Gill, C. Allen, F. Giganti, A. Freeman, S. Morris, S. Punwani, N.R. Williams, C. Brew-Graves, J. Deeks, Y. Takwoingi, M. Emberton, and C.M. Moore, for the PRECISION Study Group Collaborators*

ABSTRACT

BACKGROUND

Multiparametric magnetic resonance imaging (MRI), with or without targeted biopsy, is an alternative to standard transrectal ultrasonography–guided biopsy for prostate-cancer detection in men with a raised prostate-specific antigen level who have not undergone biopsy. However, comparative evidence is limited.

METHODS

In a multicenter, randomized, noninferiority trial, we assigned men with a clinical suspicion of prostate cancer who had not undergone biopsy previously to undergo MRI, with or without targeted biopsy, or standard transrectal ultrasonography–

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Kasivisvanathan at the Division of Surgery and Interventional Science, UCL, 3rd Fl., Charles Bell House, 43-45 Foley St., London W1W 7TS, United Kingdom, or at veeru.kasi@ucl.ac.uk.

*A complete list of members of the PRECISION Study Group is provided in

Overview

- Is redesignation even an option or it is: cancer is cancer?
- Public health benefits of redesignation
- Effects of redesignation on urologic practice

 **Andrew Vickers** @VickersBiostats · Jan 11

On redesignating GG1 as non-cancer: urologist says "nice idea, but just had a GG1 patient on active surveillance who went from PSA 4, negative MRI, to PSA of 12, SVI on MRI in one year". I asked: what would you have done different if GG1 called not cancer? Answer: nothing.

The diagnosis and management of Gleason pattern 3 prostate disease should be based on best evidence and established principles of good medical practice rather than being influenced by the highly emotive word “cancer”

FINAL DIAGNOSIS:

PART 1: PROSTATE, BILATERAL SEMINAL VESICLE DEFERENTIA, LAPAROSCOPIC ROBOTIC-ASSISTED A. INVASIVE PROSTATIC ADENOCARCINOMA, AC EXTRACELLULAR MUCIN, GLEASON SCORE 3 + 4 : GLEASON PATTERN 4 (CRIBRIFORM, GLOMERUL CARCINOMA COMPONENT ACCOUNTS FOR APPX VOLUME (See Comment).

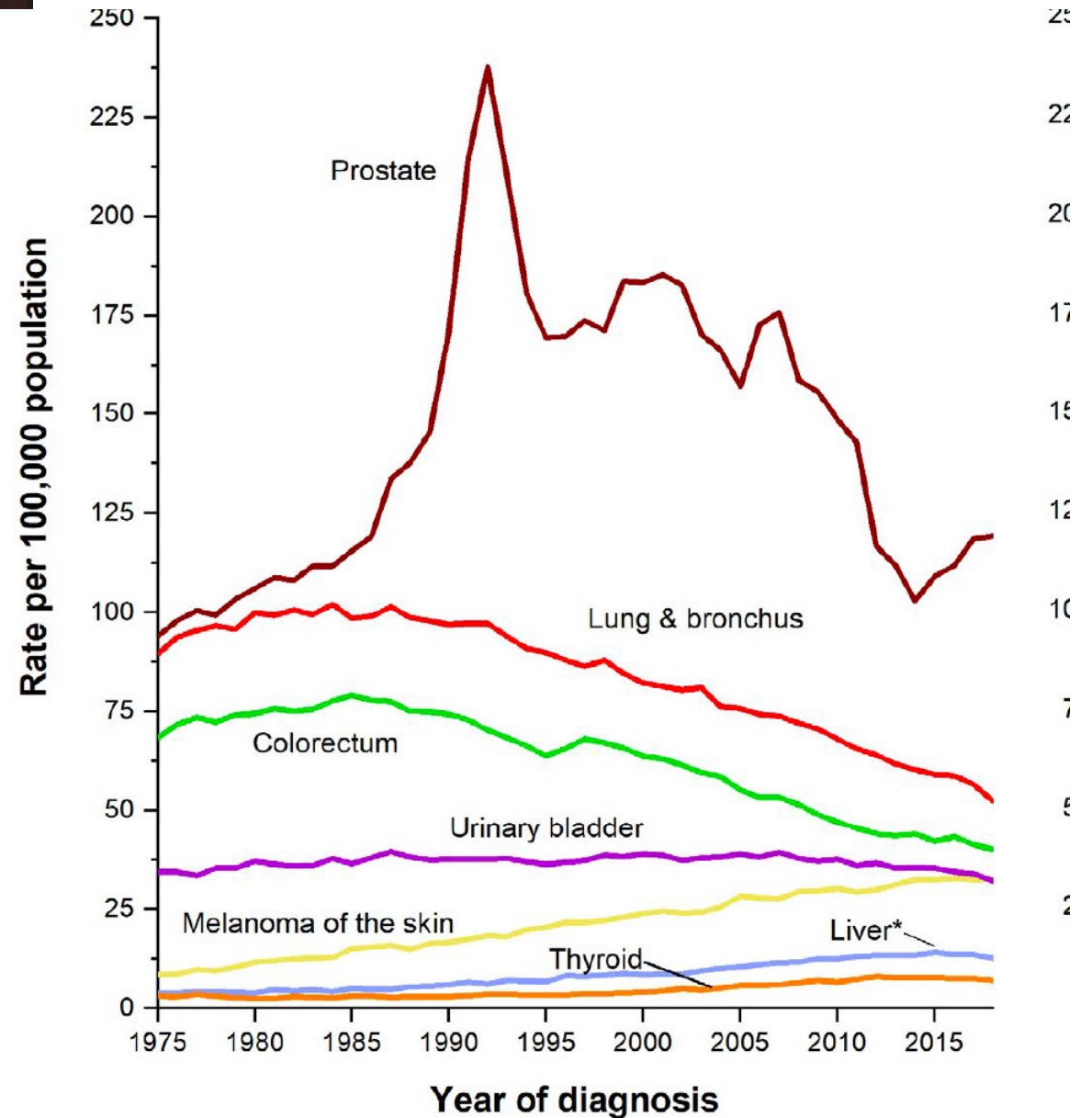
B. PROSTATIC ADENOCARCINOMA INVOLVES TH (APEX THROUGH BASE, WITH DOMINANT NODU DIAMETER OF 2.2 CM ON ONE HISTOLOGIC SECT C. PROSTATIC ADENOCARCINOMA INVOLVES API PROSTATE VOLUME.

D. ESTABLISHED EXTRAPROSTATIC EXTENSION IS URETHRA / PROSTATE BASE (SLIDE 1G).

E. BLADDER NECK EXTENSION IS IDENTIFIED ON F. FOCAL PERINEURAL INVASION IS IDENTIFIED (S

G. NO LYMPHOVASCULAR INVASION IDENTIFIED. H. HIGH-GRADE PROSTATIC INTRAEPITHELIAL NE

I. CARCINOMA IS FOCALLY PRESENT AT THE LEFT AND LEFT POSTERIOR URETHRA / LEFT BASE (SLII



Molecular hallmarks of cancer?
Undersampling?
“We should do more education”?

