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Prostate Cancer: Disease Localization and Risk Stratification

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Memorial Sloan Kettering Cancer Center

New York, NY

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MOVIECLIPS

COSMIC CRISP™

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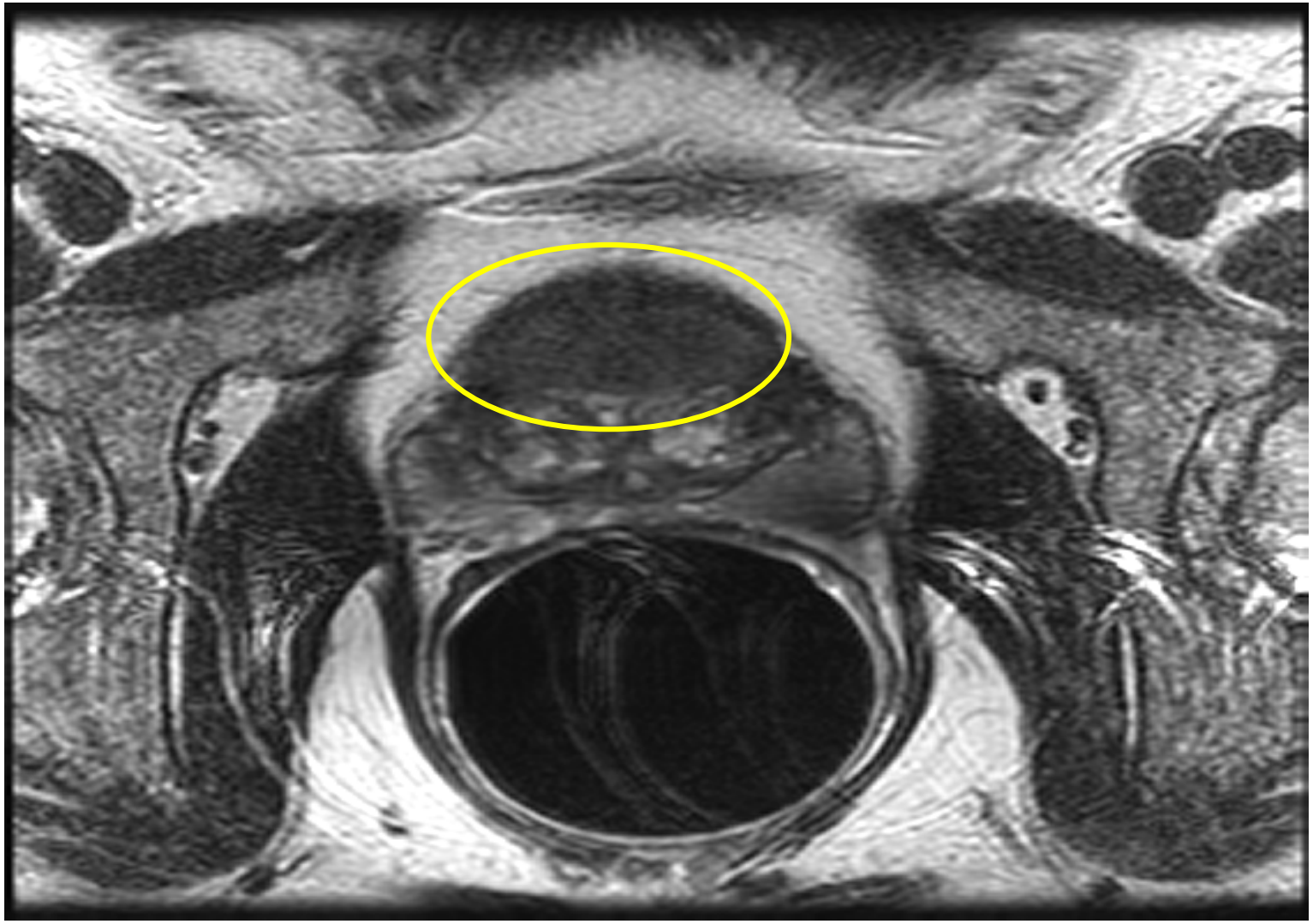
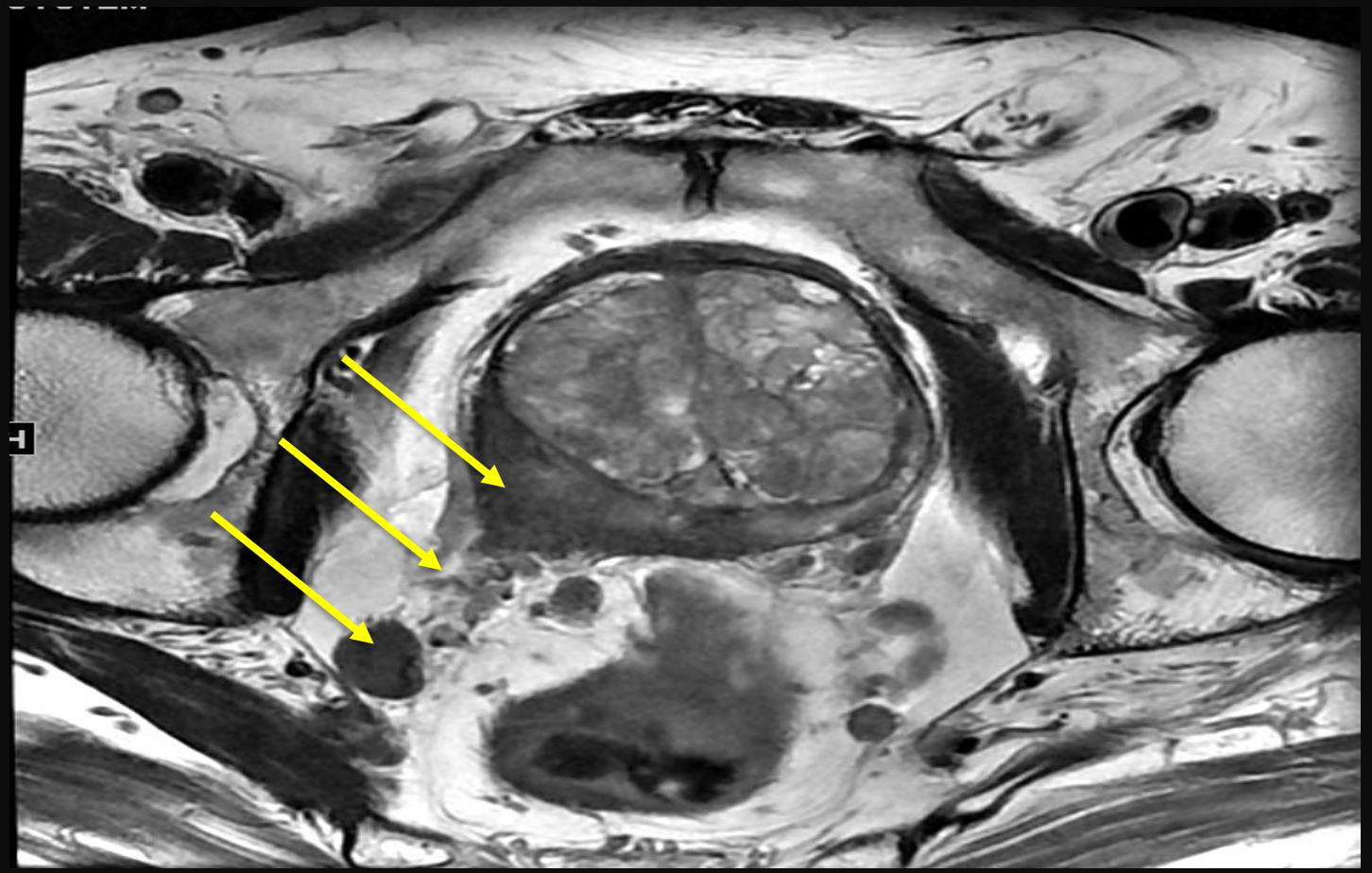
Localization of the Cancer is Critical, Beginning with the Biopsy

Normal DRE (T1c)
PSA: 14
Gleason 8 anterior bx



Localization of the Cancer is Necessary For Staging and Treatment Planning



T3a, N1

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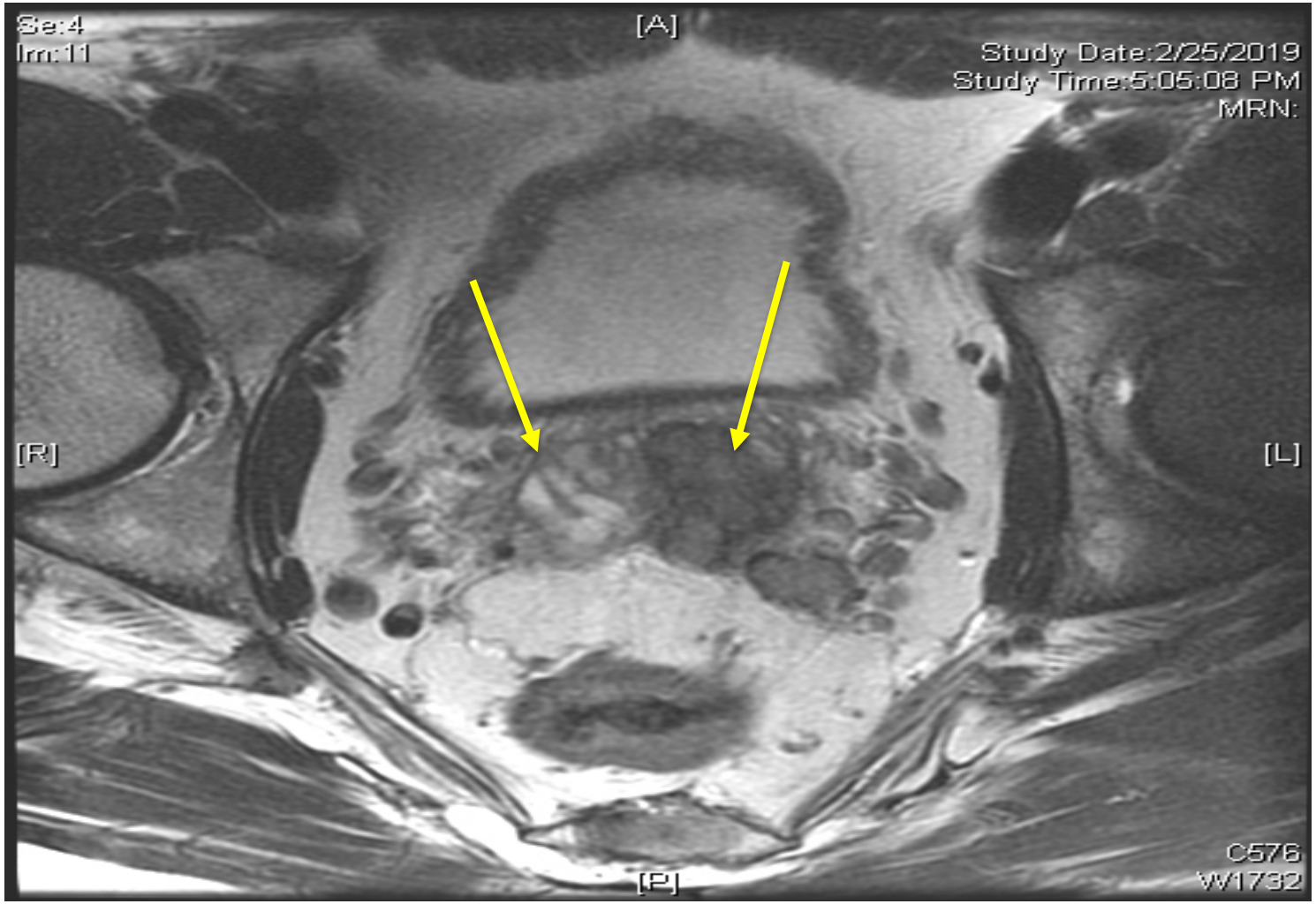
Localization of the Cancer is Necessary For Staging and Treatment Planning



T3b

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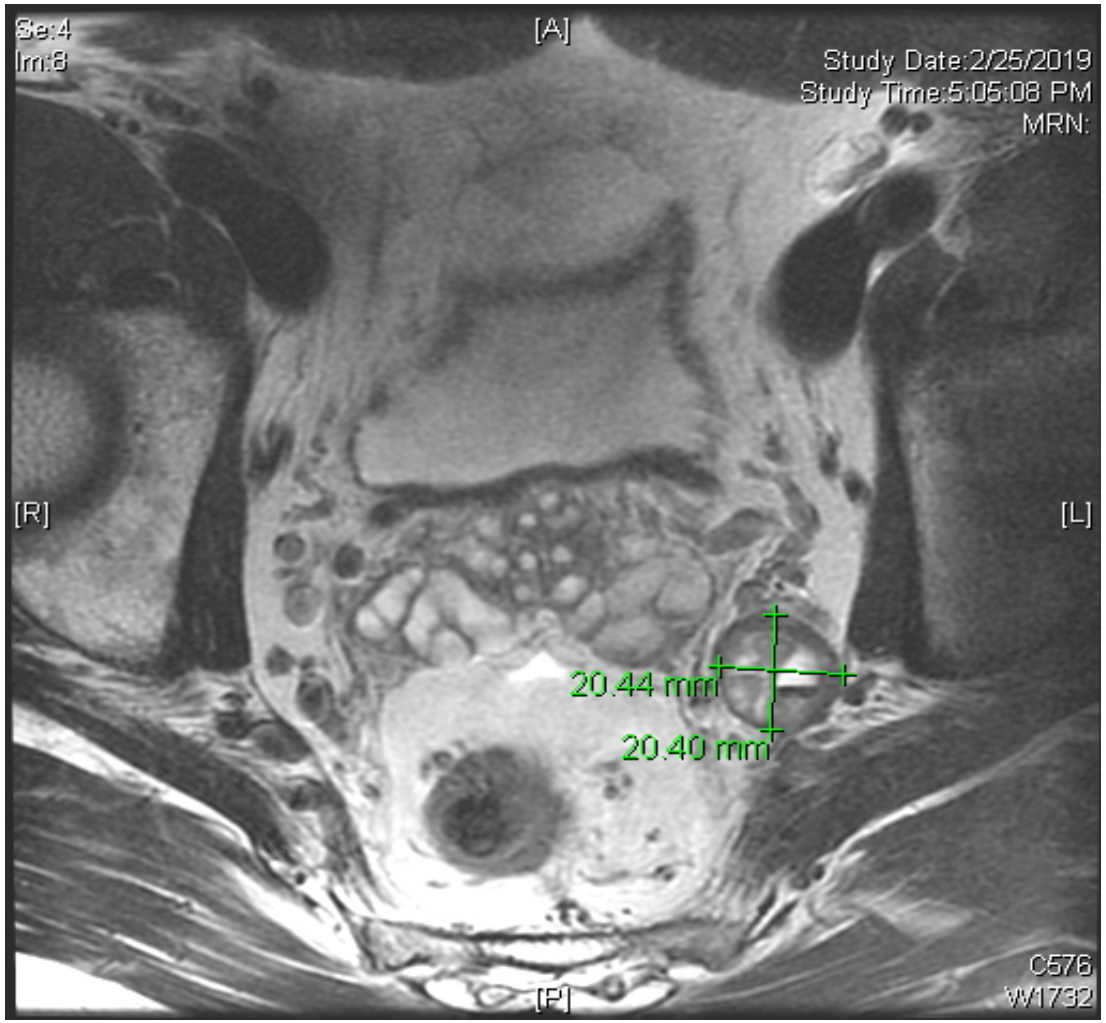
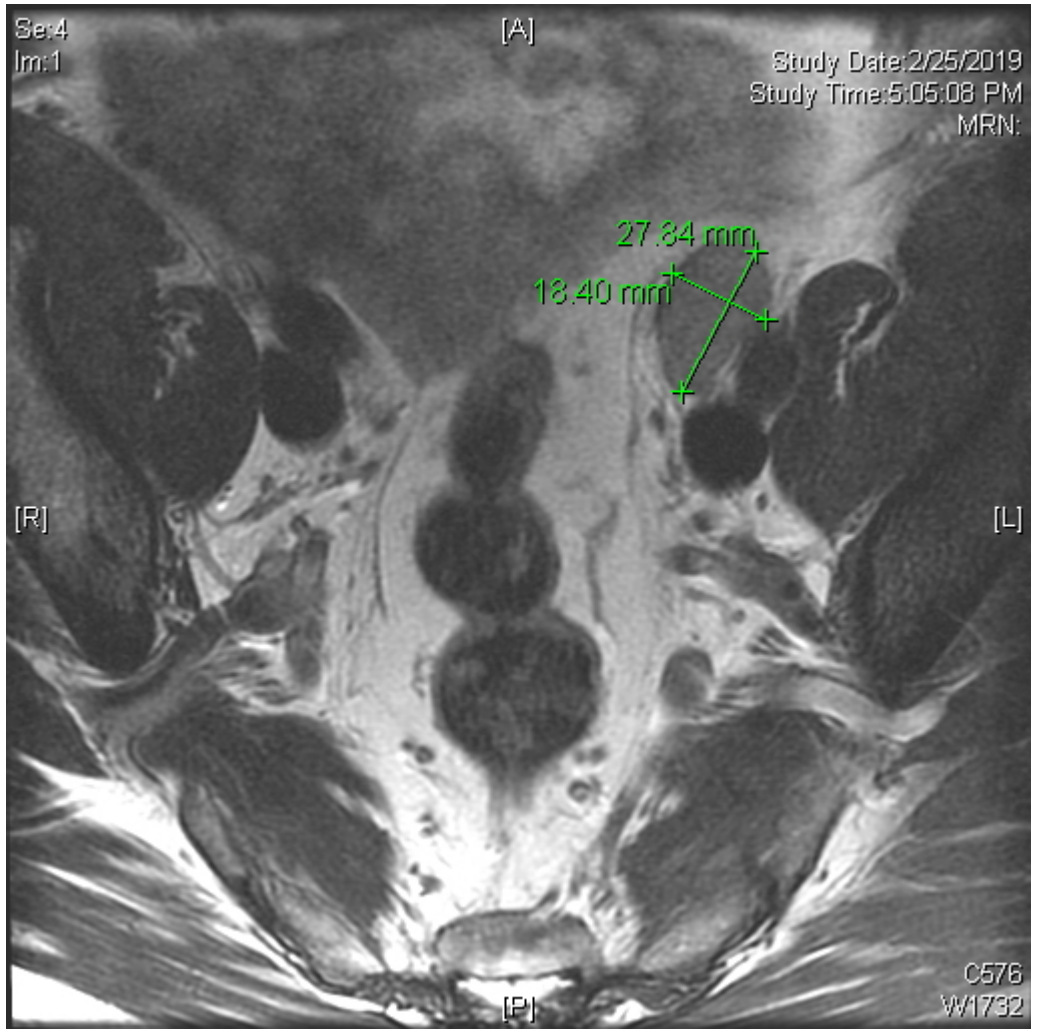
Localization of the Cancer is Critical For Staging and Treatment Planning





N1/M1a

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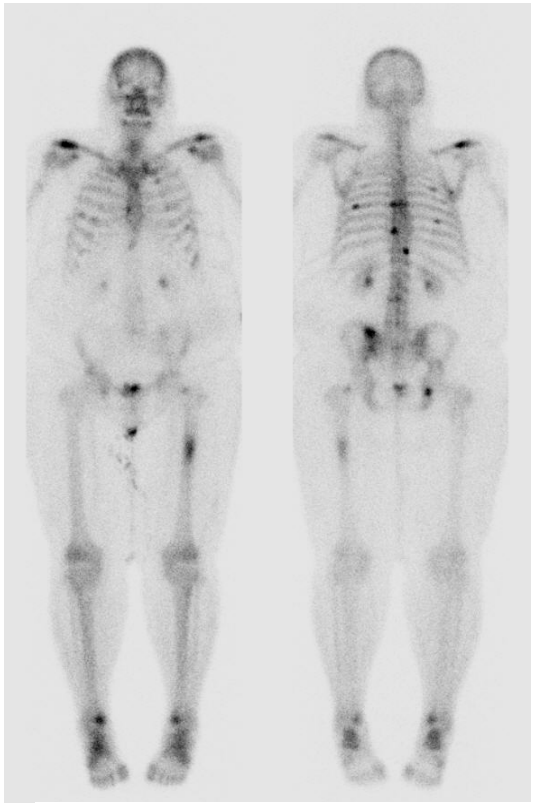
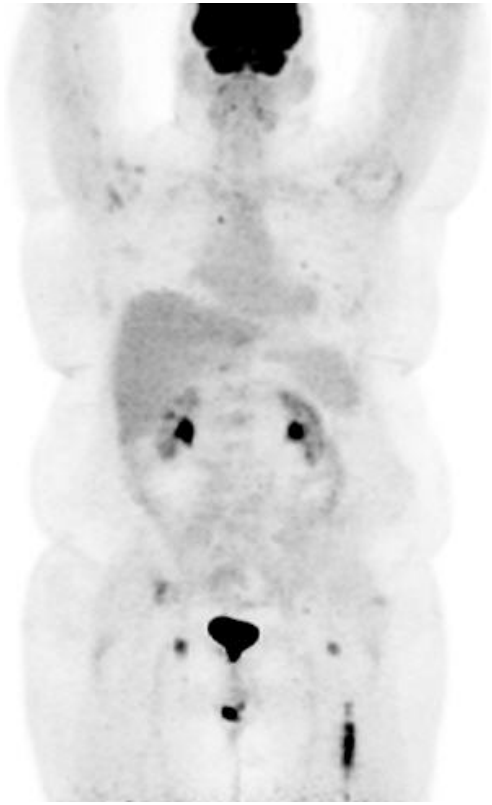
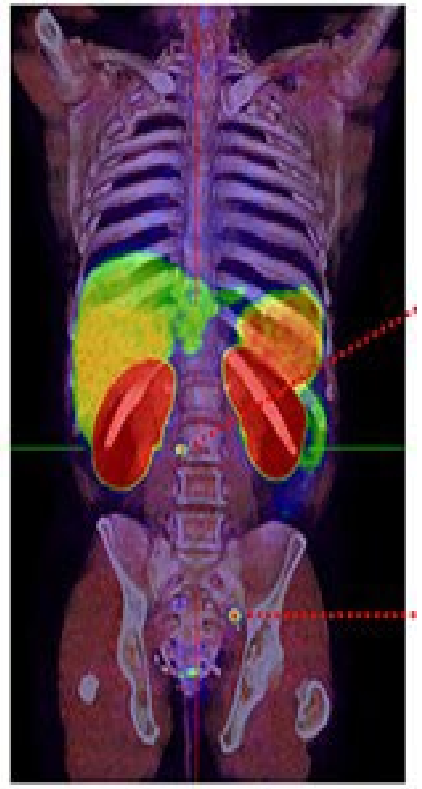
Molecular Imaging for prostate cancer



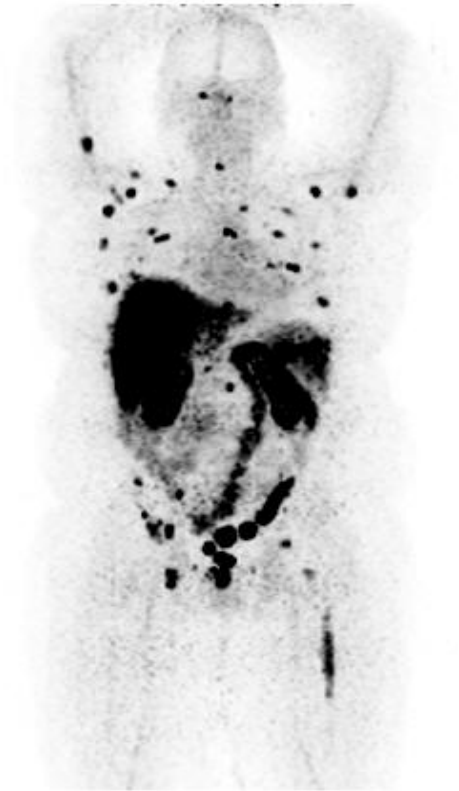
Standard BONE SCAN
detects some bone
metastasis



Standard PET SCAN
detects some soft
tissue mets



AXIMUN PET SCAN
can detect more sites
of disease



PSMA PET SCAN
detects many more
bone and
soft tissue mets

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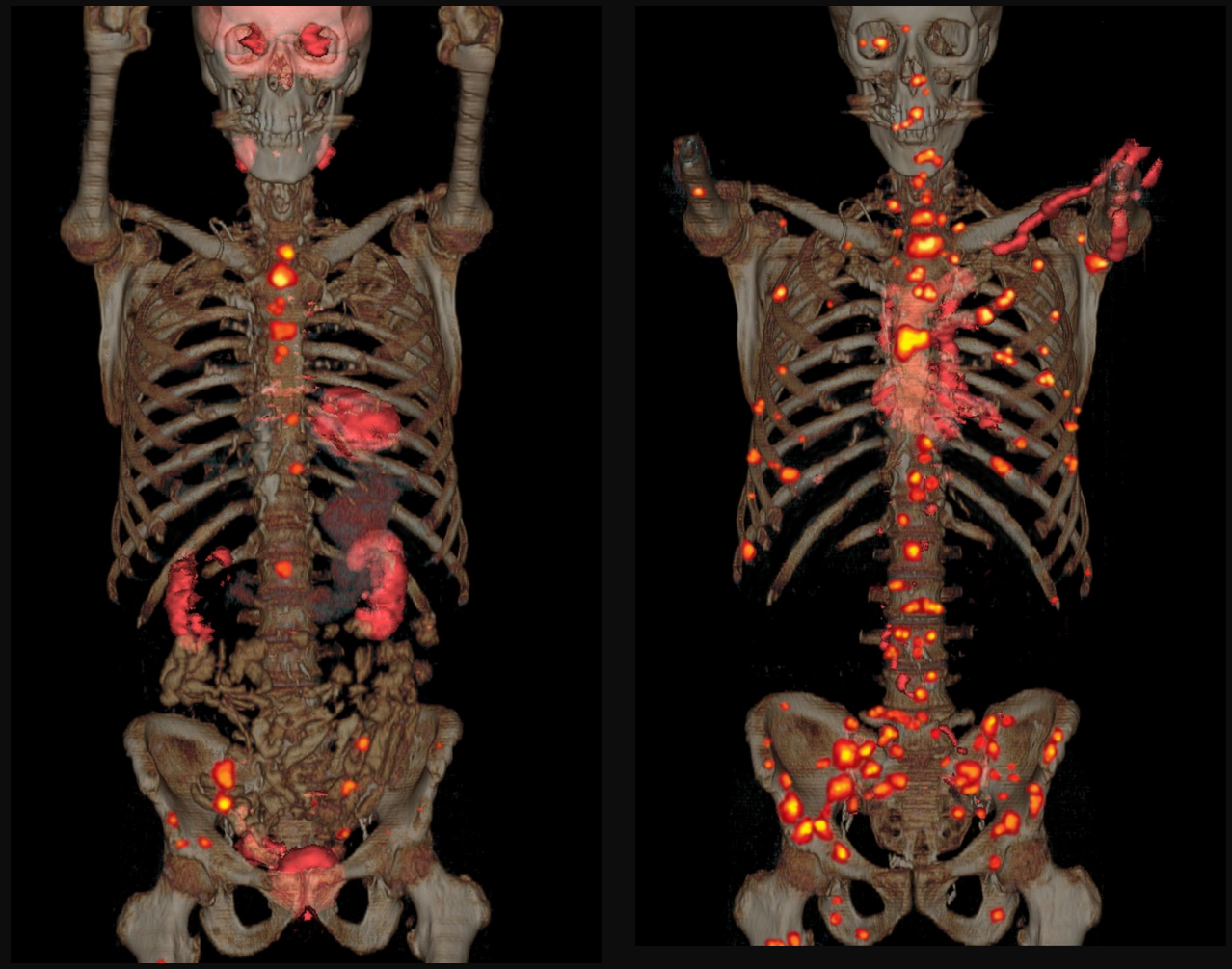
FDG and FDHT PET/CT in the same Pca patient



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Risk Stratification

- No two prostate cancers and no two prostate cancer patients are alike.
- It is the basis for all treatment decisions
- Multiple factors are considered including grade, stage, PSA, cancer volume, and genomics as well as patient characteristics

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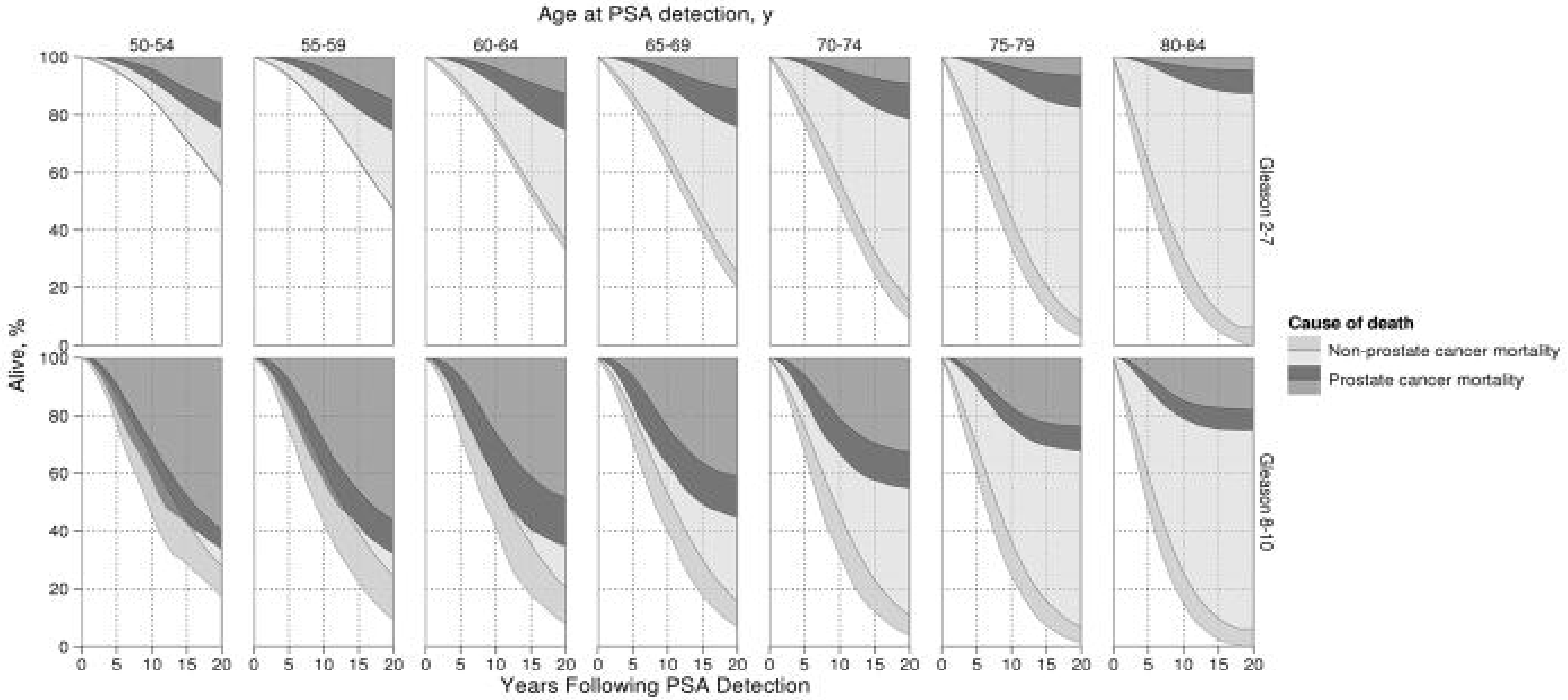
The Importance of Risk Stratification

MORTALITY OF UNTREATED PROSTATE CANCER BY AGE AND GRADE –



Gulati, Cancer Epidemiol Biomarkers Prev. 2011 May; 20(5): 740–750

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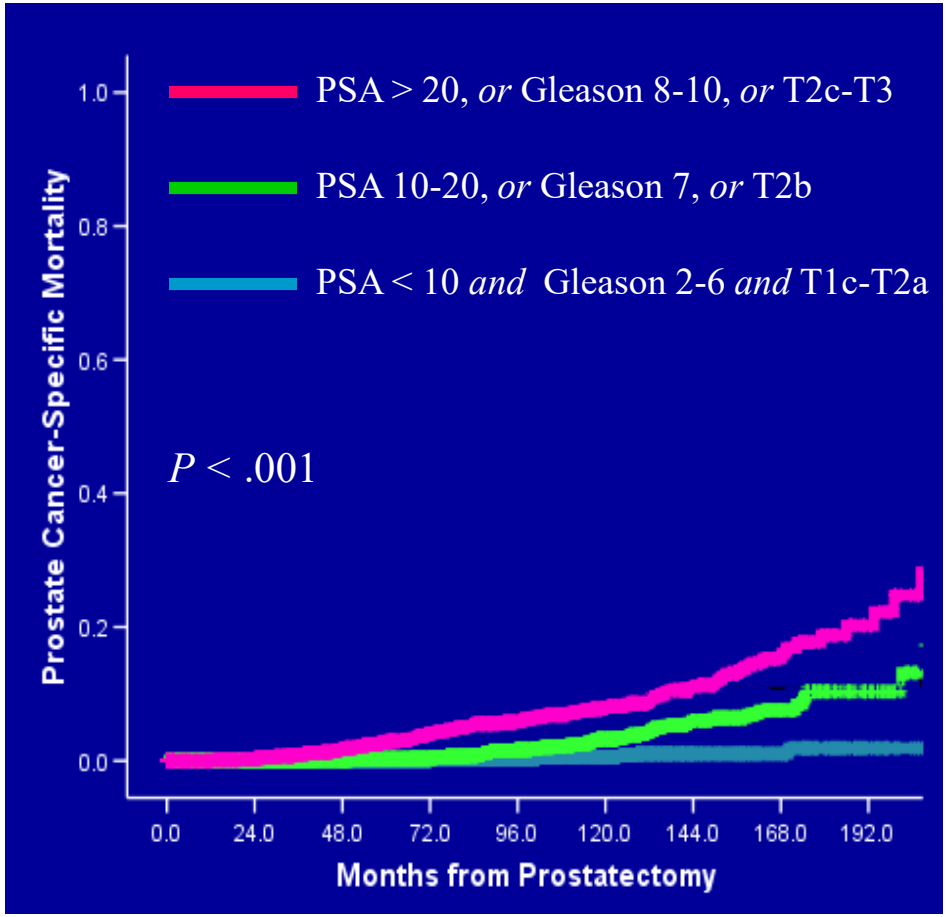
Basic Risk Assesment



From Stephenson A et al. JCO 2009; 27:4300.

*AUA Prostate Cancer Guidelines, 2008

Risk Group	Pts	PCa Death
High	1816	19%
Intermediate	3327	10%
Low	4338	2%

Majority of deaths were among high risk group, but the risk of death from PCa (19%) was still less than from other causes (31%).

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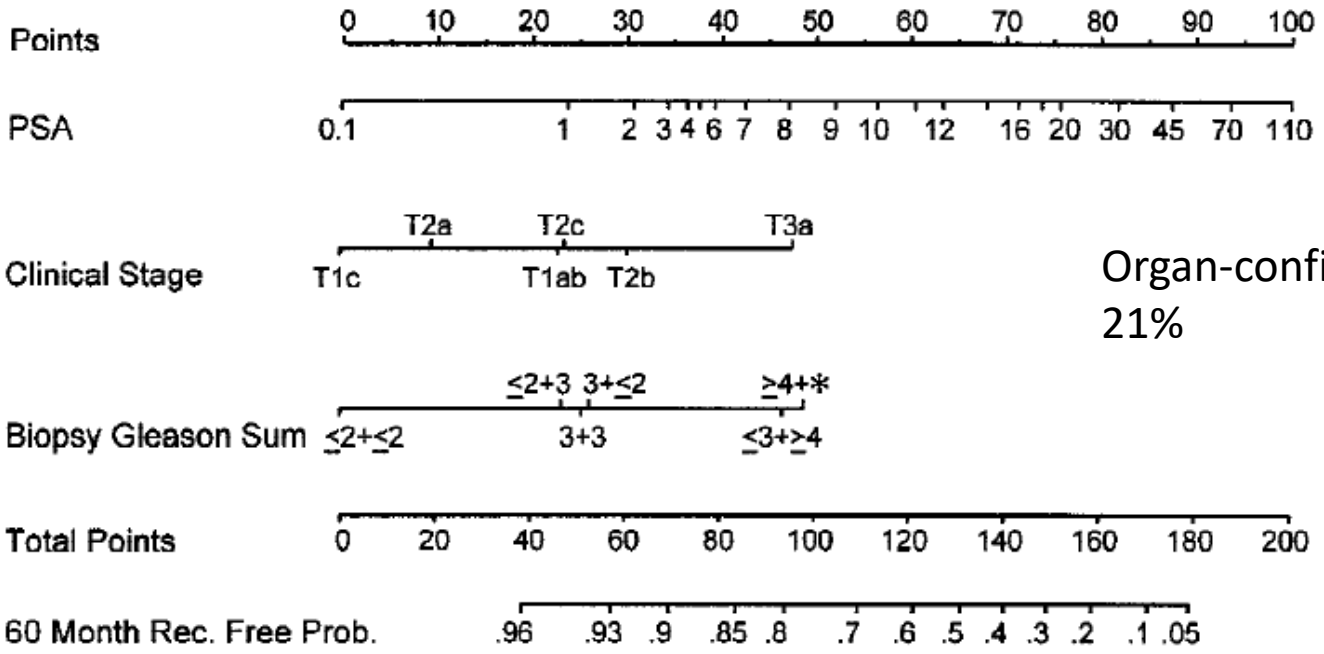
Preoperative nomogram for prostate cancer recurrence



Organ-confined
21%

Instructions for Physician: Locate the patient's PSA on the **PSA** axis. Draw a line straight upwards to the **Points** axis to determine how many points towards recurrence the patient receives for his PSA. Repeat this process for the **Clinical Stage** and **Biopsy Gleason Sum** axes, each time drawing straight upward to the **Points** axis. Sum the points achieved for each predictor and locate this sum on the **Total Points** axis. Draw a line straight down to find the patient's probability of remaining recurrence free for 60 months assuming he does not die of another cause first.

Note: This nomogram is not applicable to a man who is not otherwise a candidate for radical prostatectomy. You can use this only on a man who has already selected radical prostatectomy as treatment for his prostate cancer.

Instruction to Patient: "Mr. X, if we had 100 men exactly like you, we would expect between <predicted percentage from nomogram - 10%> and <predicted percentage + 10%> to remain free of their disease at 5 years following radical prostatectomy, and recurrence after 5 years is very rare."

Kattan MW et al. *JNCI* 1997;90:766-71

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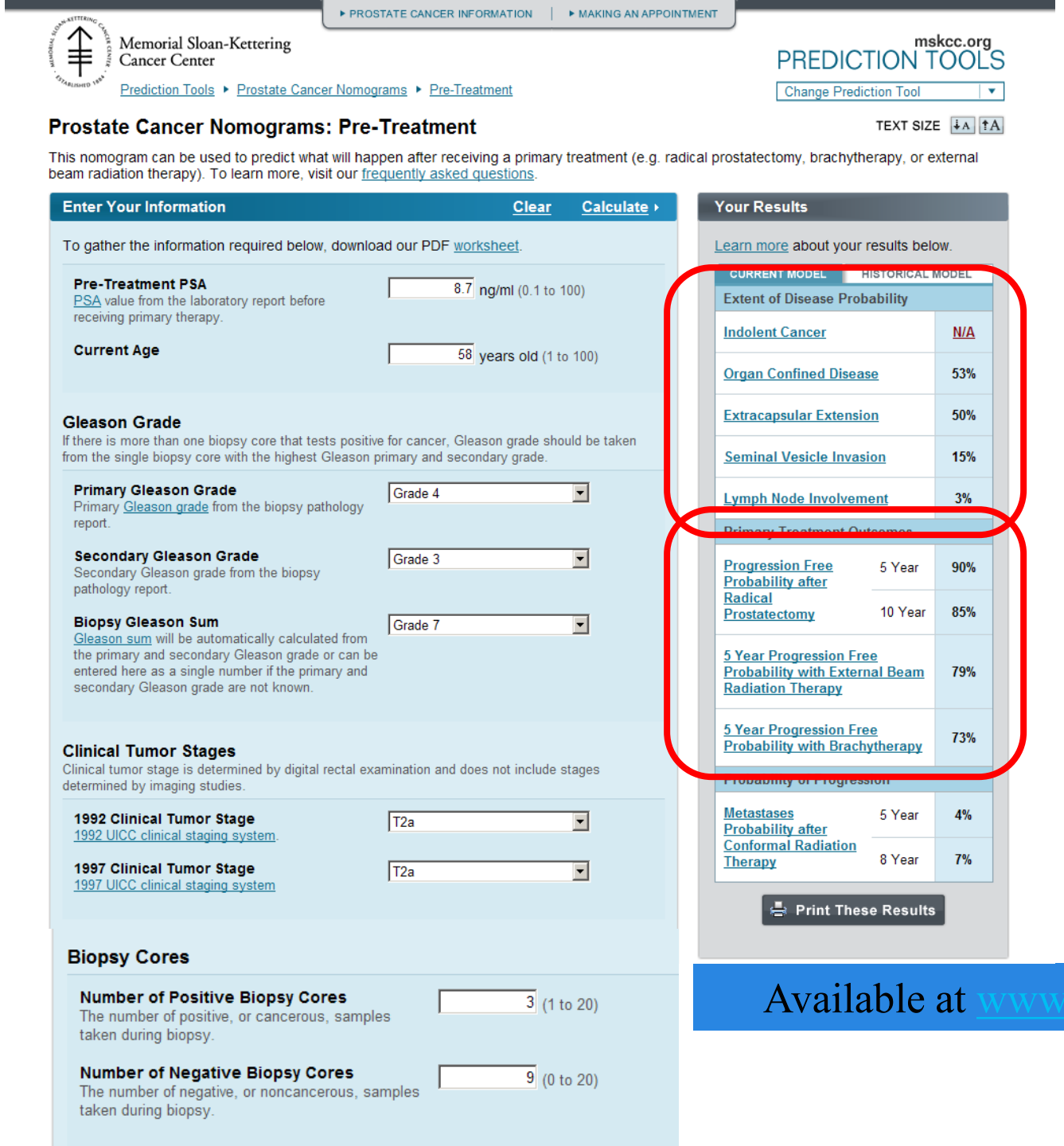

Predicition Tools at MSKCC.org

Uses published nomograms to make pretreatment and postoperative predictions for many cancers.

For prostate cancer, predicts likelihood of indolent cancer, pathologic stage, long term recurrence-free probabilities and risk of dying of prostate cancer after surgery or radiation therapy based on clinical and pathological features of the patient and the cancer.

Available at www.mskcc.org/nomograms

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INITIAL RISK STRATIFICATION AND STAGING WORKUP FOR CLINICALLY LOCALIZED DISEASE

Risk group	Clinical/pathologic features			Imaging[h,i]	Germline testing	Molecular and biomarker analysis of tumor[l]	Initial therapy
Very low[f]	• T1c AND • Grade Group 1 AND • PSA <10 ng/mL AND • Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core[g] AND • PSA density <0.15 ng/mL/g			Not indicated	Recommended if family history positive or intraductal histology See PROS-1	Not indicated	See PROS-4
Low[f]	• T1-T2a AND • Grade Group 1 AND • PSA <10 ng/mL			Not indicated	Recommended if family history positive or intraductal histology See PROS-1	Consider if life expectancy ≥10y[m]	See PROS-5
Intermediate[f]	Has no high- or very-high-risk features and has one or more intermediate risk factors (IRF): • T2b-T2c • Grade Group 2 or 3 • PSA 10–20 ng/mL	Favorable intermediate	• 1 IRF and • Grade Group 1 or 2 and • <50% biopsy cores positive[g]	• Bone imaging[j]: not recommended for staging • Pelvic ± abdominal imaging: recommended if nomogram predicts >10% probability of pelvic lymph node involvement • If regional or distant metastases are found, see PROS-9	Recommended if family history positive or intraductal histology See PROS-1	Consider if life expectancy ≥10y[m]	See PROS-6
		Unfavorable intermediate	• 2 or 3 IRFs and/or • Grade Group 3 and/or • ≥50% biopsy cores positive[g]	• Bone imaging[j]: recommended if T2 and PSA >10 ng/mL • Pelvic ± abdominal imaging: recommended if nomogram predicts >10% probability of pelvic lymph node involvement • If regional or distant metastases are found, see PROS-9	Recommended if family history positive or intraductal histology See PROS-1	Not routinely recommended	See PROS-7
High	• T3a OR • Grade Group 4 or Grade Group 5 OR • PSA >20 ng/mL			• Bone imaging[j]: recommended • Pelvic ± abdominal imaging: recommended if nomogram predicts >10% probability of pelvic lymph node involvement • If regional or distant metastases are found, see PROS-9	Recommended[c,k]	Not routinely recommended	See PROS-8
Very high	• T3b-T4 OR • Primary Gleason pattern 5 OR • >4 cores with Grade Group 4 or 5			• Bone imaging[j]: recommended • Pelvic ± abdominal imaging: recommended if nomogram predicts >10% probability of pelvic lymph node involvement • If regional or distant metastases are found, see PROS-9	Recommended[c,k]	Not routinely recommended	See PROS-8

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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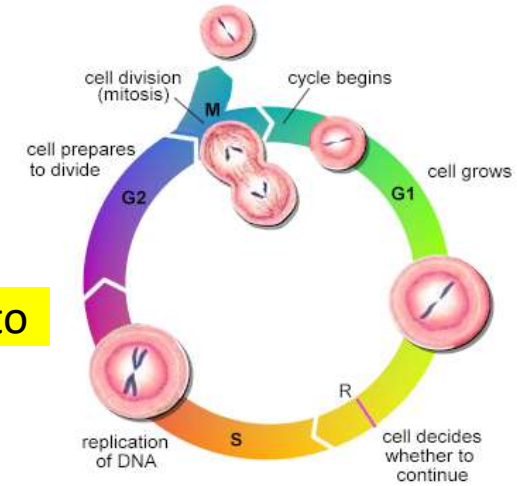
Cell cycle progression (CCP) profile

(Myriad *Prolaris*®)

Cuzick J et al. *Lancet Oncol* 2011;12:245-55

- RNA expression profile of 31 cell cycle progression (CCP) genes and 15 housekeeper genes
- Each 1-unit change in CCP score corresponds roughly to a doubling of risk
- Evaluated in tumor samples from needle biopsy, TURP and RP
- Adds independent prognostic information to Gleason grade and PSA, and to models that include clinical stage, grade, PSA and extent of cancer
- Predicts risk of biochemical recurrence (BCR), metastasis, and death from cancer



Function	Genes
DNA repair/replication	*FOXM1, KIAA0101, RRM2, TOP2A, TK1, RAD54L,PTTG1, RAD51C, ORC6*
Microtubule function/stability	*CDC20, CDCA8, KIF11, NUSAP1, CENPF, ASPM, DLGAP5, PLK1, C18orf24*
Cell cycle regulators	*CDKN3, CDC2, CDCA3, BUB1B, PBK, DTL*
Chromosome structure	*ASF1B, MCM10, CENPM*
Cytokinesis	*KIF20A, PRC1, CEP55*

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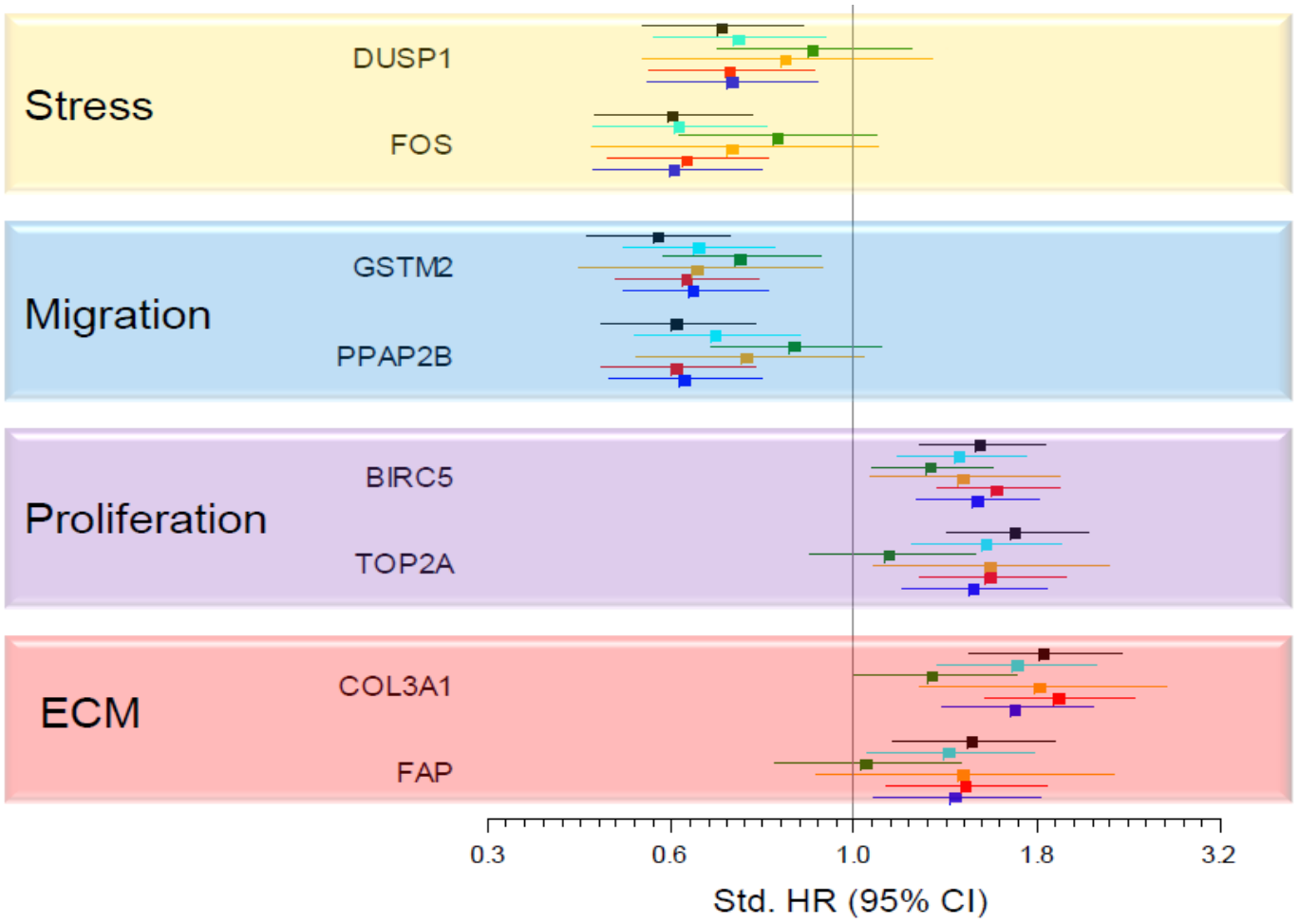
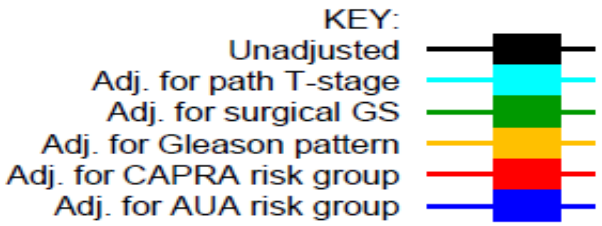
OncotypeDx gene expression profile

Multiple gene groups add prognostic value beyond clinical and pathologic covariates





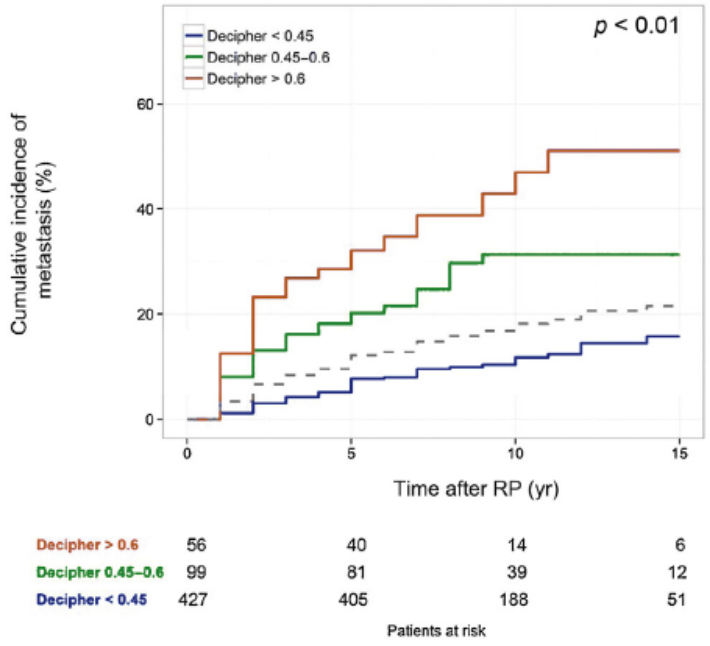
Standardized hazard ratio is the hazard ratio per 1 standard deviation increase in gene expression

Falzarano et al.

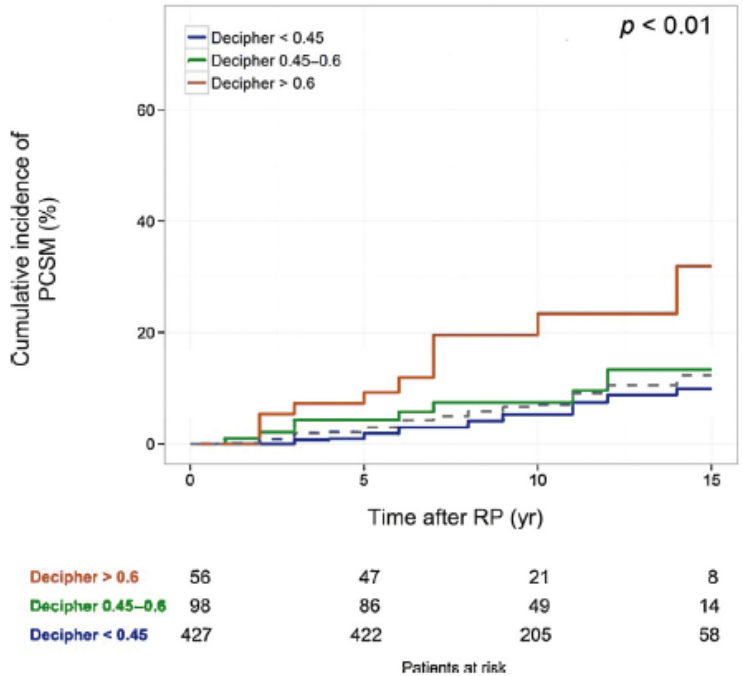
Presented at 2011 United States and Canadian Academy of Pathology Annual Meeting, San Antonio, TX

Decipher GS: Predicting risk of metastases after radical prostatectomy (RP)

Time to metastasis



Time to death from prostate cancer



Cumulative incidence curves over time stratified by Decipher score for metastasis (left) and PCSM (right).

Ross AE et al. Eur Urol 2016;69:157-65

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Integrative clinical genomics of advanced prostate cancer

Cell

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Volume 161, Issue 5, p1215–1228, 21 May 2015

Resource

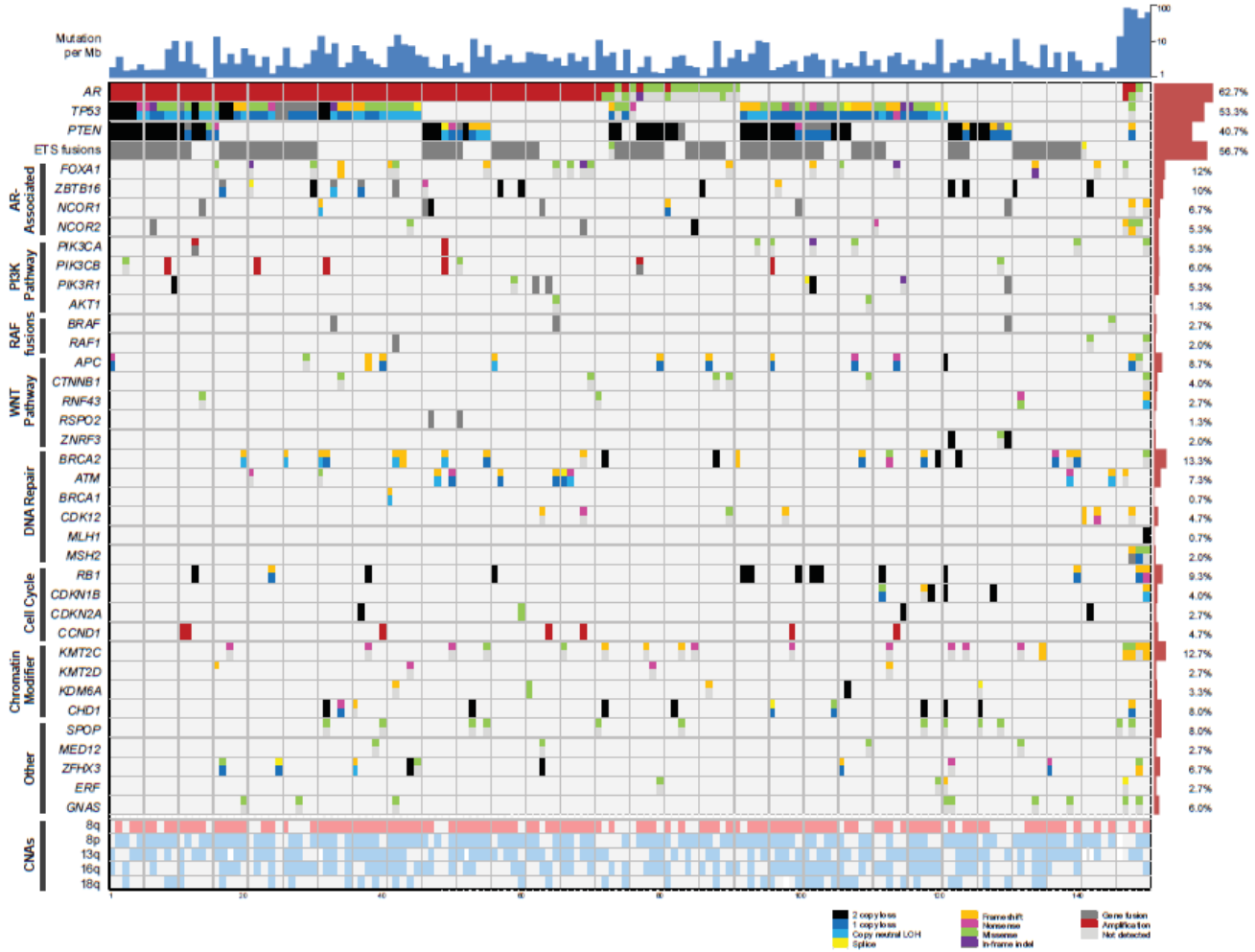
Switch to Standard View

Integrative Clinical Genomics of Advanced Prostate Cancer

Dan Robinson[43], Eliezer M. Van Allen[43], Yi-Mi Wu, Nikolaus Schultz, Robert J. Lonigro, Juan-Miguel Mosquera, Bruce Montgomery, Mary-Ellen Taplin, Colin C. Pritchard, Gerhardt Attard, Himisha Beltran, Wassim Abida, Robert K. Bradley, Jake Vinson, Xuhong Cao, Pankaj Vats, Lakshmi P. Kunju, Maha Hussain, Felix Y. Feng, Scott A. Tomlins, Kathleen A. Cooney, David C. Smith, Christine Brennan, Javed Siddiqui, Rohit Mehra, Yu Chen, Dana E. Rathkopf, Michael J. Morris, Stephen B. Solomon, Jeremy C. Durack, Victor E. Reuter, Anuradha Gopalan, Jianjiong Gao, Massimo Loda, Rosina T. Lis, Michaela Bowden, Stephen P. Balk, Glenn Gaviola, Carrie Sougnez, Manaswi Gupta, Evan Y. Yu, Elahe A. Mostaghel, Heather H. Cheng, Hyojeong Mulcahy, Lawrence D. True, Stephen R. Plymate, Heidi Dvinge, Roberta Ferraldeschi, Penny Flohr, Susana Miranda, Zafeiris Zafeiriou, Nina Tunariu, Joaquin Mateo, Raquel Perez-Lopez, Francesca Demichelis, Brian D. Robinson, Marc Schiffman, David M. Nanus, Scott T. Tagawa, Alexandros Sigaras, Kenneth W. Eng, Olivier Elemento, Andrea Sboner, Elisabeth I. Heath, Howard I. Scher, Kenneth J. Pienta, Philip Kantoff[44], Johann S. de Bono[44], Mark A. Rubin[44], Peter S. Nelson[44], Levi A. Garraway[44], Charles L. Sawyers[44], Arul M. Chinnaiyan[44]

[43] Co-first author

[44] Co-senior author



Courtesy of Wassim Abida, MD

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Disease Localization -
Intraoperative real-time molecular imaging:

will it decrease +SM, increase precision of PLND, improve recovery of function?

TECHNICAL REPORTS

nature medicine

Intraoperative tumor-specific fluorescence imaging in ovarian cancer by folate receptor-α targeting: first in-human results

Gooitzen M van Dam[1], George Themelis[2], Lucia M A Crane[1], Niels J Harlaar[1,2], Rick G Pleijhuis[1], Wendy Kelder[1], Athanasios Sarantopoulos[2], Johannes S de Jong[1], Henriette J G Arts[3], Ate G J van der Zee[3], Joost Bart[4], Philip S Low[2] & Vasilis Ntziachristos[2]

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PNAS

Surgery with molecular fluorescence imaging using activatable cell-penetrating peptides decreases residual cancer and improves survival

Quyen T. Nguyen[a], Emilia S. Olson[b,c], Todd A. Aguilera[b,c], Tao Jiang[b,d], Miriam Scadeng[e], Lesley G. Ellies[f], and Roger Y. Tsien[b,d,1]

Ann Surg Oncol (2009) 16:2943–2952
DOI 10.1245/s10434-009-0594-2

Annals of SURGICAL ONCOLOGY

ORIGINAL ARTICLE – TRANSLATIONAL RESEARCH AND BIOMARKERS

The FLARE™ Intraoperative Near-Infrared Fluorescence Imaging System: A First-in-Human Clinical Trial in Breast Cancer Sentinel Lymph Node Mapping

Susan L. Troyan, MD[1], Vida Kianzad, PhD[2], Summer L. Gibbs-Strauss, PhD[2], Sylvain Gioux, MEng[2], Aya Matsui, MD, PhD[2], Rafiou Oketokoun, MEng[2,3], Long Ngo, PhD[4], Ali Khamene, PhD[3], Fred Azar, PhD[3], and John V. Frangioni, MD, PhD[2,5]

[1]Breast Care Center, Department of Surgery, Beth Israel Deaconess Medical Center, Boston, MA; [2]Division of Hematology/Oncology, Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA; [3]Siemens Corporate Research, Princeton, NJ; [4]Division of General Medicine, Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA; [5]Department of Radiology, Beth Israel Deaconess Medical Center, Boston, MA

LETTERS

nature biotechnology

Fluorescent peptides highlight peripheral nerves during surgery in mice

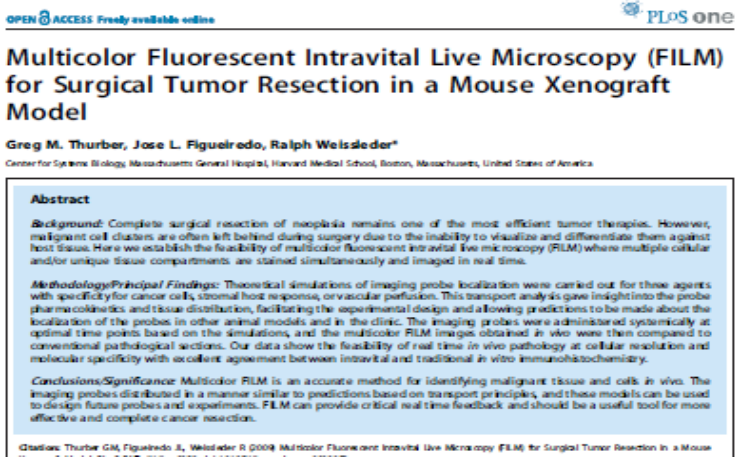
Michael A Whitney[1], Jessica L Crisp[2], Linda T Nguyen[3], Beth Friedman[1], Larry A Gross[4], Paul Steinbach[4], Roger Y Tsien[1,2,4] & Quyen T Nguyen[3]

Nerve preservation is an important goal during surgery because accidental transection or injury leads to significant morbidity,

visualization of the optic or other superficial nerves and may not be generally applicable for viewing nerves in a surgical setting.

Current methods for nerve labeling during surgery depend on retrograde or anterograde tracing of individual axonal tracts using fluorescent dyes[9–12]. The dyes are applied either to the innervation target and travel in a retrograde fashion to label the innervating nerve fibers or directly to identified nerves and label nerve fibers in both anterograde and retrograde directions. Local injections have the drawback of only labeling one nerve fiber tract at a time and that axonal labeling is limited. Axonal transport is relatively slow and it can take days to label a single human nerve. Furthermore, the direct injection of fluorescent dyes contaminates the surgical site with excess fluorescent dyes and may be damaging to the target organs or nerve of interest.

In this study, we describe the development of peptides by phage display[13] that preferentially bind to peripheral nerve tissue compared to adjacent non-nerve tissue after systemic administration.



OPEN ACCESS Freely available online

PLoS one

Multicolor Fluorescent Intravital Live Microscopy (FILM) for Surgical Tumor Resection in a Mouse Xenograft Model

Greg M. Thurber, Jose L. Figueiredo, Ralph Weissleder*

Center for Systems Biology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, United States of America

Abstract

Background: Complete surgical resection of neoplasia remains one of the most efficient tumor therapies. However, malignant cell clusters are often left behind during surgery due to the inability to visualize and differentiate them against host tissue. Here we establish the feasibility of multicolor fluorescent *intravital* live microscopy (FILM) where multiple cellular and/or unique tissue compartments are stained simultaneously and imaged in real time.

Methodology/Principal Findings: Theoretical simulations of imaging probe localization were carried out for three agents with specificity for cancer cells, stromal host response, or vascular perfusion. This transport analysis gave insight into the probe pharmacokinetics and tissue distribution, facilitating the experimental design and allowing predictions to be made about the localization of the probes in other animal models and in the clinic. The imaging probes were administered systemically at optimal time points based on the simulations, and the multicolor FILM images obtained *in vivo* were then compared to conventional pathological sections. Our data show the feasibility of real time *in vivo* pathology at cellular resolution and molecular specificity with excellent agreement between intravital and traditional *in vitro* immunohistochemistry.

Conclusions/Significance: Multicolor FILM is an accurate method for identifying malignant tissue and cells *in vivo*. The imaging probes distributed in a manner similar to predictions based on transport principles, and these models can be used to design future probes and experiments. FILM can provide critical real time feedback and should be a useful tool for more effective and complete cancer resection.

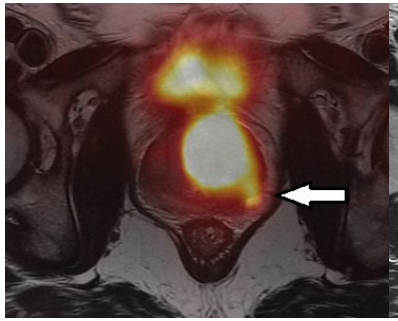
Citation: Thurber GM, Figueiredo JL, Weissleder R (2009) Multicolor Fluorescent Intravital Live Microscopy (FILM) for Surgical Tumor Resection in a Mouse

European Association of Urology

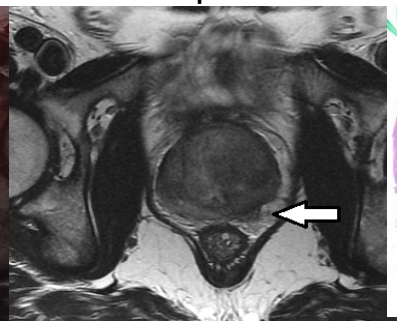
Prospective Study of the Radiolabeled GRPR Antagonist BAY86-7548 for Positron Emission Tomography/Computed Tomography Imaging of Newly Diagnosed Prostate Cancer

Large, high grade primary tumor with ECE

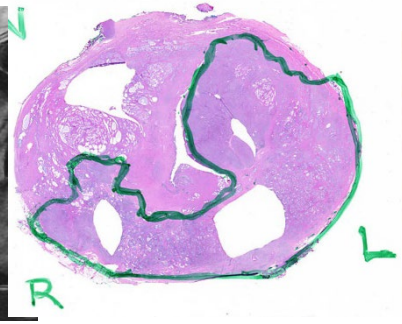
Pre-op PET imaging



Pre-op MRI

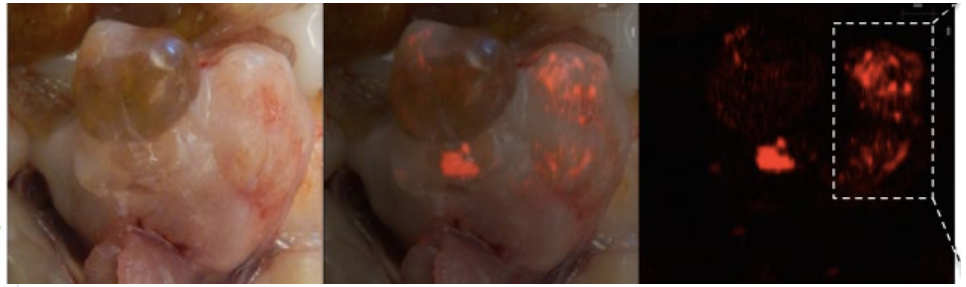


RP section

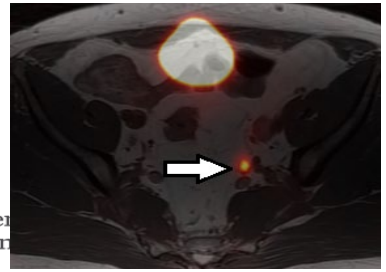


Intraop fluorescence imaging

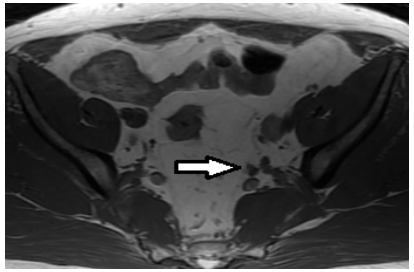
Intraoperative imaging to detect surgical margins



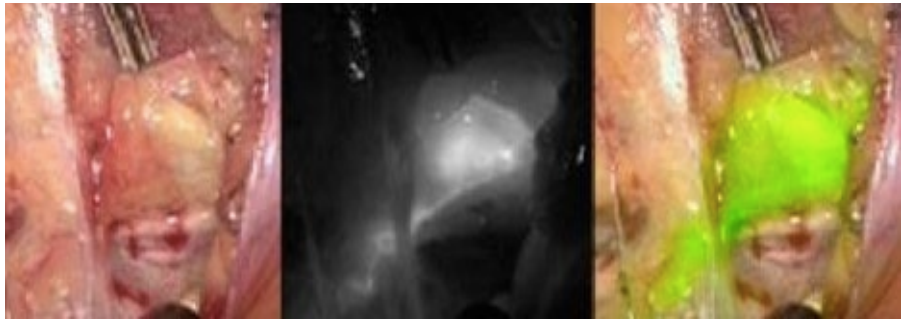
Deep obturator LN met detected with PET



Normal LN on MRI

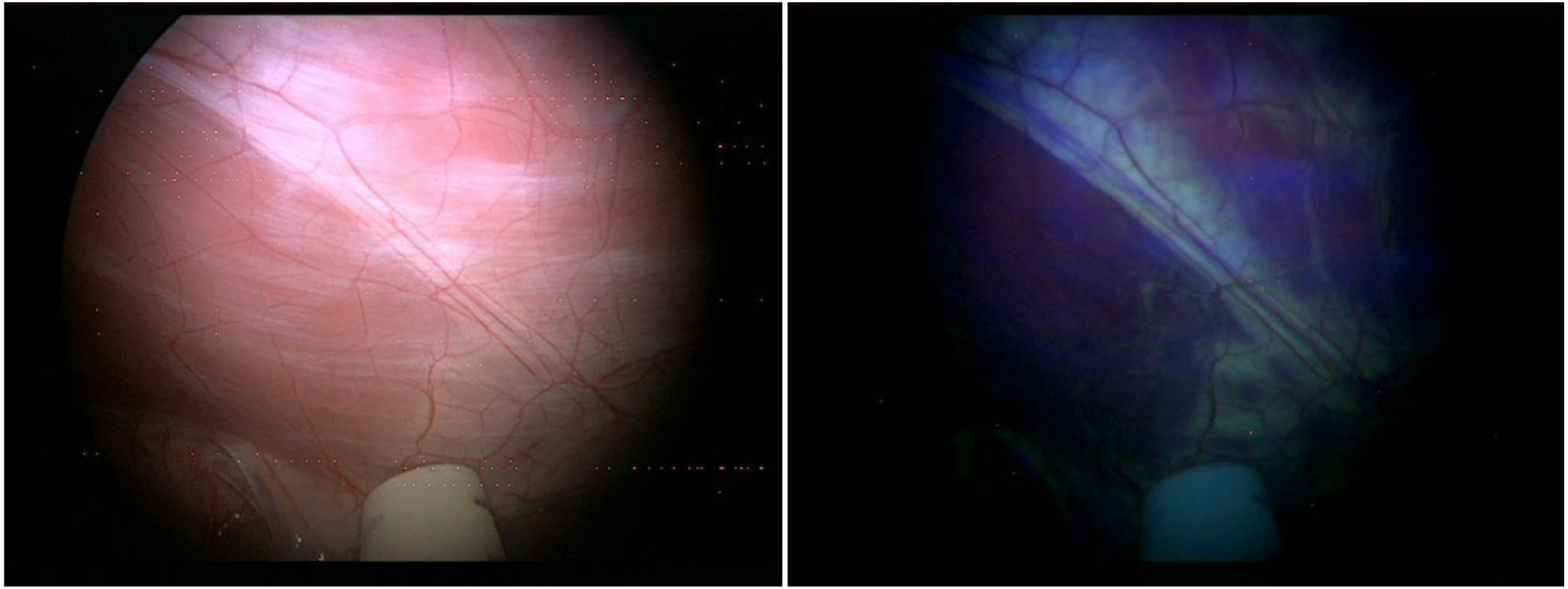


Intraoperative fluorescence imaging to guide LN dissection



Enhanced visualization of nerves during surgery

with a small molecule fluorescent probe, *illuminaire-1,*
begins 5 min after injection and lasts for >3 hr.



Courtesy of Dr. Tim Donahue, MSKCC and Illuminaire, Inc.