Prima Sessione **NUOVO SISTEMA DI GRADING**

Moderatori ***Matteo Brunelli, Giuseppe Zamboni***

14,30 ILLUSTRAZIONE del nuovo sistema di Grading **Enrico Munari**

14,45 Impatto nella pratica clinica. *Confronto tra esperti:*
Urologo **Alberto Lapini**
Oncologo **Claudia Caserta**
Radioterapista **Stefano Arcangeli**

Con il Patrocinio di

AIOM Associazione Italiana di Oncologia Medica

AIRO Associazione Italiana Radioterapia e Oncologia clinica

IRCCS Sacro Cuore Don Calabria
Cancer Care Center
Negrar - Verona

2° Convegno Nazionale

IL TEAM INTERDISCIPLINARE NEL CARCINOMA DELLA PROSTATA

NEGRAR DI VALPOLICELLA 6-7 DICEMBRE 2019

Sala Perez - IRCCS Ospedale Sacro Cuore Don Calabria

Coordinatori: STEFANIA GORI - FILIPPO ALONGI - STEFANO CAVALLERI

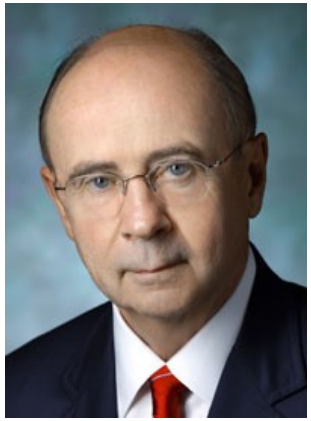
let's start at the beginning.

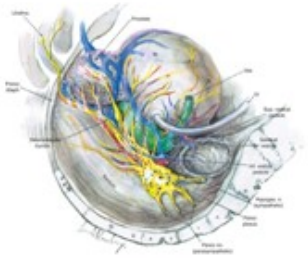
The Prostate 4:473–485 (1983)

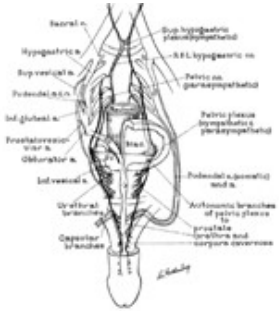
Radical Prostatectomy With Preservation of Sexual Function: Anatomical and Pathological Considerations

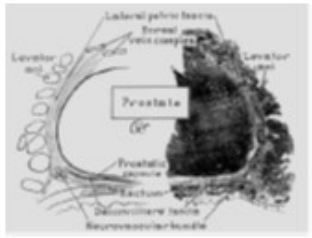
Patrick C. Walsh, Herbert Lepor, and Joseph C. Eggleston

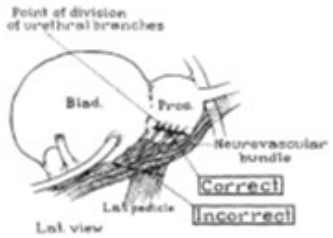
James Buchanan Brady Urological Institute, Johns Hopkins Hospital, and the Departments of Urology and Pathology, Johns Hopkins University School of Medicine, Baltimore

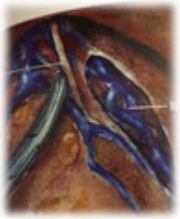












Stage A, tumor not palpable

Stage A 1 - well to moderately well differentiated carcinoma (Gleason grade 2-7) involving less than 5% of the resected specimen.
Stage A2 - poorly differentiated carcinoma (Gleason 8- 10) or any tumor involving more than 5% of the resected specimen

Stage B, tumor confined to the prostate

Stage C, tumor extending locally beyond the prostate

Stage D, tumor with metastases

The Role of Radical Prostatectomy in the Management of Prostatic Cancer

PATRICK C. WALSH, MD, AND HERBERT LEPOR, MD

Cancer 60:526–537, 1987.

IDEAL CANDIDATES FOR RADICAL PROSTATECTOMY

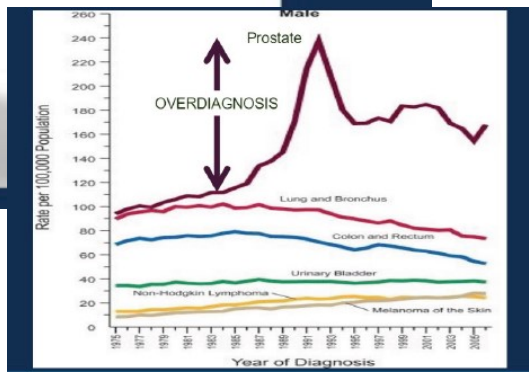
Young men with **Stage A1** prostatic
However, it must be recognized that this may also be over treatment for many patients who would not experience progression.

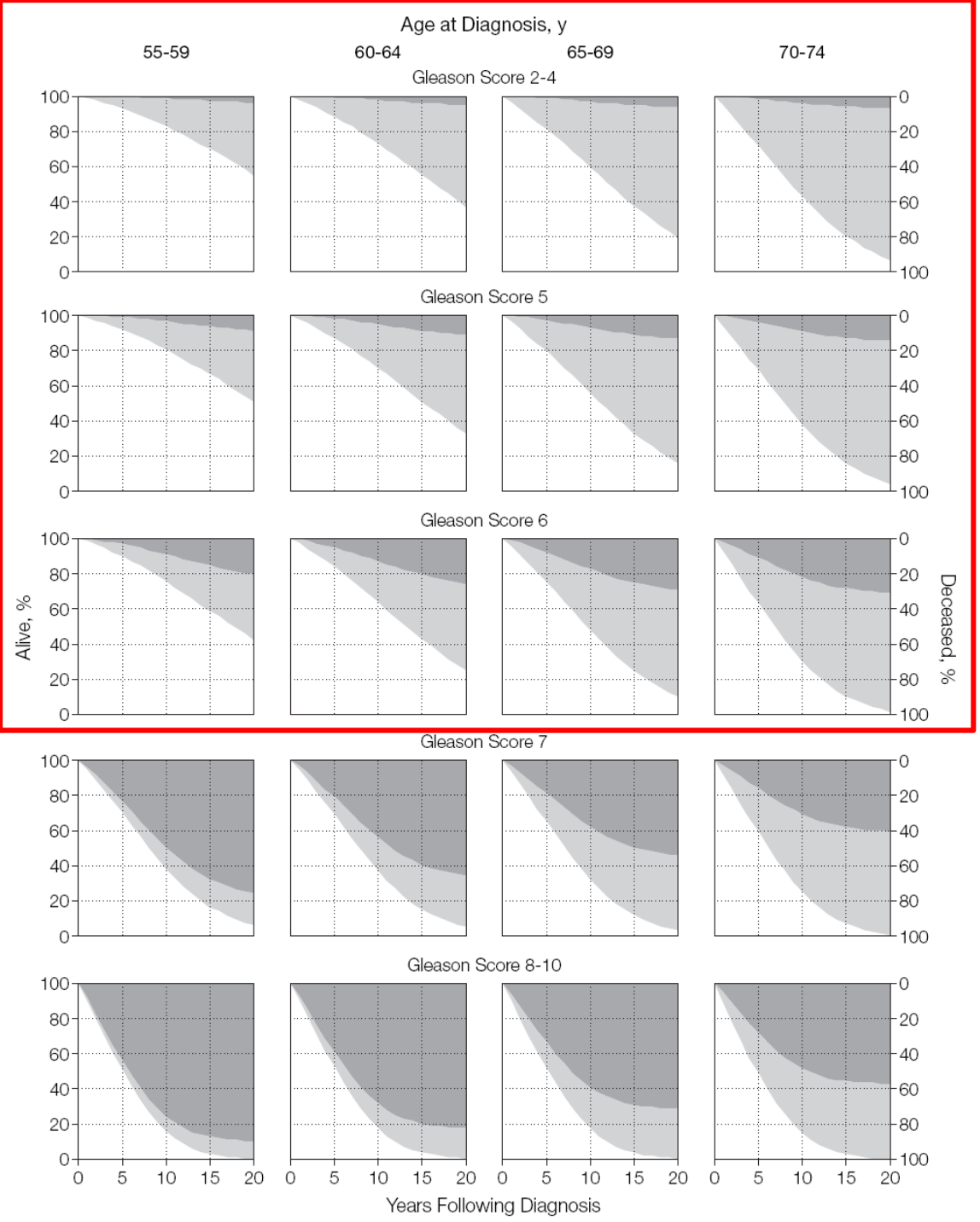
Stage A2 prostatic carcinoma with some doubts because :
(I) secondary radical prostatectomy was difficult;
(2) patients often had more advanced disease than previously recognized;
(3) the incidence of incontinence and impotence in this setting was unacceptable.

Patients with **Stage B 1** disease are ideal candidates for radical prostatectomy

All patients with Stage B2 disease are not ideal candidates for treatment with radical prostatectomy because of the high incidence of extraprostatic involvement

The PSA controversy





20-Year Outcomes Following Conservative Management of Clinically Localized Prostate Cancer

Albertsen et al
JAMA 2005; 293:2095-2101

Survival
Non–Prostate Cancer Mortality
Prostate Cancer Mortality

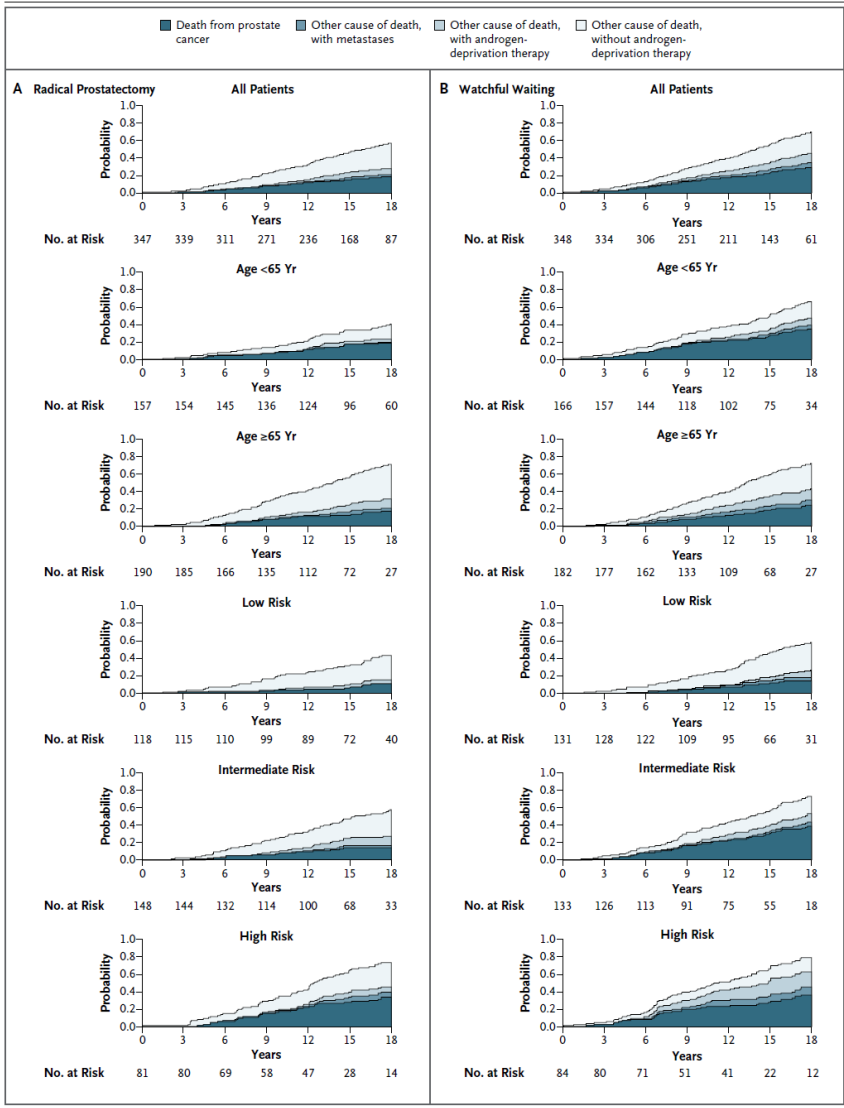
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Radical Prostatectomy or Watchful Waiting in Early Prostate Cancer

Anna Bill-Axelson, M.D., Ph.D., Lars Holmberg, M.D., Ph.D., Hans Garmo, Ph.D., Jennifer R. Rider, Sc.D., Kimmo Taari, M.D., Ph.D., Christer Busch, M.D., Ph.D., Stig Nordling, M.D., Ph.D., Michael Häggman, M.D., Ph.D., Swen-Olof Andersson, M.D., Ph.D., Anders Spångberg, M.D., Ph.D., Ove Andrén, M.D., Ph.D., Juni Palmgren, Ph.D., Gunnar Steineck, M.D., Ph.D., Hans-Olov Adami, M.D., Ph.D., and Jan-Erik Johansson, M.D., Ph.D.

N ENGL J MED 370;10 NEJM.ORG MARCH 6, 2014



Scandinavian Prostate Cancer Group
Study Number 4 (**SPCG-4**)

The benefit of surgery with respect to death from prostate cancer was largest in men younger than 65 years of age (relative risk, 0.45) and in those with intermediate-risk prostate cancer (relative risk, 0.38). However, radical prostatectomy was associated with a reduced risk of metastases among older men (relative risk, 0.68; P = 0.04).

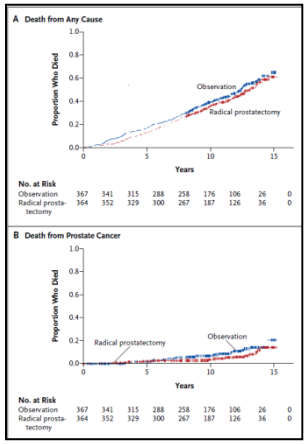
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 19, 2012 VOL. 367 NO. 3

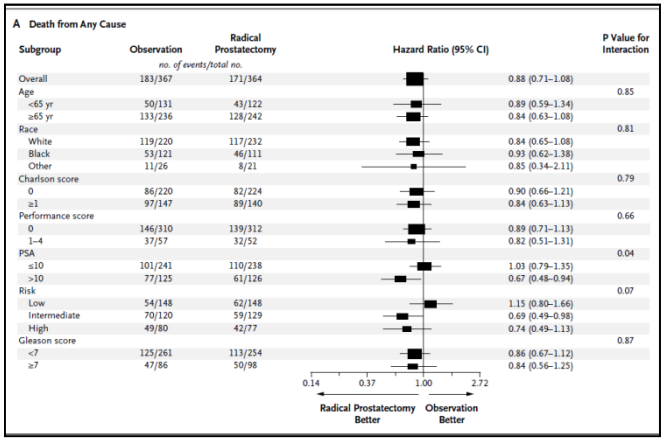
Radical Prostatectomy versus Observation for Localized Prostate Cancer

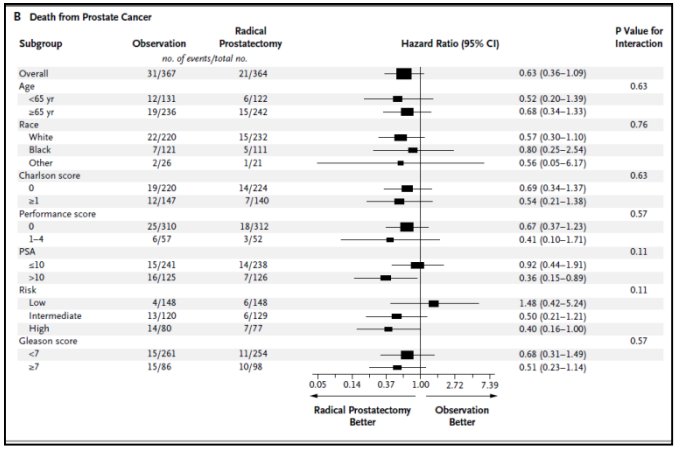
Timothy J. Wilt, M.D., M.P.H., Michael K. Brawer, M.D., Karen M. Jones, M.S., Michael J. Barry, M.D., William J. Aronson, M.D., Steven Fox, M.D., M.P.H., Jeffrey R. Gingrich, M.D., John T. Wei, M.D., Patricia Gilhooly, M.D., B. Mayer Grob, M.D., Imad Nsouli, M.D., Padmini Iyer, M.D., Ruben Cartagena, M.D., Glenn Snider, M.D., Claus Roehrborn, M.D., Ph.D., Roohollah Sharifi, M.D., William Blank, M.D., Parikshit Pandya, M.D., Gerald L. Andriole, M.D., Daniel Culkin, M.D., and Thomas Wheeler, M.D., for the Prostate Cancer Intervention versus Observation Trial (PIVOT) Study Group

N ENGL J MED 367;3 NEJM.ORG JULY 19, 2012



In conclusion, our study showed that, as compared with observation, radical prostatectomy did not significantly reduce all-cause or prostate-cancer mortality through at least 12 years among men with clinically localized prostate cancer that had been diagnosed in the era of PSA testing. Absolute differences in mortality between the study groups were less than 3 percentage points. Subgroup analyses suggested that surgery might reduce mortality among men with higher PSA values and possibly among men with higher-risk tumors, but not among men with PSA levels of 10 ng per milliliter or less or among men with low-risk tumors.





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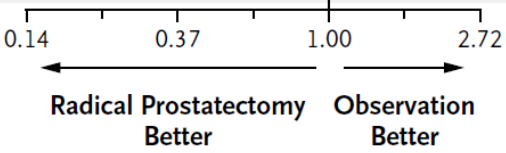
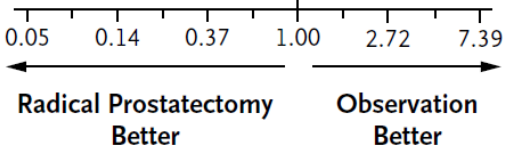
A Death from Any Cause

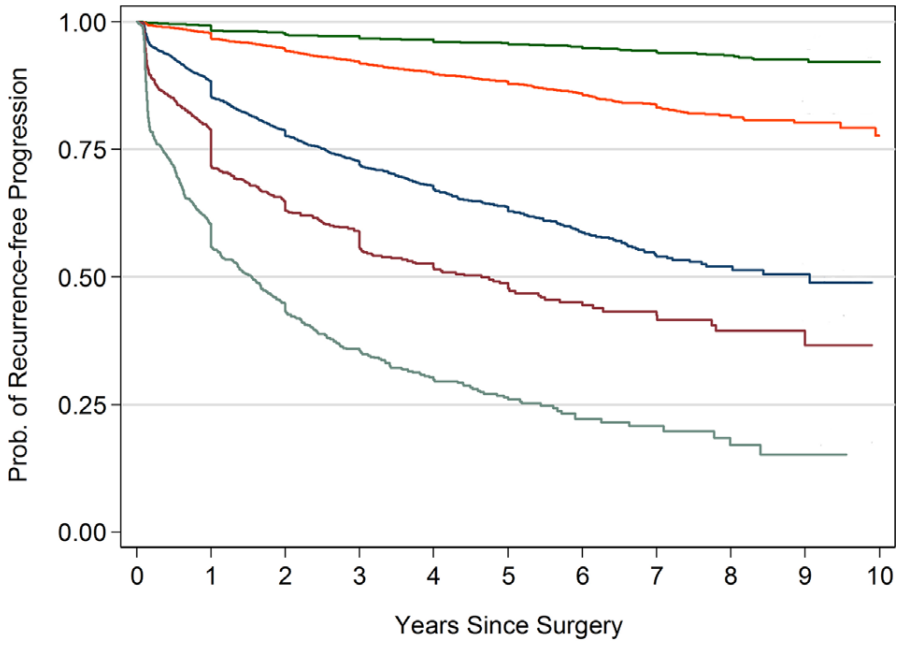
Subgroup	Observation	Radical Prostatectomy	Hazard Ratio (95% CI)	P Value for Interaction
	no. of events/total no.			
Overall	183/367	171/364	0.88 (0.71–1.08)	
Risk				0.07
Low	54/148	62/148	1.15 (0.80–1.66)	
Intermediate	70/120	59/129	0.69 (0.49–0.98)	
High	49/80	42/77	0.74 (0.49–1.13)	



B Death from Prostate Cancer

Subgroup	Observation	Radical Prostatectomy	Hazard Ratio (95% CI)	P Value for Interaction
	no. of events/total no.			
Overall	31/367	21/364	0.63 (0.36–1.09)	
Risk				0.11
Low	4/148	6/148	1.48 (0.42–5.24)	
Intermediate	13/120	6/129	0.50 (0.21–1.21)	
High	14/80	7/77	0.40 (0.16–1.00)	





"Grade Group 1 (Gleason score 3+3=6) is very homogeneous composed of individual discrete glands with an excellent prognosis. We have not observed distant metastasis or prostate cancer-specific mortality in more than 6,000 men with organ-confined, margin negative pure Gleason score 6 disease at radical prostatectomy and such man can be told that their risk of progression is approaching 0%"

Clinically Significant VS Non - signigficant prostate cancer

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.

Histopathology

Histopathology 2019, **74**, 135–145. DOI: 10.1111/his.13712

REVIEW

Defining clinically significant prostate cancer on the basis of pathological findings

Andres Matoso & Jonathan I Epstein

Departments of Pathology, Urology and Oncology, Johns Hopkins Medical Institutions, Baltimore, MD, USA

There is general agreement among experts that any tumour with adverse findings at RP should be considered to be clinically significant. Various features have been considered to be adverse, including any one of the following: Gleason score of 4 + 3 =7or higher [Grade Group (GrG) ≥ 3], non-focal EPE, seminal vesicle invasion, lymph node metastasis, or tumour volume of >2.0 cm^3 .

McNeal JE, Villers AA, Redwine EA, Freiha FS, Stamey TA.
Histologic differentiation, cancer volume, and pelvic lymph node metastasis in adenocarcinoma of the prostate. Cancer 1990; 66; 1225–1233

EAU - EANM - ESTRO - ESUR - SIOG Guidelines on

Prostate Cancer

N. Mottet (Chair), R.C.N. van den Bergh, E. Briers (Patient Representative), P. Cornford (Vice-chair), M. De Santis, S. Fanti, S. Gillessen, J. Grummet, A.M. Henry, T.B. Lam, M.D. Mason, T.H. van der Kwast, H.G. van der Poel, O. Rouvière, D. Tilki, T. Wiegel
Guidelines Associates: T. Van den Broeck, M. Cumberbatch, N. Fossati, T. Gross, M. Lardas, M. Liew, L. Moris, I.G. Schoots, P-P.M. Willemse

Multiparametric magnetic resonance imaging (mpMRI)

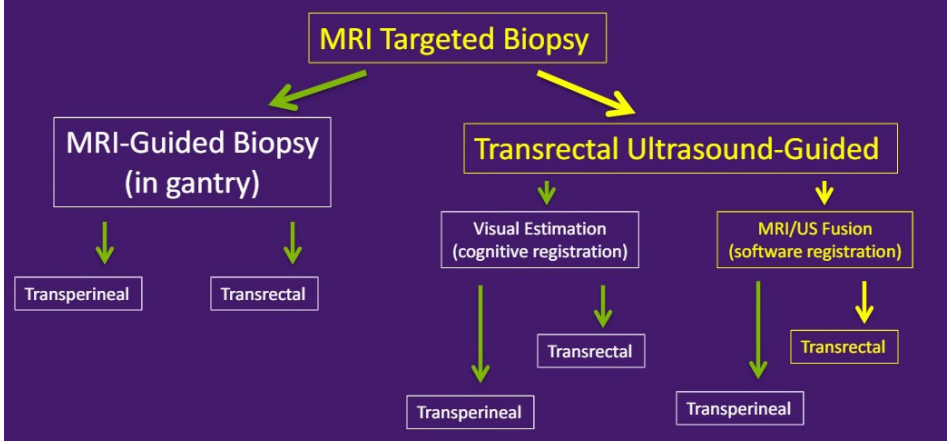
MpMRI performance in detecting ISUP grade > 2 Pca

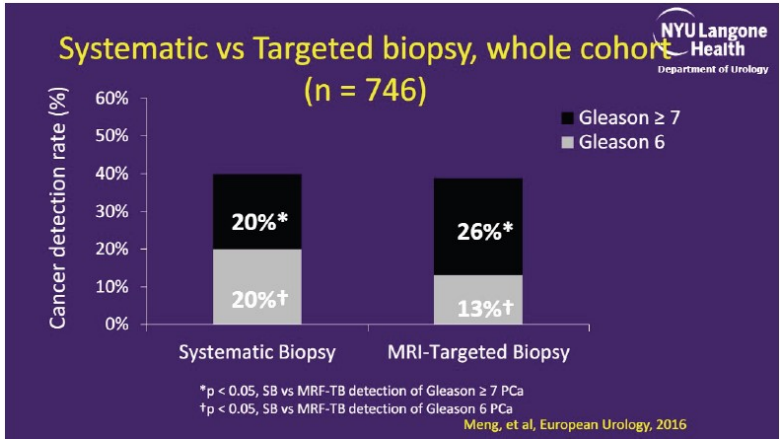
Correlation with RP specimens shows that mpMRI, associating T2 weighted imaging with at least one functional imaging technique (DWI, DCE), has good sensitivity for the detection and localisation of ISUP grade > 2 cancers

ISUP grade group	Tumour volume (mL)		
	< 0.5	0.5-2	> 2
ISUP grade 1	21-29%	43-54%	67-75%
ISUP grade 2-3	63%	82-88%	97%
ISUP grade ≥ 4	80%	93%	100%

Evolution of MRI in Urologic Practice

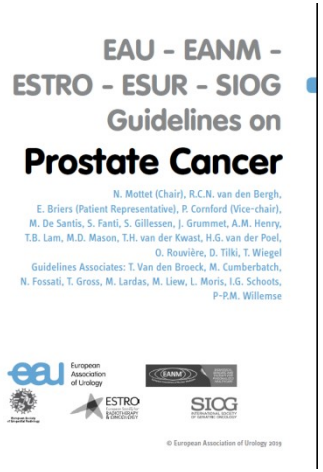
- Staging post positive biopsy
- Post-biopsy disease localization/staging
  - Previous negative biopsy
  - Active surveillance vs treatment
  - Treatment planning
- Pre-Biopsy disease localization
  - Better detection
  - Improved risk stratification





Does MRI-TBx improve the detection of ISUP grade ≥ 2 as compared to systematic biopsy?

In pooled data of 25 reports **MRI-TBx significantly outperformed systematic biopsy in detecting clinically significant (cs)PCa in patients with prior negative systematic biopsy, but not in biopsy-naïve men .**



European Association of Urology

Recommendations in biopsy naïve patients	LE	Strength rating
Perform mpMRI before prostate biopsy.	1a	Weak
When mpMRI is positive (i.e. PI-RADS ≥ 3), combine targeted and systematic biopsy.	2a	Strong
When mpMRI is negative (i.e. PI-RADS ≤ 2), and clinical suspicion of prostate cancer is low, omit biopsy based on shared decision making with the patient.	2a	Weak

Recommendations in patients with prior negative biopsy	LE	Strength rating
Perform mpMRI before prostate biopsy.	1a	Strong
When mpMRI is positive (i.e. PI-RADS ≥ 3), perform targeted biopsy only.	2a	Weak
When mpMRI is negative (i.e. PI-RADS ≤ 2), and clinical suspicion of prostate cancer is high, perform systematic biopsy based on shared decision making with the patient.	2a	Strong

Considerazioni:

mpMRI capace di identificare tumori significativi

La biopsia Fusion appare superiore alla sistematica nella dimostrazione dei tumori significativi solo alla rebiopsia

Molti studi valutano la capacità di identificare "index lesion ", concetto non ancora completamente accettato considerando la multifocalità del tumore prostatico ???

Il 3-20% dei pazienti con mpMRI negativa può presentare un tumore significativo.

Inoltre cosa da non trascurare …….

AZIENDA OSPEDALIERO-UNIVERSITARIA CAREGGI

Frequenza prestazioni ambulatoriali

7049 ES. ISTOPATOLOGICO APP. GENITALE - AGOBIOPSIA PROSTATICA e

7050 ES. ISTOPATOLOGICO APP. GENITALE - AGOBIOPSIE PROSTATICHE - MAPPING

ANNO 2018

Report 'Prestazioni 7049+7050' del file 'ARCHIVIO PRESTAZIONI AMBULATORIALI EROGATE 01-12 - GEN - DIC 2018'
Estrazione dati da archivio 'Prestazioni Ambulatoriali(Spa2)' del 29/03/19

Anno	SOD EROGANTE	Codice Centro Erogante	Codice Prestazione	Descrizione Prestazione	Quantuni
2018	1422 ISTOLOGIA PATOLOGICA E DIAGNOSTICA MOLECOLARE	21961422	7049	ES. ISTOPATOLOGICO APP. GENITALE - AGOBIOPSIA PROSTATICA	1.009
2018	1422 ISTOLOGIA PATOLOGICA E DIAGNOSTICA MOLECOLARE	21961422	7050	ES. ISTOPATOLOGICO APP. GENITALE - AGOBIOPSIE PROSTATICHE - MAPPING	2
2018	SOD non def		7049	ES. ISTOPATOLOGICO APP. GENITALE - AGOBIOPSIA PROSTATICA	24
				Somma:	1.035

RM Multiparametrica 510

ASL Toscana Centro		
	Biopsie prostatiche	RM
Area Fiorentina	390	375
Presidio Empoli	257	0
Presidio Prato	316	135
Presidio Pistoia	350	85
Totale	**1313**	**595**

Elenco dei Componenti del Gruppo di lavoro	
Componenti	Qualifica
Simone Agostini	Responsabile Unit Diagnostica per immagini urogenitale nefrologica e del trapianto del rene - AOU Careggi
Franco Blefari	
Roberto Carpi	Radiologia Osp. SMN
Angela Coppola	Medicina Nucleare Osp. di Prato
Christian Dattilo	Urologia Osp. di Prato
Giovanni Luca Dedola	Radiologia Osp. NSD-Torregalli
Jacopo Frizzi	Urologia Osp. S. Giuseppe di Empoli
Andrea Gavazzi	
Alessandro Ierardi	Urologia OSMA
Alberto Lapini	Responsabile Coordinatore Prostate Cancer Unit - AOU Careggi
Antonio Mottola	Urologia Osp. S. Giuseppe di Empoli
Fabrizio Rubini	Radiologia Osp. di Prato
Niceta Stomaci	Direttore U.O. Urologia Osp. S.Maria Annunziata
Luca Vaggelli	Responsabile Unit Imaging molecolare oncologica nei tumori solidi polmono prostata - AOU Careggi
Gruppo di Coordinamento	
Grazia Campanile	RSD DAI Servizi - AOU Careggi
Maddalena Innocenti	Medico Specializzando in Igiene e Medicina Preventiva
Ilaria Baccini	Segreteria organizzativa DAI Servizi - AOU Careggi

In presenza di un paziente con un tumore low-risk come dovremmo comportarci ?

<u>Illustrare le diverse opzioni fornendo informazioni equilibrate e non di parte</u>

“Diciamo che sono un po’ confuso e frastornato e che in un primo tempo ero un po’ più orientato verso l’operazione chirurgica; però la terza possibilità cioè quella della sorveglianza attiva non c’era ancora perché il dottore non me l’aveva detto“

VERY LOW RISK GROUP

EXPECTED PATIENT SURVIVAL[n]	INITIAL THERAPY	ADJUVANT THERAPY
	Active surveillance (preferred)[p] • Consider mpMRI and/or prostate biopsy to confirm candidacy for active surveillance • PSA no more often than every 6 mo unless clinically indicated • DRE no more often than every 12 mo unless clinically indicated • Repeat prostate biopsy no more often than every 12 mo unless clinically indicated • Repeat mpMRI no more often than every 12 mo unless clinically indicated	Progressive disease[v] See Initial Clinical Assessment (PROS-1)
≥20 y	EBRT[q] or brachytherapy[q]	
	Radical prostatectomy (RP)[r]	Adverse feature(s):[t] EBRT[q] ± ADT[u] (6 mo) or Observation[s] See Evidence Blocks for ADT on PROS-F (EB-1) No adverse features
		See Monitoring for Initial Definitive Therapy (PROS-11)
10–20 y[o]	Active surveillance[p] • Consider mpMRI and/or prostate biopsy to confirm candidacy for active surveillance • PSA no more often than every 6 mo unless clinically indicated • DRE no more often than every 12 mo unless clinically indicated • Repeat prostate biopsy no more often than every 12 mo unless clinically indicated • Repeat mpMRI no more often than every 12 mo unless clinically indicated	Progressive disease[v] See Initial Clinical Assessment (PROS-1)
<10 y[f]	Observation[s]	See Monitoring (PROS-11)

[f] For asymptomatic patients in very-low-, low-, and intermediate-risk groups with life expectancy ≤5 years, no further workup or treatment is indicated until the patient becomes symptomatic.
[n] See Principles of Life Expectancy Estimation (PROS-A).
[o] The panel remains concerned about the problems of overtreatment related to the increased diagnosis of early prostate cancer from PSA testing. See NCCN Guidelines for Prostate Cancer Early Detection. Active surveillance is recommended for this subset of patients.
[p] Active surveillance involves actively monitoring the course of disease with the expectation to intervene with potentially curative therapy if the cancer progresses. See Principles of Active Surveillance and Observation (PROS-C).
[q] Principles of Radiation Therapy (PROS-D).
[r] Principles of Surgery (PROS-E).
[s] Observation involves monitoring the course of disease with the expectation to deliver palliative therapy for the development of symptoms or a change in exam or PSA that suggests symptoms are imminent. Principles of Active Surveillance and Observation (PROS-C).
[t] Adverse laboratory/pathologic features include: positive margin(s); seminal vesicle invasion; extracapsular extension; or detectable PSA.
[u] Principles of Androgen Deprivation Therapy (PROS-F).
[v] Criteria for progression are not well defined and require physician judgment; however, a change in risk group strongly implies disease progression. See Discussion.

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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National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2019
Prostate Cancer
NCCN Evidence Blocks™

NCCN Guidelines Index
Table of Contents
Discussion

LOW RISK GROUP

EXPECTED PATIENT SURVIVAL[n]	INITIAL THERAPY	ADJUVANT THERAPY
	Active surveillance (preferred)[p] • Consider mpMRI and/or prostate biopsy to confirm candidacy for active surveillance • PSA no more often than every 6 mo unless clinically indicated • DRE no more often than every 12 mo unless clinically indicated • Repeat prostate biopsy no more often than every 12 mo unless clinically indicated • Repeat mpMRI no more often than every 12 mo unless clinically indicated	Progressive disease[v] See Initial Clinical Assessment (PROS-1)
≥10 y	EBRT[q] or brachytherapy[q]	
	RP[r]	Adverse feature(s):[t] EBRT[q] ± ADT[u] (6 mo) or Observation[s] See Evidence Blocks for ADT on PROS-F (EB-1) No adverse features
		See Monitoring for Initial Definitive Therapy (PROS-11)
<10 y[f]	Observation[s]	See Monitoring (PROS-11)

[f] For asymptomatic patients in very-low-, low-, and intermediate-risk groups with life expectancy ≤5 years, no further workup or treatment is indicated until the patient becomes symptomatic.
[n] See Principles of Life Expectancy Estimation (PROS-A).
[q] Principles of Radiation Therapy (PROS-D).
[p] Active surveillance involves actively monitoring the course of disease with the expectation to intervene with potentially curative therapy if the cancer progresses. Principles of Active Surveillance and Observation (PROS-C).
[r] Principles of Surgery (PROS-E).
[s] Observation involves monitoring the course of disease with the expectation to deliver palliative therapy for the development of symptoms or a change in exam or PSA that suggests symptoms are imminent. Principles of Active Surveillance and Observation (PROS-C).
[t] Adverse laboratory/pathologic features include: positive margin(s); seminal vesicle invasion; extracapsular extension; or detectable PSA.
[u] Principles of Androgen Deprivation Therapy (PROS-F).
[v] Criteria for progression are not well defined and require physician judgment; however, a change in risk group strongly implies disease progression. See Discussion.

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Criteria for active surveillance

JOURNAL OF CLINICAL ONCOLOGY | COMMENTS AND CONTROVERSIES

Gleason Score 6 Adenocarcinoma: Should It Be Labeled As Cancer?

H. Ballentine Carter, Alan W. Partin, Patrick C. Walsh, Bruce J. Trock, Robert W. Veltri, William G. Nelson, and Donald S. Coffey, *The Johns Hopkins University and Johns Hopkins Hospital, Baltimore, MD*
Eric A. Singer, *National Cancer Institute, National Institutes of Health, Bethesda, MD*
Jonathan I. Epstein, *The Johns Hopkins University and Johns Hopkins Hospital, Baltimore, MD*

Overtreatment of low-grade prostate cancer (Gleason score ≤ 6) is a recognized problem today, with systematic prostate gland sampling triggered by prostate-specific antigen (PSA) measurements.[1] The extent to which overtreatment is caused by fear of death resulting from cancer, fear of litigation from undertreatment, and misaligned incentives that reimburse more for treating rather than monitoring when appropriate is not known. Nevertheless, fear of death resulting from cancer likely plays some role, and removing the label "cancer" could reduce unnecessary treatment of low-grade disease.[2,3] On the other hand, undertreatment of prostate cancer and a missed opportu-

cohort studies, and randomized trials, has demonstrated the similarity of outcomes for men with Gleason score 6 tumors treated or not in the PSA era.[4-12] Taken together, these data demonstrate that using a time horizon of 10 to 15 years, less than 3% of men diagnosed with Gleason score ≤ 6 and classified as low risk (based on a PSA < 10 ng/mL and stage ≤ T2a) will die as a result of prostate cancer whether treated or not. The evidence calls into question the need for treating men with Gleason score 6 tumors (graded in the modified system) who have a life expectancy of fewer than 10 to 15 years, especially if considered *low risk*.[2] But the reality is that today, men older than age 65 years with

Prostate cancer Research International: Active Surveillance

Criteri di inclusione

1) diagnosi istologica di cancro prostatico
2) possibilità di sottoporsi ad un trattamento radicale standard
3) PSA alla diagnosi ≤ 10 ng/ml
4) stadio clinico: T1c-T2a
5) biopsia prostatica adeguata al volume prostatico
(se campionamento inadeguato, ripetizione della biopsia)
6) max 2 campioni positivi, Gleason Score ≤ 3+3=6
Se saturation biopsy, n. campioni positivi < 15%, max 3 campioni se 20-26 prelievi e 4 se > 26 prelievi, Gleason Score ≤ 3+3=6
7) > 2 campioni positivi, Gleason Score ≤ 3+3=6 se Risonanza Magnetica multiparametrica della prostata all'inclusione, eventualmente seguita da biopsia mirata delle lesioni sospette
7) PSA Density < 0.2 ng/ml/cc
8) compliance del paziente al calendario dei controlli e degli esami

Prostatic volume (cc)	Number of biopsy cores
0-40	8
40-60	10
> 60	12

Criteri di esclusione

1. Pazienti che non vogliono sottoporsi a trattamento attivo
2. Pazienti trattati per cancro prostatico

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 13, 2016 VOL. 375 NO. 15

10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer

F.C. Hamdy, J.L. Donovan, J.A. Lane, M. Mason, C. Metcalfe, P. Holding, M. Davis, T.J. Peters, E.L. Turner, R.M. Martin, J. Oxley, M. Robinson, J. Staffurth, E. Walsh, P. Bollina, J. Catto, A. Doble, A. Doherty, D. Gillatt, R. Kockelbergh, H. Kynaston, A. Paul, P. Powell, S. Prescott, D.J. Rosario, E. Rowe, and D.E. Neal, for the ProtecT Study Group*

CONCLUSIONS

At a median of 10 years, prostate-cancer–specific mortality was low irrespective of the treatment assigned, with no significant difference among treatments. Surgery and radiotherapy were associated with lower incidences of disease progression and metastases than was active monitoring. (Funded by the National Institute for Health Research; ProtecT Current Controlled Trials number, ISRCTN20141297; ClinicalTrials.gov number, NCT02044172.)

Table 2. Deaths from Prostate Cancer, According to Subgroup.*

Variable	No. of Deaths Due to Prostate Cancer†			P Value‡
	Active Monitoring (N=545)	Surgery (N=553)	Radiotherapy (N=545)	
Age at randomization				0.09
<65 yr	1	3	1	
≥65 yr	7	2	3	
PSA level at diagnosis				0.72
<6 ng/ml	5	3	4	
≥6 ng/ml	3	2	0	
Gleason score at diagnosis§				0.69
6	3	3	2	
≥7	5	2	2	
Clinical stage at diagnosis¶				0.95
T1c	5	3	3	
T2	3	2	1	

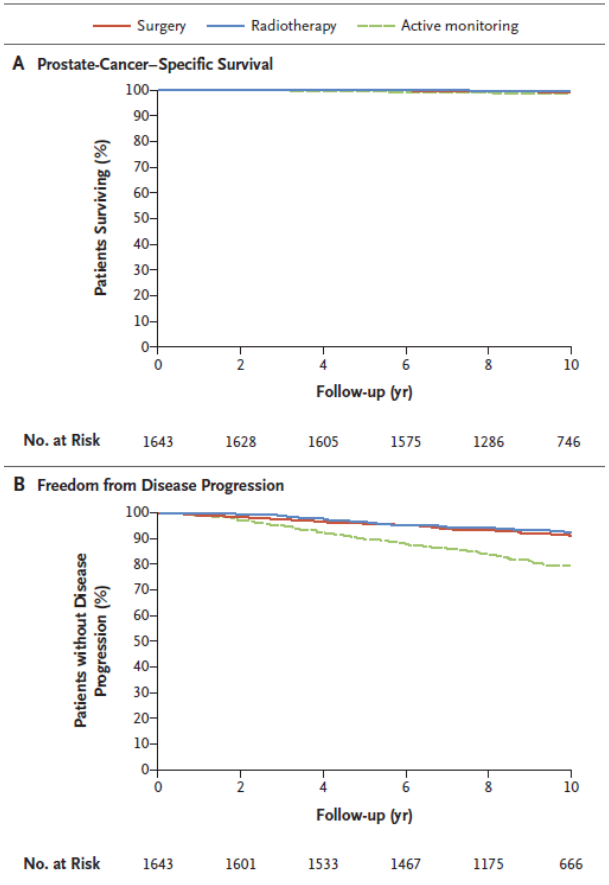


Figure 3. Kaplan–Meier Estimates of Prostate-Cancer–Specific Survival and Freedom from Disease Progression, According to Treatment Group.

Panel A shows the rate of prostate-cancer–specific survival. Prostate-cancer–specific deaths were those that were definitely or probably due to prostate cancer or its treatment, as determined by an independent cause-of-death evaluation committee whose members were unaware of the treatment assignments. Panel B shows the rate of freedom from disease progression. Clinical progression of prostate cancer included metastasis and death due to prostate cancer or its treatment.

Upgrading
in literature range 22.5-43%

Pathological upgrading at radical prostatectomy

Bullock et al. BMC Urology (2019) 19:94
https://doi.org/10.1186/s12894-019-0526-9

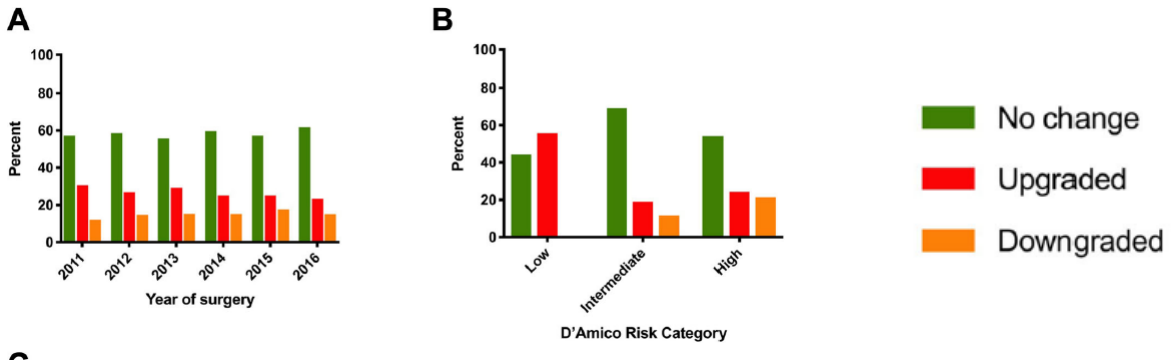
BMC Urology

RESEARCH ARTICLE Open Access

Pathological upgrading in prostate cancer treated with surgery in the United Kingdom: trends and risk factors from the British Association of Urological Surgeons Radical Prostatectomy Registry

Nicholas Bullock[1,2*], Andrew Simpkin[3], Sarah Fowler[4], Murali Varma[5], Howard Kynaston[1,2] and Krishna Narahari[2]

A total of 17,598 patients met full inclusion criteria.
Absolute concordance between initial biopsy and pathological grade was 58.9% (n = 10,364), whilst **upgrade** and downgrade rates were **25.5%** (n = 4489) and 15.6% (n = 2745) respectively. Upgrade rate was highest in those with D'Amico low risk compared with intermediate and high-risk disease (55.7% versus 19.1 and 24.3% respectively, P < 0.001).



Pathological upgrading at radical prostatectomy

Journal of Cancer 2018, Vol. 9

Research Paper

Risk of upgrading from prostate biopsy to radical prostatectomy pathology: Is magnetic resonance imaging-guided biopsy more accurate?

Ning Xu*, Yu-Peng Wu*, Xiao-Dong Li*, Min-Yi Lin, Qing-Shui Zheng, Shao-Hao Chen, Jun-Feng Li, Yong Wei✉, Xue-Yi Xue✉

Upgraded GS between biopsy and RP specimen occurred to 22.7% (52/229) of the cohort overall.

In univariate analysis, prostate-specific antigen density (PSAD) (*P*<0.001), prostate volume (PV) < 30 ml (*P*<0.001), biopsy modality (*P*=0.027), biopsy GS (*P*=0.032) and measured MRI lymph node metastasis (*P*=0.018) were prognostic factors. Multivariate logistic regression analysis showed PV < 30 ml (*P*<0.001) and biopsy modality (*P*=0.001) were independent predictors of upgraded GS.

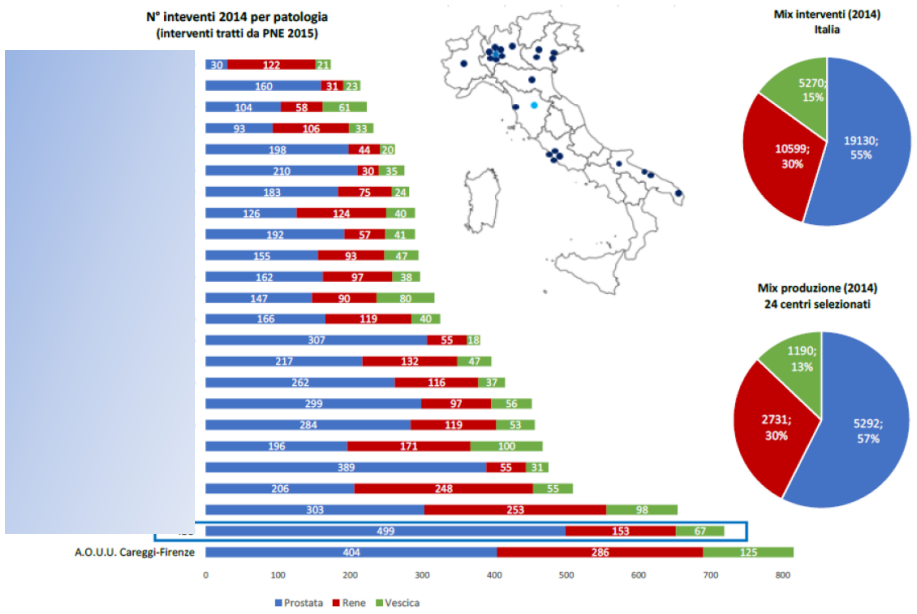
PSAD, ng/ml/ml(rang)	0.4 (0.0- 2.7)	0.5 (0.0-14.8)	<0.001 *
Prostate volume			<0.001*
<30ml	24 (13.6%)	40 (76.9%)	
≥30ml	153 (86.4%)	12 (23.1%)	
Biopsy modality, n (%)			0.027*
mpMRI-TB	78 (44.1%)	14 (26.9%)	
TRUS-GB	99 (55.9%)	38 (73.1%)	

Table 5. Multivariate logistic regression of independent predictors of upgraded GS after radical prostatectomy

Variable	*P value*	*Odd ratio (95% confidence interval)*
PSAD	0.273	0.8 (0.6, 1.1)
PV (<30ml vs. ≥30ml)	<0.001*	0.7 (0.6, 0.8)
Biopsy modality	0.001 *	12.1 (2.6, 55.4)
Biopsy Gleason score (<7 vs.≥7)	0.367	0.4 (0.1, 3.0)
Lymph node metastasis	0.734	0.8 (0.3, 2.3)

*P<0.05; PSAD: prostate-specific antigen density, PV: prostate volume.

FOCUS mix produzione prostata-rene-vescica (centri di riferimento in almeno una patologia)
Fonti: AGENAS



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La classifica dei migliori ospedali italiani

Di ValentinaRorato | giovedì 6 luglio 2017

- **Protesi d'anc**a: Istituto ortopedico Rizzoli di Bologna (1.737 interventi), Istituto clinico Humanitas di Rozzano, Milano (1.652), Istituto ortopedico Galeazzi di Milano (1.566), Istituto ortopedico Gaetano Pini di Milano (789), Casa di cura Giovanni XXIII di Monastier di Treviso (782)
- **Protesi di ginocchio**: Galeazzi di Milano (1.824 interventi), Policlinico Abano Terme di Abano Terme, Padova (921), ospedale Sacro Cuore Don Calabria di Negrar, Verona (780), Giovanni XXIII di Monastier di Treviso (739), casa di cura Policlinico di Monza (725)
- **Protesi di spalla**: ospedale Cervesi di Cattolica (177 interventi), ospedale Santa Maria di Misericordia di Albenga, Savona (95), Galeazzi di Milano (91), Istituto Marco Pasquali-Icot di Latina (89), casa di cura Frate Sole di Figline e Incisa Valdarno, Firenze (85).
- **Prostatectomia**: Aou Careggi di Firenze (401 interventi), Policlinico Abano Terme (305), casa di cura Dott. Pederzoli di Peschiera Del Garda, Verona (298), casa di cura San Raffaele Turro di Milano (290), ospedale San Raffaele di Milano (287)
- **Isterectomia**: Policlinico universitario A. Gemelli di Roma (1.193 interventi), ospedale Sant'Anna di Torino (746), Sant'Orsola-Malpighi di Bologna (575), ospedale Filippo del Ponte di Varese (532), casa di cura C.B.H. Presidio Mater Dei di Bari (523)
- **Tumore all'utero**: Gemelli di Roma (681 interventi), Ieo-Istituto europeo di oncologia di Milano (354), casa di cura Villa dei Platani di Avellino (173), Sant'Orsola di Bologna (173), Consorziale Policlinico di Bari (172);
- **Tumore alla tiroide**: Aou pisana (854 interventi), ospedale di Padova (522), Gemelli di Roma (422), Policlinico di Monserrato, Cagliari (167), Spedali Civili di Brescia (147).

Azienda Ospedaliero Universitaria Careggi

UNIVERSITÀ DEGLI STUDI FIRENZE

Prostatectomie radicali 2018 n° 640

Group 1	176	27.6%
Group 2	212	33.1%
Group 3	135	21.1%
Group 4	94	14.6%
Group 5	23	3.6%

The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma

Definition of Grading Patterns and Proposal for a New Grading System

Jonathan I. Epstein, MD, Lars Egevad, MD, PhD,† Mahul B. Amin, MD,‡ Brett Delahunt, MD,§ John R. Srigley, MD,‖ Peter A. Humphrey, MD, PhD,¶ and and the Grading Committee*

TABLE 5. Histological Definition of New Grading System

Grade Group 1 (Gleason score ≤6) – Only individual discrete well-formed glands

Grade Group 2 (Gleason score 3+4 = 7) – Predominantly well-formed glands with lesser component of poorly- formed/fused/cribriform glands

Grade Group 3 (Gleason score 4+3 = 7) – Predominantly poorly-formed/fused/cribriform glands with lesser component of well-formed glands†

Grade Group 4 (Gleason score 4+4 = 8; 3+5 = 8; 5+3 = 8)
Only poorly-formed/fused/cribriform glands *or*
Predominantly well-formed glands and lesser component lacking glands†† or
Predominantly lacking glands and lesser component of well-formed glands††

Grade Group 5 (Gleason scores 9-10) – Lacks gland formation (or with necrosis) with or w/o poorly formed/fused/cribriform glands†

†For cases with > 95% poorly-formed/fused/cribriform glands or lack of glands on a core or at RP, the component of < 5% well-formed glands is not factored into the grade.

††Poorly-formed/fused/cribriform glands can be a more minor component.

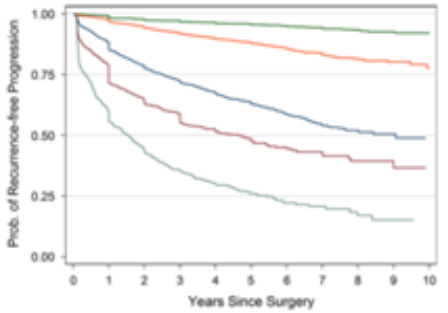
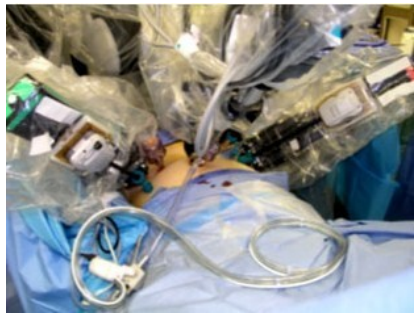
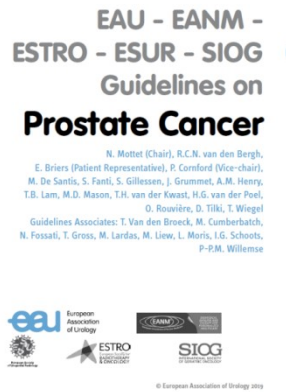


FIGURE 3. Biochemical recurrence-free progression after RP stratified by grade (green line—Gleason score 6 [grade group 1], orange—Gleason score 3+4 [grade group 2], dark blue—Gleason score 4+3 [grade group 3], brown—Gleason score 8 [grade group 4], gray—Gleason score ≥ 9 [grade group 5]).





Investigational therapies

Besides RP, EBRT and brachytherapy, other modalities have emerged as potential therapeutic options in patients with clinically localised PCa .

About High-intensity focused US (HIFU), cryotherapeutic ablation of the prostate (cryotherapy) and focal photodynamic therapy, sufficient data are available to form the basis of some initial judgements.

Other options, such as radiofrequency ablation and electroporation, among others, are considered to be in the early phases of evaluation .

<u>In addition, a relatively newer development is focal ablative therapy , whereby lesion-targeted ablation is undertaken in a precise, organ-sparing manner.</u>

All these modalities have been developed as minimally invasive procedures with the aim of providing equivalent oncological safety, reduced toxicity and improved functional outcomes.

CLINICAL IMPLICATIONS OF BASIC RESEARCH

The Index Lesion and the Origin of Prostate Cancer

Hashim Uddin Ahmed, M.R.C.S., B.M., B.Ch.

N ENGL J MED 361;17 NEJM.ORG OCTOBER 22, 2009

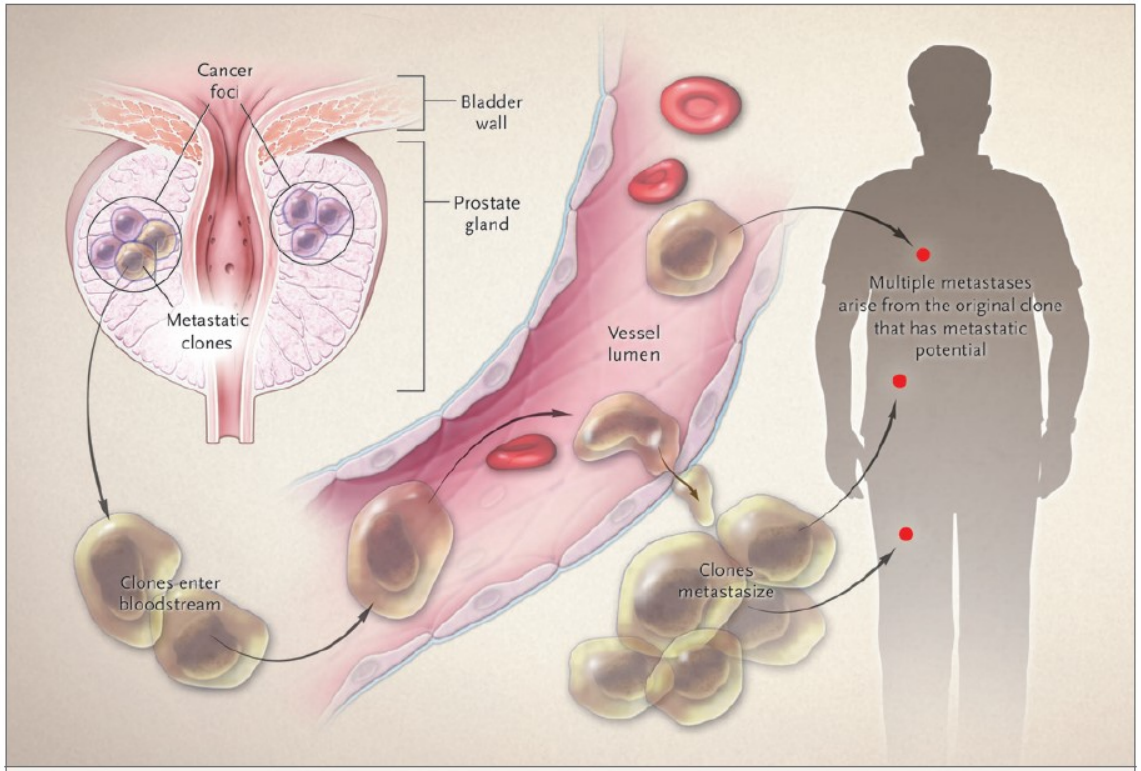


Figure 1. Monoclonal Origin of Prostate-Cancer Metastases.

A recent study by Liu and colleagues[3] has shown that metastases in prostate cancer have a common origin — that is, they originate from the same clone. If the single lesion harboring this metastatic clone could be accurately identified and then targeted, it seems likely that the side effects of treatment for prostate cancer would be reduced. The other lesions (depicted as purple cells in the prostate) would undergo surveillance.

EUROPEAN UROLOGY 74 (2018) 537–539

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Opinion

Focal Therapy for Prostate Cancer: A More Vehement View of the Approach Could Translate into Real Benefits for Our Patients

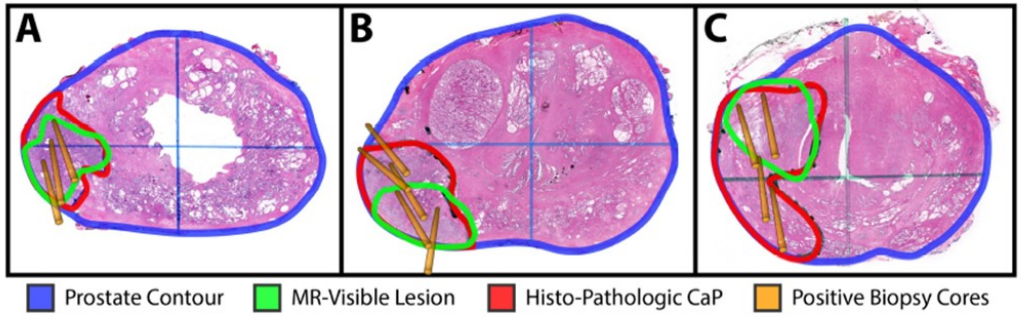
Rafael Sanchez-Salas [a,], Jean de la Rosette [b], Thomas J. Polascik [c], Arie Carneiro [d], Arjun Sivaraman [e], Xavier Cathelineau [a], Jochen Walz [f]*

Focal therapy (FT) for the treatment of localised prostate cancer (PCa) is a technologically interactive approach at its point of diffusion.

The aim of the approach is to offer a personalised, effective, and less aggressive treatment for localised PCa.

The definition of focal therapy should be confined to organ-sparing approaches ranging from targeted focal ablation to subtotal treatment on the basis of lesion characteristics.

Current limitations of prostate imaging and actual knowledge of the natural history of the index lesion and the low risk potential of satellite would perhaps preclude anything less than quadrant or hemi-ablation being considered as FT today.



EUROPEAN UROLOGY 75 (2019) 712–720

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European Association of Urology

Platinum Priority – Prostate Cancer – Editor's Choice

Editorial by Anwar R. Padhani, Masoom A. Haider, Arnauld Villers and Jelle O. Barentsz on pp. 721–722 of this issue

Detection of Individual Prostate Cancer Foci via Multiparametric Magnetic Resonance Imaging

David C. Johnson[a,b,], Steven S. Raman[c], Sohrab A. Mirak[c], Lorna Kwan[b], Amirhossein M. Bajgiran[c], William Hsu[c], Cleo K. Maehara[c], Preeti Ahuja[c], Izak Faiena[b], Aydin Pooli[b], Amirali Salmasi[b], Anthony Sisk[d], Ely R. Felker[c], David S.K. Lu[c], Robert E. Reiter[b,*]*

mpMRI detects less than half of all and less than two-thirds of clinically significant CaP foci. The moderate per-lesion sensitivity and significant proportion of men with undetected tumor foci demonstrate the current limitations of mpMRI.

On a per-lesion basis, mpMRI has moderate sensitivity for detecting CaP and csCaP, and multifocality appears to increase the odds of missed tumors on mpMRI. A substantial percentage of missed lesions are clinically significant, and mpMRI misses at least one csCaP in nearly half of patients.

REVIEW

OPEN

CURRENT OPINION

Contemporary treatments in prostate cancer focal therapy

Michael Ahdoot[a], Amir H. Lebastchi[a], Baris Turkbey[b], Bradford Wood[c], and Peter A. Pinto[a]

Curr Opin Oncol 2019, 31:200–206

KEY POINTS

- HIFU, FLA, IRE, focal cryotherapy, and PDT have been used as treatment modalities for localized prostate cancer treatment.
- Each of these modalities is characterized by a significant rate of prostate cancer persistence within treatment zones (6–50%) and anywhere in the prostate on rebiopsy (24–70%); however, rates of persistent clinically significant prostate cancer are lowered by treatment.
- Prostate focal therapies are associated with very low rates of high-grade complications, rare incontinence, and only mild or transient reductions in erectile function.
- Most studies evaluating focal therapy for prostate cancer have been for the treatment of Gleason 6 or 7 disease and have short/intermediate-term follow-up.

HIFU -High intensity focused ultrasound
FLA- focal laser ablation
IRE - irreversible electroporation
PDT- Photodynamic therapy

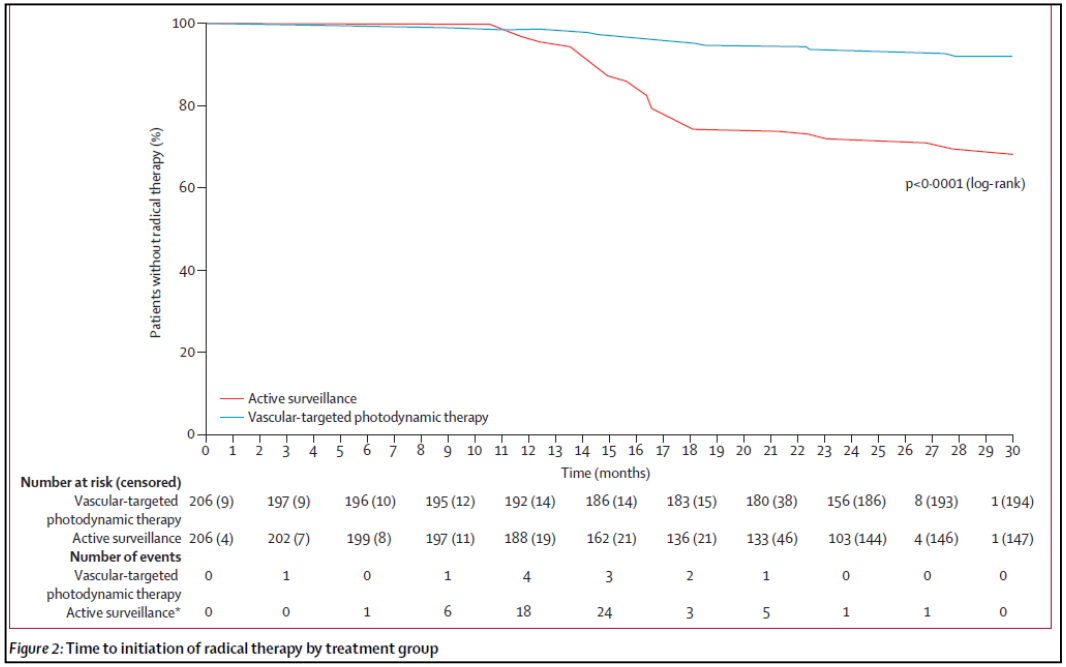
Table 1. Oncologic outcomes of focal prostate ablation

Study (references)	Ablation modality	Design	Participants (*n*)	Preoperative Gleason grade = 6	Preoperative Gleason grade = 7	Preoperative Gleason grade ≥ 8	Time to oncologic follow-up (months)	In-Field recurrence	Out-of-field recurrence	Absence of clinically significant cancer	Absence of any prostate cancer
Ahmed *et al.* 2015 [26▪]	HIFU	Prospective cohort	56	67%	28%	6%	6	50%	12%	81%	58%
Guillaumier *et al.* 2018 [25▪▪]	HIFU	Prospective cohort	625	28%	69%	2%	12	6%[c]	4%[a]	–	89%[a]
von Hardenberg *et al.* 2018 [28]	HIFU	Prospective cohort	24	–	–	0%	12	40%	–	–	50%
Eggener *et al.* 2016 [35]	FLA	Prospective cohort	27	85%	15%	0%	12	11%	30%	–	63%
Natarajan *et al.* 2016 [37]	FLA	Prospective cohort	10	18%	82%	0%	6	30%	40%	60%	30%
Lindner *et al.* 2009 [39]	FLA	Prospective cohort	12	100%	0%	0%	6	33%	17%	–	50%
Mendez *et al.* 2015 [43]	Cryotherapy	Prospective cohort	317	100%	0%	0%	12	–	–	–	86%[b]
Valerio *et al.* 2017 [44]	Cryotherapy	Prospective cohort	18	28%	72%	0%	12	–	–	–	–
Tay *et al.* *et al.* 2017 [45]	Cryotherapy	Propensity matched case controlled	166	36%	65%	0%	24–36	–	–	–	96%[c]
Van den Bos *et al.* 2018 [48▪]	IRE	Prospective cohort	63	14%	86%	0%	6	16%	9%	–	76%
Azzouzi *et al.* 2018 [50▪▪]/ Gill *et al.* 2018 [49▪▪]	PDT	Prospective Randomized Controlled	413	100%	0%	0%	24	25%	19%	–	50%

Popularization of focal treatment of prostate cancer was dependent on the development of multiparametric MRI, which allowed for tumor localization .

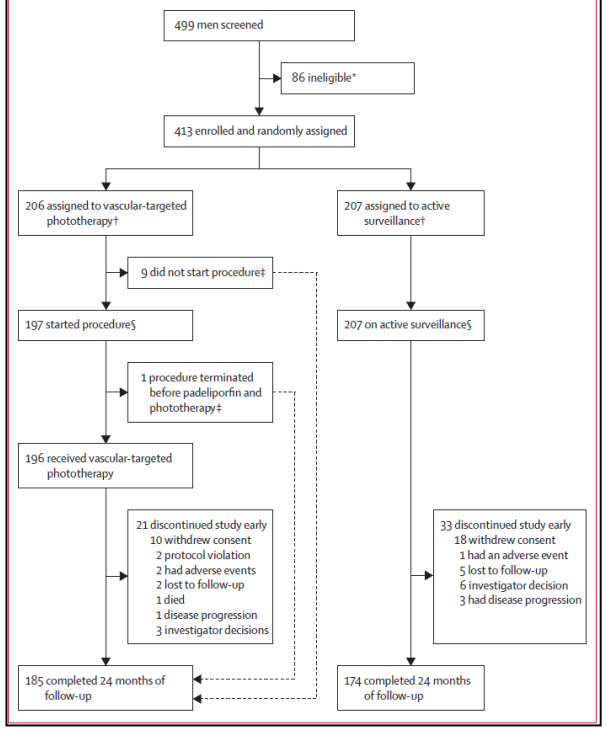
Padeliporfin vascular-targeted photodynamic therapy versus active surveillance in men with low-risk prostate cancer (CLIN1001 PCM301): an open-label, phase 3, randomised controlled trial

Abdel-Rahmène Azzouzi, Sébastien Vincendeau, Eric Barret, Antony Cicco, François Kleinclauss, Henk G van der Poel, Christian G Stief, Jens Rassweiler, Georg Salomon, Eduardo Solsona, Antonio Alcaraz, Teuvo T Tammela, Derek J Rosario, Francisco Gomez-Veiga, Göran Ahlgren, Fawzi Benzaghou, Bertrand Gaillac, Billy Amzal, Frans M J Debruyne, Gaëlle Fromont, Christian Gratzke, Mark Emberton, on behalf of the PCM301 Study Group



Number at risk (censored)											
Vascular-targeted photodynamic therapy	206 (9)	197 (9)	196 (10)	195 (12)	192 (14)	186 (14)	183 (15)	180 (38)	156 (186)	8 (193)	1 (194)
Active surveillance	206 (4)	202 (7)	199 (8)	197 (11)	188 (19)	162 (21)	136 (21)	133 (46)	103 (144)	4 (146)	1 (147)
Number of events											
Vascular-targeted photodynamic therapy	0	1	0	1	4	3	2	1	0	0	0
Active surveillance*	0	0	1	6	18	24	3	5	1	1	0

Figure 2: Time to initiation of radical therapy by treatment group



	Vascular-targeted photodynamic therapy (n=206)	Active surveillance (n=207)	Hazard ratio (95% CI)	p value
Progression	58 (28%)	120 (58%)	0·34 (0·24–0·46)†	<0·0001‡
Criteria for progression§				
>3 positive cores	23 (11%)	58 (28%)	NC	<0·0001¶
Gleason pattern ≥4	49 (24%)	91 (44%)	NC	<0·0001¶
Cancer core length >5 mm	25 (12%)	51 (25%)	NC	0·001¶
PSA >10 ng/mL in three consecutive measures	3 (1%)	14 (7%)	NC	0·007¶
Any T3 prostate cancer	0	4 (2%)	NC	NA
Metastasis	0	0	NC	NA
Prostate cancer-related death	0	0	NC	NA
Negative biopsy result at month 24	101 (49%)	28 (14%)	3·67 (2·53–5·33)‖	<0·0001¶

Interpretation Padeliporfin vascular-targeted photodynamic therapy is a safe, effective treatment for low-risk, localised prostate cancer. This treatment might allow more men to consider a tissue-preserving approach and defer or avoid radical therapy.

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Introduction

Liproca®Depot

Novel depot formulation of 2-hydroxyflutamide, in a calcium sulphate suspension (NanoZolid)

Why Liproca®Depot?

- Intraprostatic injection -> Local treatment
- Slow-release formula -> Long lasting
- Safe -> No systemic hormonal effects
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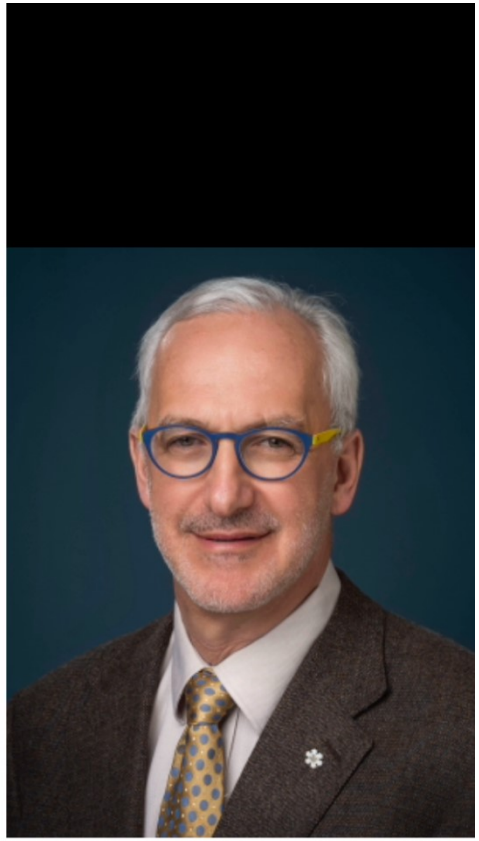

Laurence Klotz

“Progress is impossible without change, and those who cannot change their minds cannot change anything”

George Bernard Shaw