ESU Organised Course

Update in urological oncology

12 April 2019, Belgrade, Serbia

EAU Education Office

esu European School of Urology

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European School of Urology

Update in urological oncology

ESU course during the national congress of the Urological Association of Serbia

Place	Belgrade, Serbia
Date	12 April 2019
Chair	J. Van Moorselaar, Amsterdam (NL)

09.30 **European School of Urology: A unique education opportunity for urologists**
J. Van Moorselaar, Amsterdam (NL)

09.35 **EAU Guidelines recommendations on renal tumors**
P. Gontero, Turin (IT)

09.55 **Treatment of small renal masses**
S. Joniau, Leuven (BE)

10.25 **Immunotherapy for renal tumors**
J. Van Moorselaar, Amsterdam (NL)

10.55 **Break**

11.25 **EAU Guidelines recommendations on bladder cancer**
S. Joniau, Leuven (BE)

11.45 **How to optimise TURBT**
P. Gontero, Turin (IT)

12.15 **Are there alternatives for radical cystectomy?**
J. Van Moorselaar, Amsterdam (NL)

12.35 **Interactive case discussion**
Local + ESU faculty

13.15 **Break**

14.00 **EAU Guidelines recommendations on prostate cancer**
J. Van Moorselaar, Amsterdam (NL)

14.20 **Treatment of localized prostate cancer**
P. Gontero, Turin (IT)

14.50 **Oligometastatic disease: Surgery and/or radiotherapy**
S. Joniau, Leuven (BE)

15.20 **New treatment options in metastatic disease**
J. Van Moorselaar, Amsterdam (NL)

15.50 **Interactive case discussion**
Local + ESU faculty

16.30 **Close**

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30+ languages

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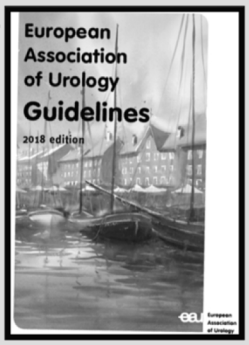


We do Publications

- European Urology
- EU Focus
- EU Oncology
- European Urology Today

We do Publications

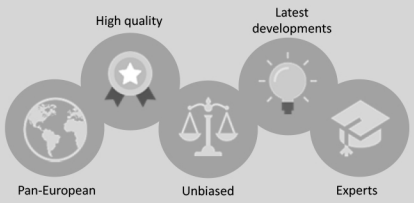
EAU Patient Information

19 topics

17 languages

We do: Education

The ESU objectives:



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200
European experts & opinion leaders

60
European experts of laparoscopic & endoscopic surgery

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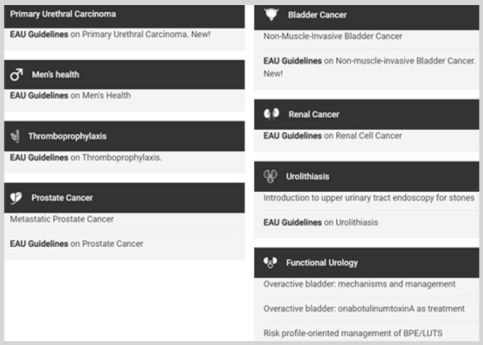
ESUT - ESUI - ERUS - EULIS - ESFFU

We do: Online Education

For Urologists
and Nurses

We do: e-Courses



We do: Webinars

Every month 30-minute webinar

International Key Opinion Leaders

16 recorded webinars

We do: Surgical Education

Online Programmes:

- Endoscopic Stone Treatment (EST)
- Laparoscopy
- Robotics in Urology

Hands-on Training:

- Robotic Surgery
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- Functional Urology
- Endoscopy
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European Urology Residents Education Programme (EUREP):

- European School of Urology's flagship teaching programme
- Annual, week-long programme for final-year urology residents
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- Distinguished European faculty



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- Challengers session
- Tips and tricks
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- Clinical cases

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20+ Courses around the World

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ESU-ESUT Masterclass on Focal therapy for localised prostate cancer


ESU-ESUT Masterclass on Lasers in Urology


ESU-ESUT-EULIS Masterclass on Urolithiasis


ESU-ESOU Masterclass on Non-Muscle-Invasive bladder cancer


ESU-ESTU Masterclass on Kidney Transplant


ESU-ESAU-ESGURS Masterclass on Erectile restoration and Peyronie's disease


ESU-ESFFU Masterclass on Functional Urology


ESU-Weill Cornell Masterclass in General urology

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- esou EAU Section of Oncological Urology
- esau EAU Section of Andrological Urology
- esuo EAU Section of Urologists in Office
- esur EAU Section of Urological Research
- erus EAU Robotic Urology Section

EAU Edu Platform

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UROONCO bladder cancer
UROONCO kidney cancer
Male LUTS
Bedwetting
Nocturia

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UROsource.com
The EAU learning library for urologists
Science at your fingertips

Visit uroweb.org/education for more information

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2. Clinical Visit (3 months)
3. Fellowship
4. Short Visit (3 weeks)
5. ViPP: Visiting Professor Programme

Application deadlines: 1 January, 1 May, 1 September

Only EAU members are eligible to apply for scholarships!

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- Premium access to nearly 60,000 items of scientific content in UROsource
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Did you know that the discount you receive as a member on the registration fee for the Annual EAU Congress is more than the annual membership fee?

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EAU GUIDELINES RECOMMENDATIONS ON RENAL TUMOURS

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Direttore Clinica Urologica
Città della Salute e della Scienza, Molinette
Università degli Studi di Torino
Torino

Guideline structure

Level	Type of evidence
1a	Evidence obtained from meta-analysis of randomised trials.
1b	Evidence obtained from at least one randomised trial.
2a	Evidence obtained from one well-designed controlled study without randomization.
2b	Evidence obtained from at least one other type of well-designed quasi-experimental study.
3	Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports.
4	Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities

Strength of rating (recommendation)

Once the LE for a particular topic or question had been determined, a guideline recommendation was made using a transparent, reproducible, and reliable process modified from the GRADE framework [6]. This approach allows the integration of the LE with other essential elements, including certainty of the evidence, magnitude of effects, balance between consequences, and patient values and preferences [7], in order to issue clinical practice recommendations

EAU GUIDELINES RECOMMENDATIONS ON RENAL TUMOURS

Summary of 2019 EAU recommendation changes

Recommendations	Strength rating
Treat Bosniak type III cysts the same as RCC or offer cautious surveillance.	Weak
Treat Bosniak type IV cysts the same as RCC.	Strong
Offer active surveillance to patients with biopsy-proven oncocytomas, as an acceptable alternative to surgery or ablation.	Weak

7.2.5.1 Summary of evidence and recommendations for adjuvant therapy

Summary of evidence	LE
After nephrectomy, in selected high-risk patients, adjuvant sunitinib improved disease-free survival in one of the two available studies, but not overall survival.	1b
Adjuvant sorafenib, pazopanib or axitinib does not improve disease-free survival or overall survival after nephrectomy.	1b

Recommendations	Strength rating
Do not offer adjuvant therapy with sorafenib, pazopanib or axitinib.	Strong

7.3.1.1.2 Summary of evidence and recommendations for local therapy of advanced/metastatic renal cell cancer

Summary of evidence	LE
Cytoreductive nephrectomy followed by sunitinib is non-inferior to sunitinib alone in patients with metastatic ccRCC.	1a
Sunitinib alone is non-inferior compared to immediate cytoreductive nephrectomy followed by sunitinib in patients with MSKCC intermediate and poor risk who require systemic therapy with VEGFR-TKIs.	1a

Recommendations	Strength rating
Do not perform cytoreductive nephrectomy (CN) in MSKCC poor-risk patients.	Strong
Do not perform immediate CN in MSKCC intermediate-risk patients who have an asymptomatic synchronous primary tumour and require systemic therapy with vascular endothelial growth factor receptor (VEGFR)-tyrosine kinase inhibitor (TKI).	Weak
Start systemic therapy without CN in MSKCC intermediate-risk patients who have an asymptomatic synchronous primary tumour and require systemic therapy with VEGFR-TKI.	Weak
Discuss delayed CN in MSKCC intermediate-risk patients under VEGFR-TKI therapy who derive long-term sustained benefit and/or minimal residual metastatic burden.	Weak
Perform immediate CN in patients with good performance who do not require systemic therapy.	Weak
Perform immediate CN in patients with oligometastases when complete local treatment of the metastases can be achieved.	Weak

Ljungberg et al., EAU RCC guidelines, 2019

EAU GUIDELINES RECOMMENDATIONS ON RENAL TUMOURS

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1 Epidemiology

Renal cell cancer represents 2-3% of all cancers with the highest incidence in Western countries. Over the last two decades the incidence of RCC increased by about 2%, both worldwide and in Europe. The incidence varies globally, with the highest rates in developed countries such as North America and Europe and the lowest rates in Asia and Africa. In Western European countries this incidence stabilised over the past decade. In 2012, there were approximately 84,400 new cases of RCC and 34,700 kidney-cancer-related deaths in the European Union [10, 11]. In Europe, overall mortality rates for RCC increased up to the early 1990s, before stabilising or declining thereafter [12]. Mortality has decreased since the 1980s in Scandinavian countries and since the early 1990s in France, Germany, Austria, the Netherlands, and Italy. However, in some European countries (Croatia, Estonia, Greece, Ireland, Slovakia), mortality rates still show an upward trend. Data from the United States also show increased incidence [13].

There is a 1.5:1 male predominance, with a peak incidence between 60 and 70 years. Aetiological factors include smoking, obesity and hypertension [14]. Having a first-degree relative with RCC also increases

Ljungberg et al., EAU RCC guidelines, 2019

EAU GUIDELINES RECOMMENDATIONS ON RENAL TUMOURS
Grading & Staging

Grading

The 4-tiered WHO/ISUP grading system has replaced the Fuhrman grading

TNM

T - Primary Tumour			
TX	Primary tumour cannot be assessed		
T0	No evidence of primary tumour		
T1	Tumour ≤ 7 cm or less in greatest dimension, limited to the kidney		
T1a	Tumour ≤ 4 cm or less		
T1b	Tumour > 4 cm but ≤ 7 cm		
T2	Tumour > 7 cm in greatest dimension, limited to the kidney		
T2a	Tumour > 7 cm but ≤ 10 cm		
T2b	Tumours > 10 cm, limited to the kidney		
T3	Tumour extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota fascia		
T3a	Tumour grossly extends into the renal vein or its segmental (muscle-containing) branches, or tumour invades perirenal and/or renal sinus fat (peripelvic fat), but not beyond Gerota fascia		
T3b	Tumour grossly extends into the vena cava below diaphragm		
T3c	Tumour grossly extends into vena cava above the diaphragm or invades the wall of the vena cava		
T4	Tumour invades beyond Gerota fascia (including contiguous extension into the ipsilateral adrenal gland)		
N - Regional Lymph Nodes			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Metastasis in regional lymph node(s)		
M - Distant Metastasis			
M0	No distant metastasis		
M1	Distant metastasis		
pTNM stage grouping			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1, T2, T3	N1	M0
Stage IV	T4	Any N	M0
	Any T	Any N	M1

A help desk for specific questions about TNM classification is available at http://www.uicc.org/tnm

Ljungberg et al., EAU RCC guidelines, 2019

EAU GUIDELINES RECOMMENDATIONS ON RENAL TUMOURS
Imaging

Contrast enhancement crucial criterion for malignancy

- **URO-CT (multiphase) is standard**
- **MRI and CEUS:**
  - **no radiation exposure**
  - **Better sensitivity in defining Bosniak cysts**
- **PET:**
  - **not standard**
  - **When suspicion of metastatic lesion to the kidney**
- **Bone and brain imaging NOT routine**
  - **in symptomatic patients**

Ljungberg et al., EAU RCC guidelines, 2019

EAU GUIDELINES RECOMMENDATIONS ON RENAL TUMOURS
Renal biopsy

- Consider renal biopsy in patients candidate for AS, before ablative treatment and to select the most suitable medical and surgical treatment strategy;
- Renal biopsy is not indicated in frail and comorbid patient;
- Not necessary for patient for whom surgical management is planned;
- Percutaneous US or CT guided procedure under local anestesia;
- sens 99.1%, spec 99.7%, non diagnostic 8%, median concordance with surgical specimen 90.3%.

Recommendations	Strength rating
Use multi-phasic contrast-enhanced computed tomography (CT) of abdomen and chest for the diagnosis and staging of renal tumours.	Strong
Use magnetic resonance imaging to better evaluate venous involvement, reduce radiation or avoid intravenous CT contrast medium.	Weak
Use non-ionising modalities, mainly contrast-enhanced ultrasound, for further characterisation of small renal masses, tumour thrombus and differentiation of unclear renal masses.	Strong
Do not routinely use bone scan and/or positron-emission tomography CT for staging of RCC.	Weak
Perform a renal tumour biopsy before ablative therapy and systemic therapy without previous pathology.	Strong
Perform a percutaneous biopsy in select patients who are considering active surveillance.	Weak
Use a coaxial technique when performing a renal tumour biopsy.	Strong
Do not perform a renal tumour biopsy of cystic renal masses.	Strong
Use a core biopsy technique rather than fine needle aspiration for histological characterisation for solid renal tumours.	Strong

Ljungberg et al., EAU RCC guidelines, 2019

EAU GUIDELINES RECOMMENDATIONS ON RENAL TUMOURS
Prognostic factors

1. Anatomical:
   1. *tumour size, venous invasion, renal capsular invasion, adrenal invasion, LN an distant mets (TNM)*
   2. *COMPLEXITY SCORES (R.E.N.A.L nephrometry score): to aid comparison of surgicaltechnique*
2. Histological:
   1. *nuclear grade (independent prognostic factor)*
   2. *RCC hystotype (sarcomatoid, pRCC type 1 vs 2…)*
3. Clinical factors:

- PS

3. Nomogram?

- none

3. Molecular markers?

- none

Ljungberg et al., EAU RCC guidelines, 2019

EAU GUIDELINES RECOMMENDATIONS ON RENAL TUMOURS
Surgical treatment – LOCALIZED RCC

Surgery = the only curative treatment for localized RCC

- Multiple retrospective series (one RCT) in organ confined RCC have demonstrated comparable CSS for PN vs RN;
- Debate on benefit of PN vs RN, elderly patients, ESRD;
- PN recommended for T1 (a/b) RCC
- Lymph node dissection in cases of cN0?
  - Not associated with any advantage (reduced metastatic disease or CSS)

Recommendations	Strength rating
Offer surgery to achieve cure in localised renal cell cancer.	Strong
Offer partial nephrectomy to patients with T1 tumours.	Strong
Do not perform ipsilateral adrenalectomy if there is no clinical evidence of invasion of the adrenal gland.	Strong
Offer an extended lymph node dissection to patients with adverse clinical features, including a large diameter of the primary tumour.	Weak
Offer embolisation to patients until for surgery presenting with massive haematuria or flank pain.	Weak

Ljungberg et al., EAU RCC guidelines, 2019

EAU GUIDELINES RECOMMENDATIONS ON RENAL TUMOURS
Surgical technique

- Less morbidity for LRN vs ORN (MacLennan Eur Urol, 2012);
  - *Shorter hospital stay and less pain killers need for LRN;*
- No differences on post op complications (of RN and PN);
  - *No differences between LRN vs RARN;*
  - *No differences between OPN and LPN;*
- Less ischaemia time for OPN;
- RAPN vs OPN (Peyronnet et al. Ann Surg Oncol, 2016): less complication for RAPN;
- RAPN vs LPN (Choi et al. Eur Urol, 2015): less conversion to open surgery, shorter warm ischaemia and smaller changes in GFR

PN can be performed as OPN, LPN or RAPN based on surgeon's expertize

Ljungberg et al., EAU RCC guidelines, 2019

Guidelines recommend PN, not a specific approach!

Partial nephrectomy can be performed, either with an open, pure laparoscopic- or robot-assisted approach, based on surgeon's expertise and skills.	2b
Partial nephrectomy is associated with a higher percentage of positive surgical margins compared with radical nephrectomy.	3

Recommendations	Strength rating
Offer laparoscopic radical nephrectomy to patients with T2 tumours and localised masses not treatable by partial nephrectomy.	Strong
Do not perform minimally invasive radical nephrectomy in patients with T1 tumours for whom a partial nephrectomy is feasible by any approach, including open.	Strong
Do not perform minimally invasive surgery if this approach may compromise oncological, functional and peri-operative outcomes.	Strong

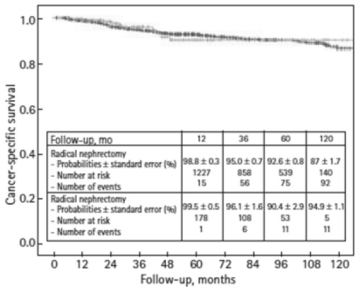
EAU Guidelines 2018

Comparative efficacy PN vs RN
(multicentric italian retrospective study)

T1b

Green line PN (N=198)
5 y CSS 90%

Blue line RN (N=1400)
5 y CSS 92%



Follow-up, mo	12	36	60	120
Radical nephrectomy				
- Probabilities ± standard error (%)	98.8 ± 0.3	95.0 ± 0.7	92.6 ± 0.8	87 ± 1.7
- Number at risk	1227	858	539	140
- Number of events	15	56	75	92
Radical nephrectomy				
- Probabilities ± standard error (%)	99.5 ± 0.5	96.1 ± 1.6	90.4 ± 2.9	94.9 ± 1.1
- Number at risk	178	108	53	5
- Number of events	1	6	11	11

Antonelli A, BJU Int 2012

What does the only level 1 evidence says?
Intergroup Study 30904

A Prospective Randomized Phase III Study Comparing *Radical Surgery* to *Kidney Sparing Surgery* in Solitary T1 T2 Renal Cell Carcinoma (UP TO 5 CM)

To show equivalence!!

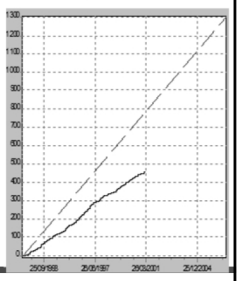
Recruitment: 1992 – 2003

Median FU: 9.3 years

47 institutes

541 pts randomized

(1300 pts required)



Van Poppel et al.: European Urology, 59:543-552, 2011

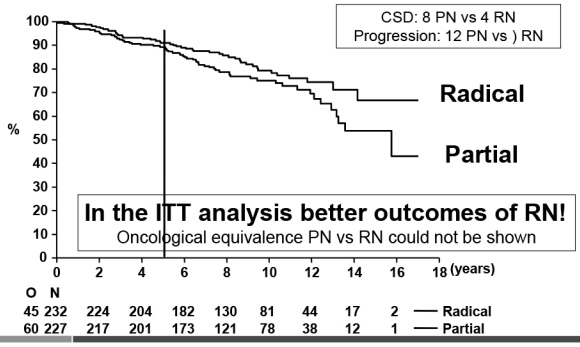
Prospective Randomized Trial
Elective PNx vs. Rad Nx

- EORTC 30904 268 Part.N vs. 273 Rad. Nx
- Solitary tumor, ≤ 5.0 cm, normal contralateral kidney
- Advantage for RN related to lower morbidity
- Advantage for PNx with respect to better renal function
  - mean serum creat. 1,2 PNx vs. 1.4 RNx

What about **overall survival**?

Van Poppel et al.: European Urology, 59:543-552, 2011

Overall Survival
Renal Cell Carcinoma

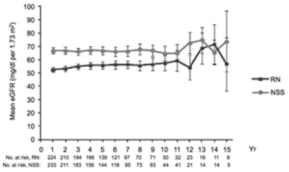


In the ITT analysis better outcomes of RN!
Oncological equivalence PN vs RN could not be shown

MORE CV EVENTS IN PN THAN RN!

H.Van Poppel et al.,Eur. Urol., 2011

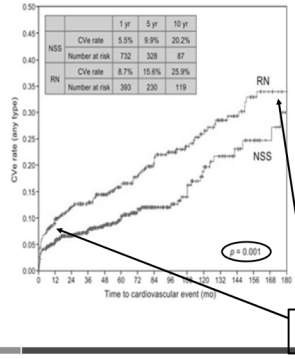
Re-analysis EORTC GU 30904



- The beneficial effect of NSS on eGFR did not result in improved survival over a median FU of 9,3 y for all cause mortality
- Moderate renal dysfunction arising from surgery may not have the same negative implications for overall health as when arising from medical causes as diabetes or hypertension

E.Scosyrev, Van Poppel et al. et al.,Eur. Urol., 2013

CV Events and RN or NSS



CVe= onset of coronary artery disease, cardiomyopathy, hypertension, heart failure, dysrhythmia...

Multi-institutional 1987-2013

1331 T1a-b renal mass

Normal initial renal function

!!!

Capitanio et al. Eur Urol 2015; 67: 683 - 689

EAU GUIDELINES RECOMMENDATIONS ON RENAL TUMOURS
Surgical margins

- **Positive surgical margins in 2-8% of NSS;**
- **PSM more frequent in imperative indication to NSS (CKD);**
- **The negative impact of PSM remain controversial;**
- **Local recurrence was found in 16% of PSM vs 3% in NSM (Wood et al. J Urol, 2018).**

Summary of evidence	LE
Laparoscopic radical nephrectomy has lower morbidity than open surgery.	1b
Short-term oncological outcomes for T1-T2a tumours are equivalent for laparoscopic and open radical nephrectomy.	2a
Partial nephrectomy can be performed, either with an open, pure laparoscopic or robot-assisted approach, based on surgeon's expertise and skills.	2b
Partial nephrectomy is associated with a higher percentage of positive surgical margins compared with radical nephrectomy.	3

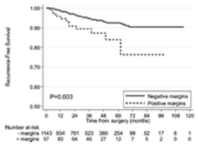
Recommendations	Strength rating
Offer laparoscopic radical nephrectomy (RC) to patients with T2 tumours and localised masses not treatable by partial nephrectomy (PN).	Strong
Do not perform minimally invasive RN in patients with T1 tumours for whom a PN is feasible by any approach, including open.	Strong
Do not perform minimally invasive surgery if this approach may compromise oncological, functional and peri-operative outcomes.	Strong

Ljungberg et al., EAU RCC guidelines, 2019

POSITIVE SURGICAL MARGINS (PSM): PROGNOSTIC ROLE

• Most studies did not find a significant association between PSM and the risk of recurrence/progression (10y RFS and PFS > 90%, not different from NSM)

• In a recent series PSM had more recurrence than NSM, particularly in high risk disease



Yossepowich O, J Urol 2008; Maurice MJ, J Endourol 2016;

EAU GUIDELINES RECOMMENDATIONS ON RENAL TUMOURS

Alternative to surgery - ablative therapy

- **Cryoablation is performed percutaneously or laparoscopically;**
- **Complication rate 8-20%;**
- **Cryo vs PN (Thompson et al. Eur Urol, 2015) no differences (selection bias);**
- **Radiofrequecy ablation perc or lap;**
- **Rivero et al. J Vasc Interv Radiol, 2018 less OS and CSS for ablative therapy vs PN;**
- **No differences between Cryo vs RFA**

Summary of evidence	LE
Most population-based analyses show a significantly lower cancer-specific mortality for patients treated with surgery compared to non-surgical management.	3
In active surveillance cohorts, the growth of small renal masses is low in most cases and progression to metastatic disease is rare (1-2%).	3
Quality of the available data does not allow definitive conclusions regarding morbidity and oncological outcomes of cryoablation and radiofrequency ablation.	3
Low quality studies suggest a higher local recurrence rate for thermal ablation therapies compared to partial nephrectomy.	3

Recommendation	Strength rating
Offer active surveillance, radiofrequency ablation and cryoablation to elderly and/or comorbid patients with small renal masses.	Weak

Ljungberg et al., EAU RCC guidelines, 2019

EAU GUIDELINES RECOMMENDATIONS ON RENAL TUMOURS

Partial nephrectomy VS ablative therapy

Guideline	PN	AT
EAU 2017	- Offer partial nephrectomy to patients with **T1** tumours (*strong recommendation*) - Favour PN over RN in patients with **T1b** tumour, whenever feasible	- Offer active surveillance, RFA and CA to **elderly and/or comorbid patients** with SRM - Low quality data, no conclusion can be made (*weak recommendation*)
AUA 2017	- Prioritize in T1a - Prioritize (**in all renal masses**) when solitary kidney, bilateral/multiple/familiar, CKD - Consider in all renal masses in young, multifocal or comorbidities favouring CKD	- Consider in patients with **T1a < 3 cm** as an alternate approach (*conditional recommendation*) - Counsel on the higher risk of **recurrence/persistence** (*strong recommendation*)

- Indication for **PN expanded**, AT unchanged
- **Low quality data for AT** a major issue

EAU GUIDELINES RECOMMENDATIONS ON RENAL TUMOURS

Alternative to surgery - active serveillance

- **Active surveillance is defined as serial monitoring of tumour size by subsequent abdominal imaging (US, CT, MRI) with deferred intervention in case of clinical progression;**
- **Pierorazio et al. Eur Urol, 2015 no differences between AS vs active treatment (selection bias).**

Summary of evidence	LE
Most population-based analyses show a significantly lower cancer-specific mortality for patients treated with surgery compared to non-surgical management.	3
In active surveillance cohorts, the growth of small renal masses is low in most cases and progression to metastatic disease is rare (1-2%).	3

Ljungberg et al., EAU RCC guidelines, 2019

EAU GUIDELINES RECOMMENDATIONS ON RENAL TUMOURS

Alternative to surgery - active serveillance

EAU

AS can be offered to **elderly and comorbid** patients

(NOTE: the phrase "…with limited life expectancy" of the 2010 version has been removed…)

Ljungberg B, EAU guidelines, 2018

AUA

- **An option** as initial management **for all patients** with small solid or Bosniak 3/4 complex cystic renal masses, especially those <2cm, AS is an option for initial management

- **Prioritize** AS for patients with a solid or Bosniak 3/4 complex cystic renal mass when the anticipated risk of intervention or **competing risks of death outweigh the potential oncologic benefits** of active treatment

Campbell S, AUA guidelines, 2017

EAU GUIDELINES RECOMMENDATIONS ON RENAL TUMOURS

Alternative to surgery - active serveillance

ASCO

(evidence quality: intermediate; strenght of recommendation: moderate)

ABSOLUTE INDICATION **WATCHFUL WAITING?**

- high risk for anesthesia and intervention
- life expectancy < 5 years

RELATIVE INDICATION

- significant risk of end-stage renal disease (ESRD) if treated
- SRM (< 1 cm)
- life expectancy < 10 years

Finelli A et al. JCO, 2017

EAU GUIDELINES RECOMMENDATIONS ON RENAL TUMOURS
Locally advanced RCC

- IN cN+ LND is justified;
- LND template is controversial;
- Tumour thrombus formation in IVC is a significant adverse prognostic factor;
- Aggressive surgical resection is widely accepted as definitive treatment;
- The surgical approach should be chosen case by case;
- Mo surgical *technique was shown to be superior*

Summary of evidence	LE
In patients with locally advanced disease due to clinically enlarged lymph nodes (LNs), the survival benefit of lymph node dissection is unproven but LN dissection adds staging information.	3
Low quality data suggest that tumour thrombus excision in non-metastatic disease may be beneficial.	3
Tumour embolisation or inferior vena cava filter do not appear to offer any benefits.	3

Recommendations	Strength rating
In patients with clinically enlarged lymph nodes (LNs), perform LN dissection for staging purposes or local control.	Weak
Remove the renal tumour and thrombus in case of venous involvement in non-metastatic disease.	Strong

Ljungberg et al., EAU RCC guidelines, 2019

EAU GUIDELINES RECOMMENDATIONS ON RENAL TUMOURS
Recurrent RCC

- For local recurrence after NSS repeat surgery is the preferred management;
- Following thermal ablation repeat ablation is still recommend;
- Only retrospective and non comparative data on frequency and efficacy of available therapeutic options have been reported;
- In selected patients surgical removal of local,u recurrent disease can obtain disease control.

Summary of evidence	LE
Isolated recurrence in the local renal fossa is rare.	3
In the absence of adverse prognostic factors such as sarcomatoid features or median time interval of < 12 months since treatment of the primary tumour, resection of local recurrences can induce durable tumour local control.	3
Most local recurrences develop within the first two years following treatment of the primary tumour. A guideline adapted follow-up regimen is advised for early detection.	3

Recommendation	Strength rating
Offer surgical resection of locally recurrent disease when a complete resection is possible and significant comorbidities are absent.	Weak

Ljungberg et al., EAU RCC guidelines, 2019

EAU GUIDELINES RECOMMENDATIONS ON RENAL TUMOURS
Adjuvant (medical) therapy

- Several rcent RCT trials have addressed the question in HR patients:
  - ASSURE: sunitinib vs sorafenib
  - PROTECT: pazopanib vs placebo
  - S-TRAC: sunitinib vs placebo
    - *Placebo better for DFS*
    - *Data immature for OS*
    - *Double G 3-4 toxicity with sunitinib*
  - ATLAS study: axitinib vs placebo

None of the TKIs currently recommended as adjuvant treatment due to lack of proven benefit

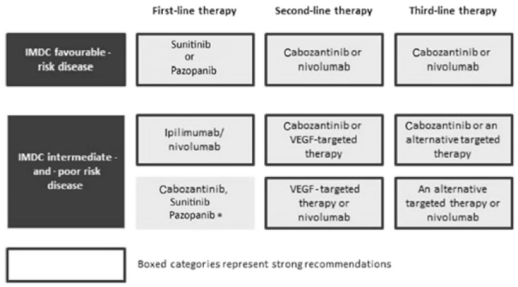
Ljungberg et al., EAU RCC guidelines, 2019

EAU GUIDELINES RECOMMENDATIONS ON RENAL TUMOURS
Cytoreductive Nephrectomy (CN)

- Based on 2 recent RCT, CT NOT recommended in MSKCC intermediate or poor risk mRCC:
  - SURTIME:
    - *CN + Sunitinib did not improve PFS over Sunitinib alone*
    - *Secondary analysis: better OS (32 vs 15 mnoths) with deferred CN*
  - CARMENA:
    - *Sunitinib NOT inferior to immediate CN followed by Sunitinib for OS*
    - *However 17% required secondary CN for symptoms/incomplete response*
- No data on the role of CN in low metastatic volume, good PS + good/intermediate risk who do not need immediate sunitinib
- Role of CN to be re-evaluated according to the shifted paradigm in treatment of mRCC (immunotherapy)

Ljungberg et al., EAU RCC guidelines, 2019

EAU GUIDELINES RECOMMENDATIONS ON RENAL TUMOURS
Systemic therapy for mRCC



Shifting the paradigm…

Ljungberg et al., EAU RCC guidelines, 2019

Treatment of small renal masses

Steven Joniau, MD, PhD
Dept of Urology
University Hospitals Leuven
Belgium

Disclosures

Receipt of honoraria, research funding, consultation fees:

- Amgen
- Astellas
- AstraZeneca
- Bayer
- Ferring
- GSK
- Ipsen
- Janssen
- MDX Health
- Pfizer
- Roche
- Sanofi

Question 1: Which treatment?

60-year-old female patient, no comorbidities. Imaging shows a 3 cm, posterior, interpolar lesion in the left kidney.
Contralateral kidney is normal and eGFR is 100.

1. Open Radical Nephrectomy
2. Laparoscopic/Robotic Radical Nephrectomy
3. Open Partial Nephrectomy
4. Laparoscopic/Robotic Partial Nephrectomy
5. Kidney ablation (RFA or CRYO)
6. Active Surveillance

Question 2: Which treatment?

75-year-old male patient, diabetis, hypertension, active smoker. Imaging shows a 3 cm, posterior, interpolar lesion in the left kidney. Contralateral kidney is normal and eGFR is 55.

1. Open Radical Nephrectomy
2. Laparoscopic/Robotic Radical Nephrectomy
3. Open Partial Nephrectomy
4. Laparoscopic/Robotic Partial Nephrectomy
5. Kidney ablation (RFA or CRYO)
6. Active Surveillance

Question 3: Which treatment?

50-year-old female patient, known Von Hippel Lindau disease. Imaging shows a 3 cm, posterior, interpolar lesion in the left kidney. Previously right-sided partial nephrectomy for 2 clear-cell RCC lesions. eGFR is 60.

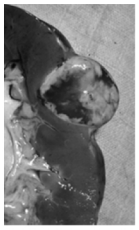
1. Open Radical Nephrectomy
2. Laparoscopic/Robotic Radical Nephrectomy
3. Open Partial Nephrectomy
4. Laparoscopic/Robotic Partial Nephrectomy
5. Kidney ablation (RFA or CRYO)
6. Active Surveillance

Partial (vs. Radical) Nx

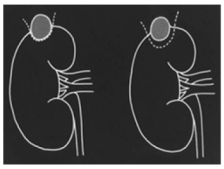
- Complication rate is higher
- Length of stay, hospital cost comparable
- Creatinine failure and dialysis need much lower
  - Adkins J.Urol 2003, Huang Lancet Oncol.2006
- Quality of life significantly better
  - Poulakis Urology 2003, Lesage Eur Urol 2007
- Still an underutilized procedure
  - Miller J.Urol 2006

Trifecta of Nephron sparing Surgery for RCC

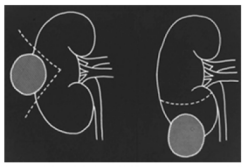
1. Oncological Cure
2. Preservation of Renal Function
3. Minimal Surgical Morbidity



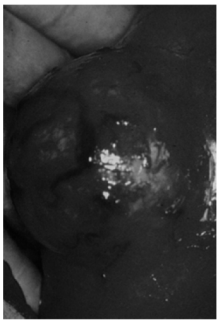
Nephron-Sparing Surgery (NSS)

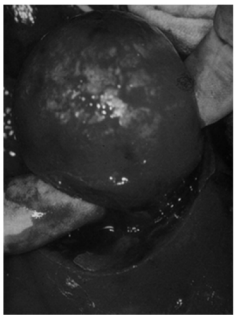


Enucleation Enucleoresection



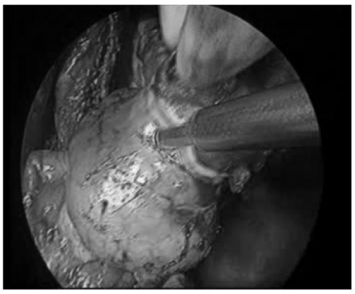
Wedge resection Polar Nephrect.

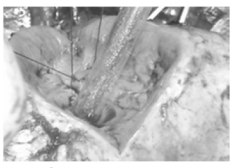




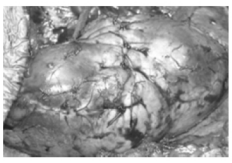
Simple Enucleation

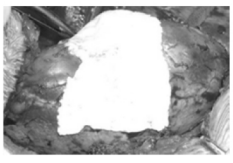
Open NSS : Enucleation



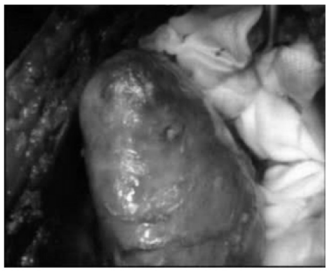


Wedge resection





Open NSS : Wedge Resection

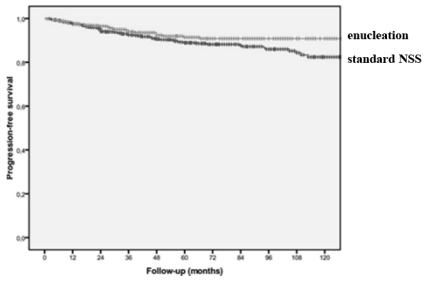


Is pure enucleation oncologically safe?

- Nonrandomized, retrospective, comparative study by SATURN Project-LUNA Foundation
- 982 standard NSS vs. 537 simple enucleation
- Cancer-specific survival at 5 and 10 y is similar
- Local recurrence is equal

Minervini et al., J.Urol. 185, 2011

Enucleation is oncologically safe



Minervini et al. J Urol 2011; 185: 1604-1610

1. NSS : Oncological Cure

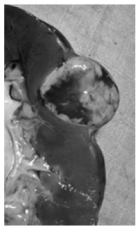
- Good exposure of the kidney
  - can sometimes be extremely tedious
  - full dissection: multifocality
- Good visualisation of the edges of the resection, mostly needing hilar clamping
- Rim of healthy parenchyma?
  - total excision is important
- EAU Guidelines : NSS for T1a-b tumors

Trifecta of Nephron sparing Surgery for RCC

1. Oncological Cure

2. Preservation of Renal Function

3. Minimal Surgical Morbidity



Chronic kidney disease after nephrectomy in patients with renal cortical tumours: a retrospective cohort study

William C Huang, Andrew S Levey, Angel M Serio, Mark Snyder, Andrew J Vickers, Ganesh V Raj, Peter T Scardino, Paul Russo

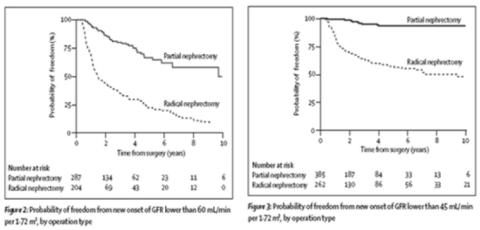
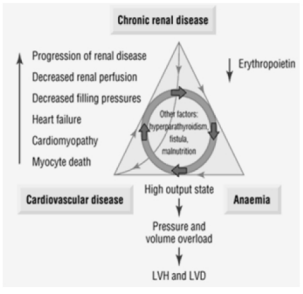


Figure 2: Probability of freedom from new onset of GFR lower than 60 mL/min per 1·72 m², by operation type

Figure 3: Probability of freedom from new onset of GFR lower than 45 mL/min per 1·72 m², by operation type

Partial Nephrectomy avoids significant renal function loss

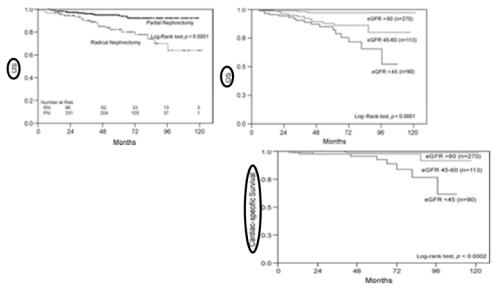
CKD leads to Cardiac disease



Kidney Cancer

Partial Nephrectomy Is Associated with Improved Overall Survival Compared to Radical Nephrectomy in Patients with Unanticipated Benign Renal Tumours

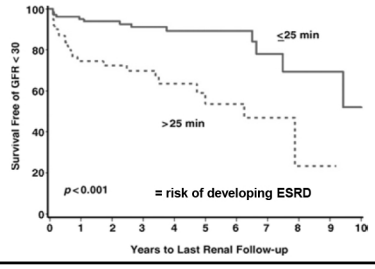
Christopher J. Weight, Gregory Lieser, Benjamin T. Larson, Tianming Gao, Brian R. Lane, Steven C. Campbell, Inderbir S. Gill, Andrew C. Novick, Amr F. Fergany



Platinum Priority – Kidney Cancer

Every Minute Counts When the Renal Hilum Is Clamped During Partial Nephrectomy

R. Houston Thompson, Brian R. Lane, Christine M. Lohse, Bradley C. Leibovich, Amr Fergany, Igor Frank, Inderbir S. Gill, Michael L. Blute, Steven C. Campbell



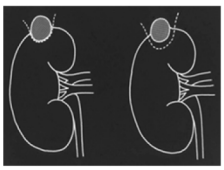
Warm Ischemia Time

WIT

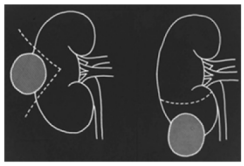
WHAT ABOUT

LARGER TUMORS ?

Nephron-Sparing Surgery (NSS)

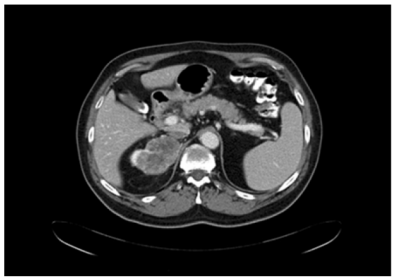


Enucleation Enucleoresection

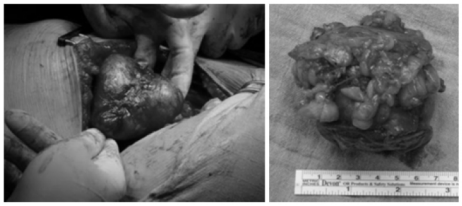


Wedge resection Polar Nephrect.

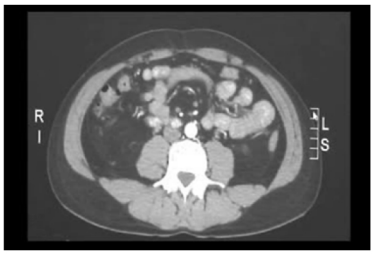
T3a Upper Pole



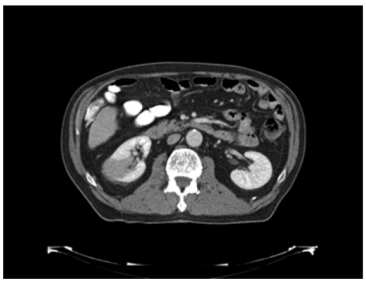
Mid - Polar resection



Larger RCC: enucleation



T2 Midpole Wedge to Enucleation



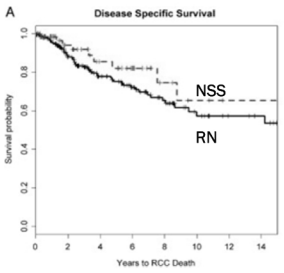
T2-T3 tumors : NSS?

- 69 patients pT2, pT3a-b Mayo Clinic
- Few complications
- Similar oncological outcomes as RN

- Deserves confirmation and further study

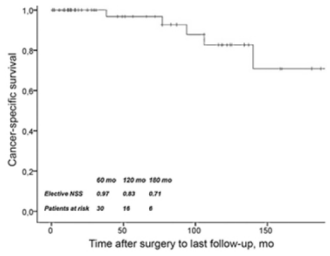
Breau R.,et al., J.Urol. 183, 2010

NSS for T2-T3 RCC



Breau et al. J Urol 2010; 183: 903 - 908

NSS for RCC > 7cm : CSS

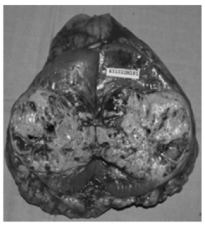


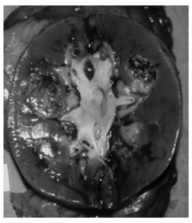
Becker et al. Eur Urol 2011; 59: 931-937

WHAT ABOUT

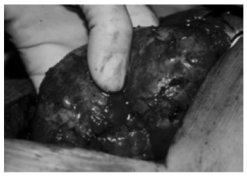
CENTRAL TUMORS ?

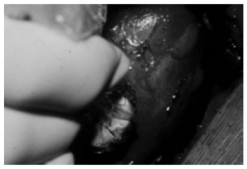
Centrally located tumors

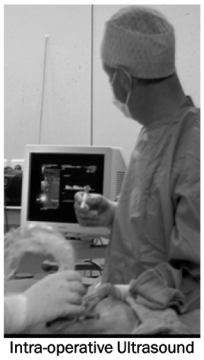




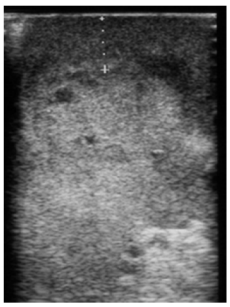
Rad.Nx **NSS ?**

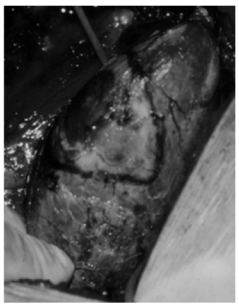




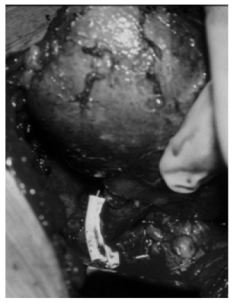


Intra-operative Ultrasound





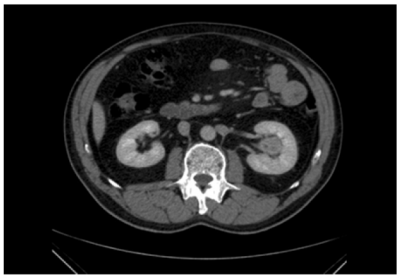
Planning intra-renal tumor resection



Hilar (A-V) Clamping

Surface Cooling

T1a Intrarenal Enucleation

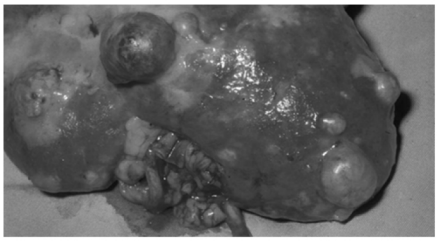


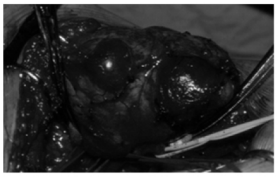
WHAT ABOUT

MULTIFOCAL

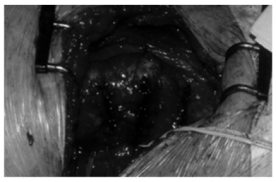
TUMORS ?

Multifocal RCC

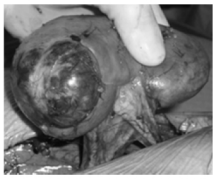


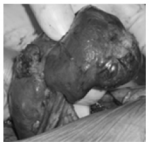


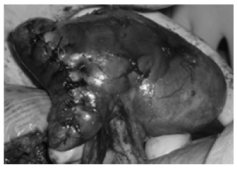
Multifocal tumors

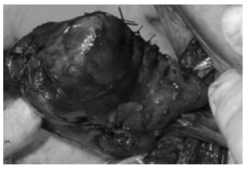


Multiple resections

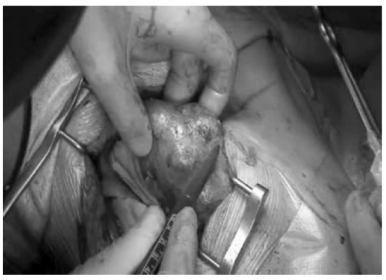








Multifocal RCC



Open NSS for T1a-b RCC

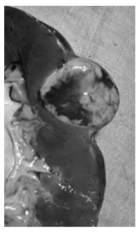
- Equals the oncological results of Radical Nx
- Enables the fastest and safest NSS, yielding the best preservation of renal function (WIT mostly around 10-15 minutes)
- Also in complex cases open NSS will be succesful, and a radical nephrectomy can thus be avoided …

Trifecta of Nephron sparing Surgery for RCC

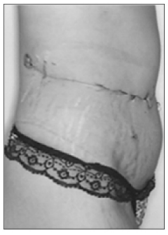
1. Oncological Cure

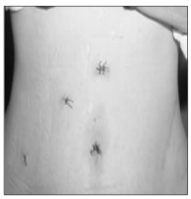
2. Preservation of Renal Function

3. Minimal Surgical Morbidity



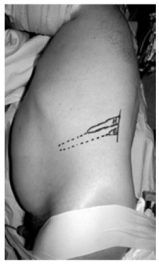
Major (only) disadvantage
of Open NSS



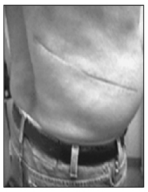


Painful wound
Cosmestic aspects

Major (only) disadvantage
of Open NSS



Neuralgia
Hernia
Bulging

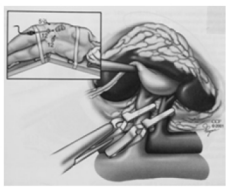


3. Minimal Surgical Morbidity

- Incision(s): Lumbotomy to be done cautiously, XIIth intercostal nerve, XIIth rib, females mobile kidneys, spinal-epidural combined
- Bleeding is usually minimal in open surgery
- Fistula or acute hemorrhage is exceptional
- Hospital stay: 5d = OK!
- Difficult cases can be done without severe complications

WHAT ABOUT

LAPAROSCOPY ?



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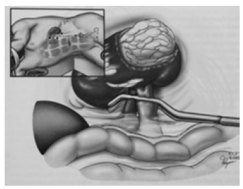
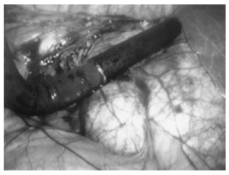
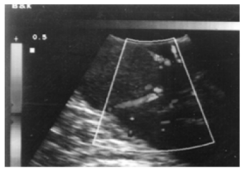
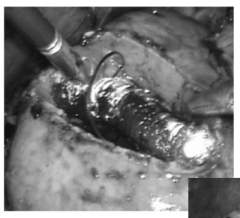
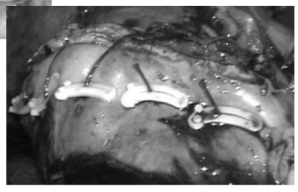








Hemostasis



Open Partial Nephrectomy

- Allows all difficult resections with very low morbidity, except for wound discomfort
- Cooling, clamping, intra-operative US applicable
- Duration of surgery and of WIT is short
- Cost for technical tools very low

Laparoscopic NSS

- Expert centers reproduce open surgery
- Hilar clamping, cooling, intraoperative ultrasound…all have been developed
- **Hemostasis and warm ischemia are the most important issues**
- The complication rate is higher than that of open surgery

⇒ **Open Partial Nx remains the gold standard**

Conclusion 1

- NSS is an established treatment in tumors < 4cm, in 4-7 cm in expert centers in selected cases, maybe even in larger tumors
- Open NSS is still standard care but laparoscopy (+/- Robot assisted) is evolving in high volume expert centers

In a regular urological department, open NSS is a guarantee for oncological cure, maximal nephron preservation, minimal WIT, but needs careful incision and closure and perioperative care.

Conclusion 2

- Laparoscopic/Robotic NSS is suboptimal for renal function preservation and should be reserved for experts
- In other hands, it should be reserved for the easy exorenal smaller tumors ☺

Expert centers have the task to further develop laparoscopic and robot techniques that can be safely used by a majority (and not by a selected minority) of urological surgeons in a majority (…) of patients

Radiofrequency Ablation (RFA) in Renal Cancer

Steven Joniau, MD, PhD
University Hospitals Leuven
Leuven
Belgium

Mechanism of radiofrequency ablation

It is a "heat based" ablative technique

- High-frequency alternating current emitted through electrode placed within targeted tissue

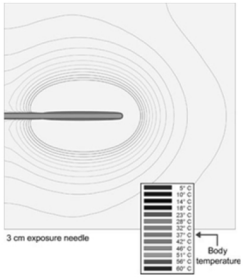
↓

- Ionic agitation with frictional heating

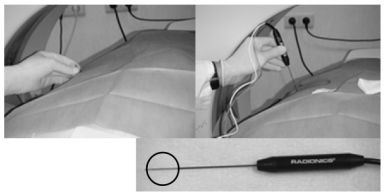
↓

- T°> 60°C → denaturation of proteins → melting of cell membranes, loss of enzymatic function, destruction of cytoplasm

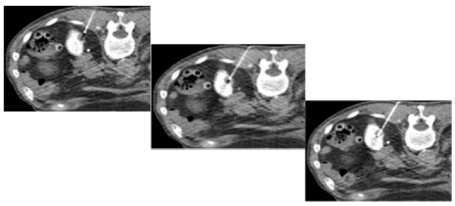
- almost spherical necrosis diameters in vivo of up to 3 cm
- in tumours larger than that several overlapping ablations are needed



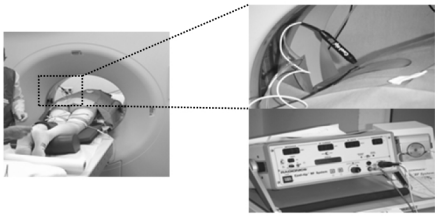
Percutaneous RFA technical points



RFA technical points



RFA technical points



Patient selection: guidelines

Why guidelines on kidney ablation?

- Detection of SRM has **increased in frequency** and is now a **common clinical scenario** for the practicing urologist.
- The **biology** of these tumors is **heterogeneous**.
  - Approx 20% are benign
  - Only 20-30% of malignant tumors demonstrate potentially aggressive features.
- **Multiple management options** are available: open/lap RN, open/lap/robotic NSS, thermal ablation, active monitoring.

EAU guidelines on kidney ablation

Recommendations	GR
Bosniak cysts ≥ type III should be regarded as RCC and be treated accordingly.	C
In angiomyolipomas, treatment (surgery, thermal ablation, and selective arterial embolisation) can be considered in: • large tumours (the recommended threshold of intervention does not exist, the formerly recommended size of > (3) 4 cm wide is disputed); • females of childbearing age; • patients in whom follow-up or access to emergency care may be inadequate. A nephron-sparing procedure is preferred.	C

http://www.uroweb.org/gls/pdf/10%20Renal%20Cell%20Carcinoma_LR.pdf

EAU guidelines on kidney ablation

Conclusions	LE
Population-based analyses show a significantly lower cancer-specific mortality for patients treated with surgery compared to non-surgical management. However, the same benefit in cancer-specific mortality is not confirmed in analyses focusing on older patients (> 75 years old).	3
In active surveillance cohorts, the growth of small renal masses is low in most cases and progression to metastatic disease is rare (1-2%).	3
The quality of the available data does not allow any definitive conclusions regarding morbidity and oncological outcomes of cryoablation and radiofrequency ablation.	3
Low quality studies suggest a higher local recurrence rate for minimally invasive therapies compared to partial nephrectomy.	3

Recommendations	GR
Due to the low quality of the available data no recommendation can be made on radiofrequency ablation and cryoablation.	C
In the elderly and/or comorbid patients with small renal masses and limited life expectancy, active surveillance, radiofrequency ablation and cryoablation can be offered.	C

http://www.uroweb.org/gls/pdf/10%20Renal%20Cell%20Carcinoma_LR.pdf

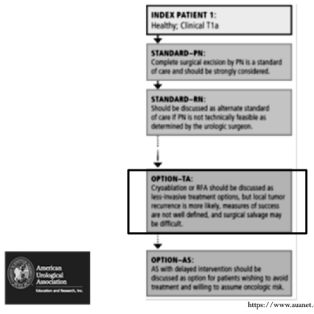
AUA guidelines on kidney ablation

Meta-analysis of outcomes for patients with clinical T1 renal masses according to treatment approach

	RADICAL NEPHRECTOMY*	PARTIAL NEPHRECTOMY*	RADIOFREQUENCY ABLATION	CRYOABLATION	ACTIVE SURVEILLANCE
Number of patients	6,235	6,418	745	644	390
Median age (years)	63	60	70	66	68
Median tumor size (cm)	5.4	3.0	2.7	2.6	2.2
Median follow-up (months)	58	47	19	17	29
Urologic complication rate (%)	1.3	6.3	6.0	4.9	NA
Local recurrence-free survival rate (%)	98.1	98.0	87.0	90.6	NA
Metastatic recurrence-free survival rate (%)	89.8	96.7	97.8	95.3	97.7
Reduction in renal function and potential impact on cardiovascular morbidity	High	Minimal	Minimal	Minimal	None

*Both radical and partial nephrectomy data are from open approaches because these provide more mature data.

AUA guidelines on kidney ablation

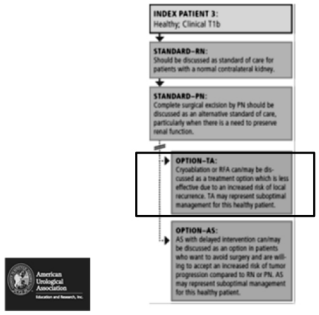


https://www.auanet.org/education/guidelines/renal-mass.cfm

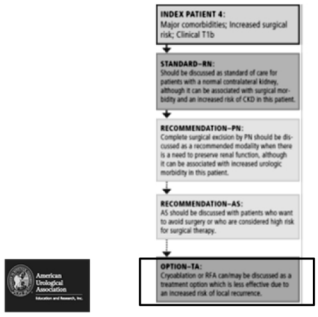
AUA guidelines on kidney ablation

https://www.auanet.org/education/guidelines/renal-mass.cfm

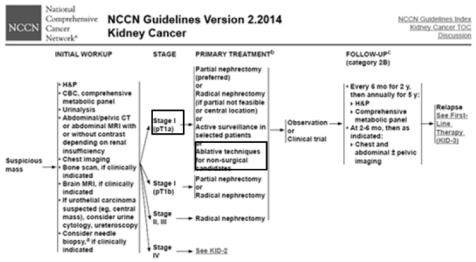
AUA guidelines on kidney ablation



AUA guidelines on kidney ablation



NCCN guidelines on kidney ablation



Summary on patient selection

- Older individuals with comorbidities who are not candidates for surgery
- Peripheral and posterior small masses (<3 cm).

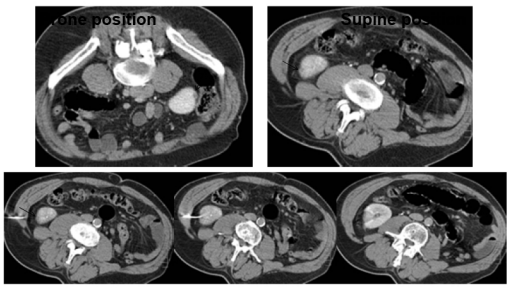
- Anterior masses, centrally located masses, large masses (>3 cm) and hilar masses **remain contraindications** because of higher local recurrence rates, potential for damaging vital organs along the needle tract and the heat sink phenomenon

Patient selection: practical issues

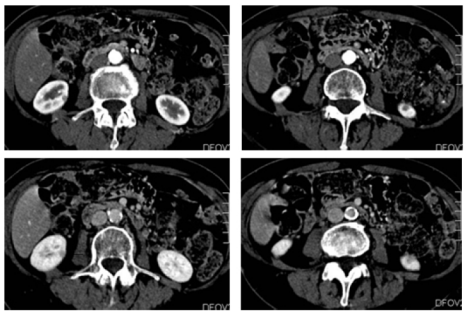
Pre-procedural imaging

- Urologist and radiologist assess technical feasibility together
- Check for anatomic location of the kidney:
  - Lungs, ribs, liver, spleen
  - Bowel (anterior lesions)
  - Ureter (medial lesions, lower pole)
- Check for tumor location (need for bowel displacement, patient positioning, ureteral stent,…)
- Eventually, patient is examined in 'intra-procedural' positioning

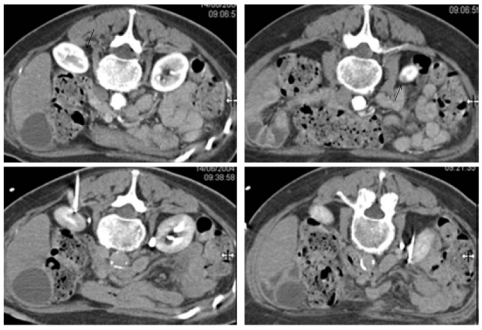
Venkatesan AM et al. Radiology 2011; Stone MJ, et al. Tech Vasc Interv Radiol 2007



Ablation performed in supine position

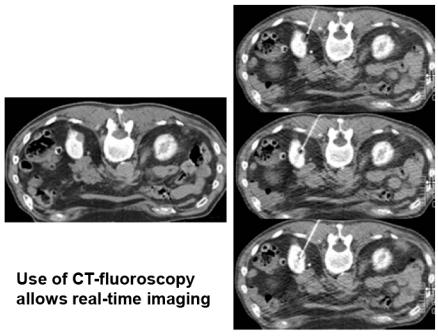


Pre-ablation: Bilateral contrast-enhancing lesion, medial and lower pole position



Proximity of the ureters: wait for excretion phase

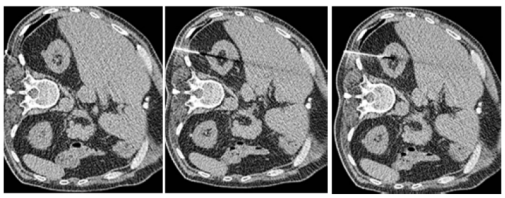
Intra-procedural imaging



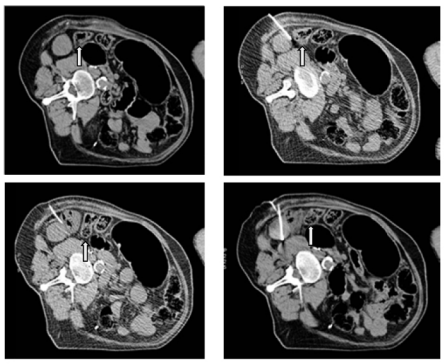
Use of CT-fluoroscopy allows real-time imaging

- Clear communication with the anesthesiologist or the patient in order to coordinate breathing

C13981528 19/05/08

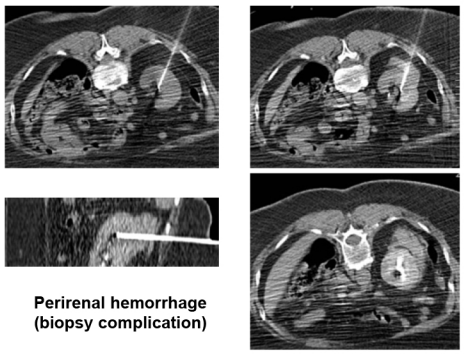


Probe placement in expiration phase
Ablation performed in lateral position



Patient follow-up: practical issues

EARLY Post-procedural imaging



Perirenal hemorrhage (biopsy complication)

Definition of succesful ablation

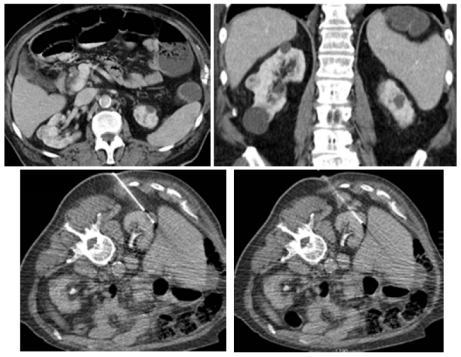
- Generally accepted:
  Absence of enhancement on contrast-enhanced CT or MRI.
- Often used as well:
  Progressive decrease in lesion size.
- Controversies: false positives / false negatives

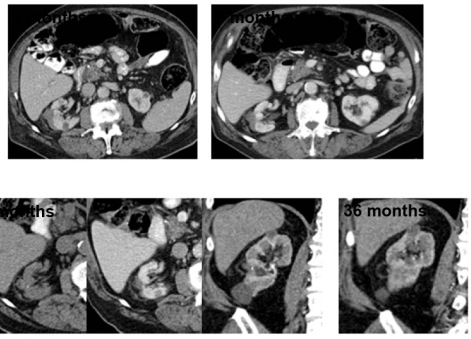
EAU guidelines on Follow-up

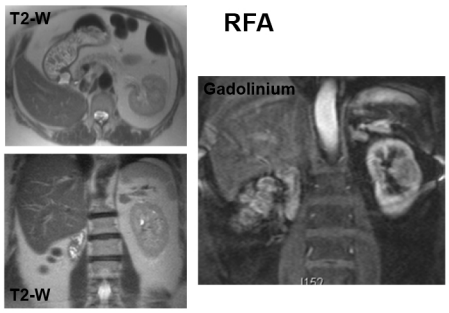
Conclusions	LE
The aim of surveillance is to detect either local recurrence or metastatic disease while the patient is still surgically curable. Renal function should be assessed.	4
Risk stratification should be based on preexisting classification systems; like the UISS integrated risk assessment score (http://urology.ucla.edu/body.cfm?id=443 [27]).	4

		Surveillance						
Risk profile	**Treatment**	**6 mo**	**1 y**	**2 y**	**3 y**	**4 y**	**5 y**	**> 5 y**
Low	RN/PN only	US	CT	US	CT	US	CT	Discharge
Intermediate	RN/PN/ cryo/RFA	CT	CT	CT	US	CT	CT	CT once every 2 years
High	RN/PN/ cryo/RFA	CT	CT	CT	CT	CT	CT	CT once every 2 years

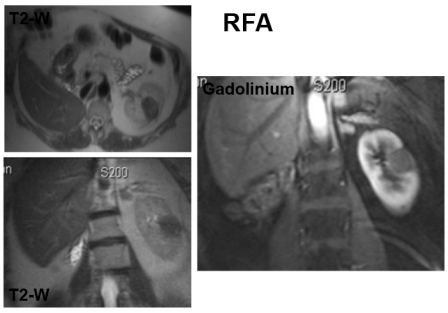
Cryo = cryotherapy; CT = computed tomography of chest and abdomen, or MRI = magnetic resonance imaging; PN = partial nephrectomy; RFA = radiofrequency ablation; RN = radical nephrectomy; US = ultrasound of abdomen, kidneys and renal bed.







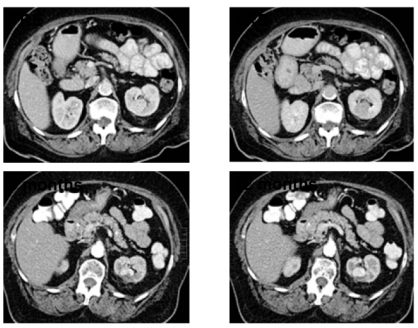
Pre-ablation contrast-enhanced MRI



Post-ablation contrast-enhanced MRI

Definition of unsuccesful ablation / recurrence

- Nodular enhancement in the ablation bed
- "Crescent" at the edge of the ablation bed
- Important: early (<3 months) post-ablation imaging may give false positive results !!!



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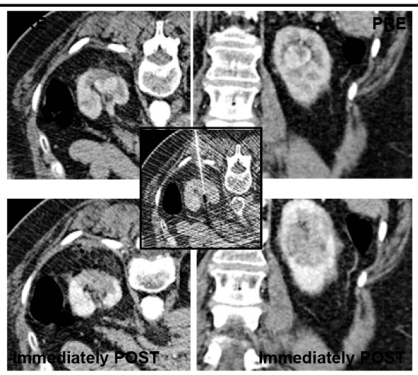
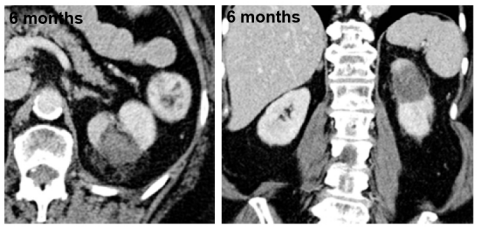




Salvage RFA is feasible, with high success rates
However, probably at a higher cost of loss of nephrons

Factors limiting the achievable ablation volumes

RFA Tissue charring that increases the electrical impedance.

- "wet" RFA (i.e. the infusion of saline into tissue to improve electrical conductivity)
- "cool-tip" RFA (i.e. probe tip cooled to prevent charring)

Vascular bed surrounding the tumour acts as a heat sink

- ablation potential of centrally located tumours is less than that of exophytic lesions

Tumour size and location - Does it matter?

Tumour size (cm)	No. of tumours with complete necrosis after one single ablation
Gervais et al. [34,35]	
≤3	52/52 (100%)
3-5	36/39 (53%)
>5	2/8 (28%)
Farrell et al. [33]	
<3.5 cm	35/35 (100%)

> 3 cm lesions require repeated cycles

Central located tumour more difficult to ablate

Location	Complete response/no. of tumours
Exophytic	68/68 (100%)
Central	7/9 (78%)
Mixed	11/18 (61%)
Parenchymal	5/5 (100%)

Data from Gervais et al. [34,35].

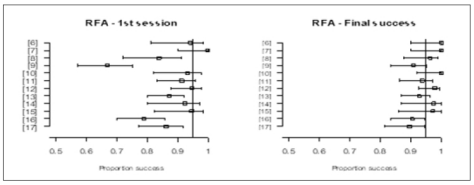
Kidney ablation: oncological outcomes

RFA re-ablation rate

Study	Nr P	Nr T	biopsy proven RCC (%)	Tum size (mm) Mean (range)	FU (months) Mean (range)	2nd - 3rd session N pts (%)
Su, 2003	29	35	31.4	22 (10-40)	9 (0-23)	2 (6.9)
Farrell, 2003	20	35	5.7	17 (9-36)	9 (1-23)	0
Varkarakis, 2005	46	56	48.2	22 (10-40)	27.5 (12-48)	5 (10.9)
Gervais, 2005	85	100	90.0	32 (11-89)	27.6 (3.5-72)	21 (24.7) 2 (2.4)
Salagierski, 2006	42	45	NA	37.5 (18-59)	14 (3-36)	3 (7.1)
Hegarty, 2006	72	81	NA	25.1 (9-45)	12	2 (2.8)
Park, 2006	78	94	69.1	24 (10-42)	25 (12-48)	3 (3.8)
Zagoria, 2007	104	125	100.0	27 (6-88)	13.8 (1-75.8)	7 (6.7)
Stern, 2007	40	40	75.0	24.1	30 (18-42)	2 (5.0)
Carey, 2007	36	37	83.8	(30-50)	11.3 (1-44)	1 (2.8)
Breen, 2007	97	105	NA	32 (11-68)	16.7 (1-76)	11 (11.3) - 1(1.0)
Veltri, 2008	68	87	NA	29 (13-75)	24.4 (1-68)	3 (4.4)

Joniau S, Tsivian M, Gontero P, Minerva Urol Nefrol 2011

Proportion of successful ablation for different studies on RFA



Jonisau S, Taivian M, Gontero P, Minerva Urol Nefrol 2011

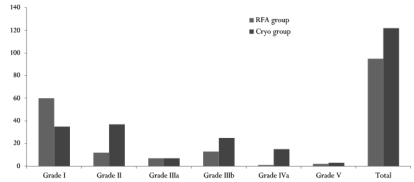
5-YEAR ONCOLOGICAL OUTCOME

	Mean FU (months)	N	Biopsy-proven RCC (%)	RFS	CSS	OS
McDougal, 2005	55.2	16	100%	94%	100%	69%
Levinson, 2008	57.4	18	100%	80%	100%	58%
Tracy, 2010	53	66	72%	93%	99%	85%
Ferakis, 2010	61.2	31	NA	87%	100%	84%
Zagoria, 2011	56 (median)	41	100%	88%	98%	59%
Olweny, 2012	78 (median)	37	100%	92%*	97%*	97%*
Psutka, 2013	77 (median)	185	100%	95%*	99%*	73%*

*** 5-year follow-up**

RFS=recurrence free survival, CSS=cancer specific survival, OS=overall survival

CRYO vs RFA: Complications



Classification following Dindo D et al. Ann Surg. 2004 Aug;240(2):205-13.

Take home messages

- The indications of image guided therapy in small renal masses are well defined and accepted by most international guidelines
- Recommended treatment in patients with SRM who have significant co-morbidity and who are unfit for surgery (EAU guidelines: GR C; AUA guidelines: RECOMMENDATION)

Take home messages

- Absence of contrast enhancement at CT or MRI is considered the gold standard definition of post-ablative success.
- Post-ablation biopsy not routinely used. Biopsy is recommended when incomplete ablation / recurrence is suspected.
- Re-ablation rates are around 10% in RFA.

Take home messages

- Convincing intermediate / long-term oncological outcomes are now available in biopsy-proven RCC.
- Complication rates are very acceptable, with mostly Grade I complications.

Immunotherapy for renal tumors

Prof. dr. Jeroen van Moorselaar
Department of Urology
Amsterdam University Medical Centers, loc. VUmc
Amsterdam, NL

I have no disclosures for this presentation

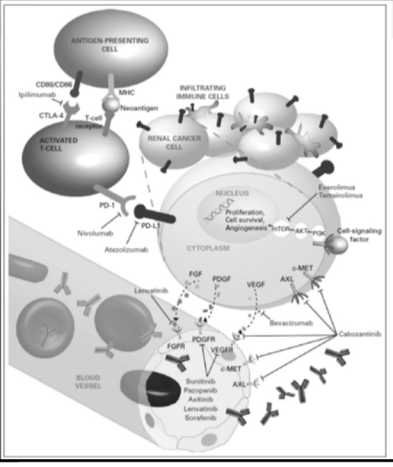
INTERFERON GAMMA-1b COMPARED WITH PLACEBO IN METASTATIC RENAL-CELL CARCINOMA

MARTIN E. GLEAVE, MOSTAFA ELHILALI, YVES FRADET, IAN DAVIS, PETER VENNER, FRED SAAD, LAURENCE H. KLOTZ, MALCOLM J. MOORE, VIRGINIA PATON, ALEX BAJAMONDE, AND THE CANADIAN UROLOGIC ONCOLOGY GROUP

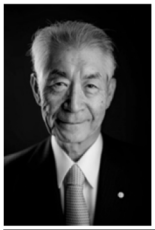
NEJM 338: 1265, 1998

VARIABLE	INTERFERON GAMMA-1b (N=91)	PLACEBO (N=90)	P VALUE
Response rates (%)*			
Overall response	4.4 (1.4 to 11.5)	6.6 (2.7 to 14.5)	0.54
Durable complete response	1 (0.1 to 6.8)	1 (0.1 to 6.9)	
Complete response	3.3	3.3	
Partial response	1.1	3.3	
Minor response	2	0	
Stable disease	31	29	
Progressive disease	63	64	
Median time to disease progression (mo)†			
Duration of response‡	>11	7	0.11
Time to progression	1.9 (1.7 to 3.9)	1.9 (1.7 to 3.8)	0.49
Median time to death (mo)†			
From first treatment	12.2 (5.2 to >19.3)	15.7 (6.5 to 18.5)	0.52
From metastatic diagnosis	18.1 (9.9 to 105.9)	21.4 (10.3 to 40.0)	0.99

*Values in parentheses are 95 percent confidence intervals.
†Values in parentheses are interquartile ranges.
‡The analysis included only patients with a complete or partial response.



McKay et al,
J. Clin. Oncol. 36: 3615, 2018



James P. Allison
7 August 1948, Alice, TX, USA

University of Texas
MD Anderson Cancer Center,
Houston, TX, USA
Parker Institute for Cancer Immunotherapy,
San Francisco, CA, USA

Tasuku Honjo
27 January 1942, Kyoto, Japan

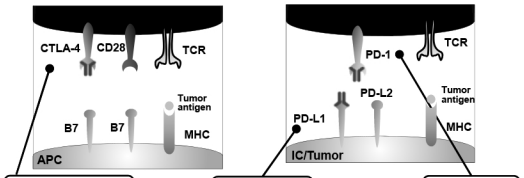
Kyoto University, Kyoto, Japan

The **Nobel Prize in Physiology or Medicine 2018** was awarded jointly to James P. Allison and Tasuku Honjo "for their discovery of cancer therapy by inhibition of negative immune regulation."

https://www.nobelprize.org/prizes/medicine/2018/summary/

Targeting the CTLA-4 and PD-1 Checkpoint Pathways

- Trials are ongoing with all of these agents in RCC



Anti–CTLA-4
- Ipilimumab
- Tremelimumab

Anti–PD-L1:
- Atezolizumab
- Avelumab
- Durvalumab

Anti–PD-1
- Nivolumab
- Pembrolizumab

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Table 6.1: Basic characteristics of three main types of RCC [38, 39, 175]

Type	Percentage of RCC (~)	Advanced disease at diagnosis (T3-4, N+, M+)	Fuhrman grade 3 or 4 [176]	CSS (HR)
clear-cell RCC	80-90%	28%	28.5%	Referent
papillary RCC	6-15%	17.6%	28.8%	0.64 - 0.85
chromophobe RCC	2-5%	16.9%	32.7%*	0.24 - 0.56

* *The Fuhrman grading system is validated for ccRCC, but is unreliable for chRCC.*
CSS = cancer-specific survival; HR = hazard ratio.

Table 6.3: Cancer-specific survival of surgically treated patients by RCC type (estimated survival rate in percentage [95% CI])

Survival time	5 years (%)	10 years (%)	15 years (%)	20 years (%)
clear-cell RCC	71 (69-73)	62 (60-64)	56 (53-58)	52 (49-55)
papillary RCC	91 (88-94)	86 (82-89)	85 (81-89)	83 (78-88)
chromophobe RCC	88 (83-94)	86 (80-92)	84 (77-91)	81 (72-90)

EAU Guidelines RCC 2018

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Ten FDA-Approved Drugs for RCC Since 2005

Approval	Agent	FDA Indication
2005	**Sorafenib**	Advanced
2006	**Sunitinib**	Advanced
2007	Temsirolimus	Advanced
2009	Bevacizumab + IFN-α	Metastatic
2009	Everolimus	After failure of sunitinib or sorafenib
2009	**Pazopanib**	Advanced
2012	**Axitinib**	Failure of prior systemic therapy
2015	Nivolumab	After failure of anti-angiogenic drug(s)
2016	**Cabozantinib**	Prior anti-angiogenic therapy
2016	**Lenvatinib** (+ everolimus)	Following 1 prior anti-angiogenic therapy

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VOLUME 27 · NUMBER 34 · DECEMBER 1 2009
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Prognostic Factors for Overall Survival in Patients With Metastatic Renal Cell Carcinoma Treated With Vascular Endothelial Growth Factor–Targeted Agents: Results From a Large, Multicenter Study

Daniel Y.C. Heng, Wanling Xie, Meredith M. Regan, Mark A. Warren, Ali Reza Golshayan, Chakshu Sahi, Bernhard J. Eigl, J. Dean Ruether, Tina Cheng, Scott North, Peter Venner, Jennifer J. Knox, Kim N. Chi, Christian Kollmannsberger, David F. McDermott, William K. Oh, Michael B. Atkins, Ronald M. Bukowski, Brian I. Rini, and Toni K. Choueiri

Table 3. Multivariable Analysis and Final Model

Parameter	Parameter Estimate ± SE	Hazard Ratio	95% CI	P
Clinical				
KPS < 80%	0.92 ± 0.14	2.51	1.92 to 3.29	< .0001
Time from diagnosis to treatment < 1 year	0.35 ± 0.13	1.42	1.09 to 1.84	.0098
Laboratory				
Hemoglobin < LLN	0.54 ± 0.14	1.72	1.31 to 2.26	.0001
Calcium > ULN	0.59 ± 0.17	1.81	1.29 to 2.53	.0006
Neutrophil count > ULN	0.88 ± 0.17	2.42	1.72 to 3.39	< .0001
Platelet count > ULN	0.40 ± 0.16	1.49	1.09 to 2.03	.0121

NOTE. Total number of patients = 564.
Abbreviations: SE, standard error; KPS, Karnofsky performance status; LLN, lower limit of normal; ULN, upper limit of normal.

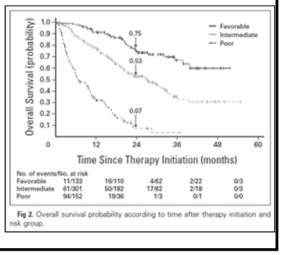

Fig 2. Overall survival probability according to time after therapy initiation and risk group.

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journal homepage: www.europeanurology.com
EUROPEAN UROLOGY 71 (2017) 518–532
eau European Association of Urology

Brief Correspondence

Updated European Association of Urology Guidelines Regarding Adjuvant Therapy for Renal Cell Carcinoma

Axel Bex[a,], Laurence Albiges[b], Börje Ljungberg[c], Karim Bensalah[d], Saeed Dabestani[c], Rachel H. Giles[e,f], Fabian Hofmann[g], Milan Hora[h], Markus A. Kuczyk[i], Thomas B. Lam[a,j], Lorenzo Marconi[a,k], Axel S. Merseburger[l], Michael Staehler[m], Alessandro Volpe[n], Thomas Powles[o]*

Study or subgroup	log[hazard ratio]	SE	Sunitinib Total	Placebo Total	Weight	Hazard ratio IV, Random, 95% CI
ASSURE	0.0198	0.0824	647	647	55.4%	1.02 [0.87, 1.20]
S-TRAC	−0.2731	0.1264	309	306	44.6%	0.76 [0.59, 0.97]
Total (95% CI)			956	953	100.0%	0.89 [0.67, 1.19]

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 3.77$, $df = 1$ ($p = 0.05$); $I^2 = 73\%$
Test for overall effect: $Z = 0.76$ ($p = 0.45$)

Hazard ratio IV, Random, 95% CI
0.01 0.1 1 10 100
Favours [Sunitinib] Favours [Placebo]

Fig. 1 – Meta-analysis of disease-free survival (DFS) for S-TRAC and ASSURE. CI = confidence interval; SE = standard error; df = degrees of freedom.

Table 1 – Recommendation of the European Association of Urology Renal Cell Cancer Guidelines Panel

Recommendation	Strength	
Adjuvant sunitinib following surgically resected high-risk clear-cell renal cell carcinoma is not recommended	Weak	↓

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Adjuvant treatment, phase 3 trials

NCT03024996
A Study of Atezolizumab as Adjuvant Therapy in Participants With Renal Cell Carcinoma (RCC) at High Risk of Developing Metastasis Following Nephrectomy (IMmotion010)

NCT03142334
Safety and Efficacy Study of Pembrolizumab (MK-3475) as Monotherapy in the Adjuvant Treatment of Renal Cell Carcinoma Post Nephrectomy (MK-3475-564/KEYNOTE-564)

NCT03138512
A Study Comparing the Combination of Nivolumab and Ipilimumab Versus Placebo in Participants With Localized Renal Cell Carcinoma (CheckMate 914)

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Neo-adjuvant treatment, phase 3 trials

NCT03055013
A Phase 3 Randomized Study Comparing Perioperative Nivolumab vs. Observation in Patients With Localized Renal Cell Carcinoma Undergoing Nephrectomy (PROSPER RCC)

CheckMate 025:
Phase 3 Trial of Nivolumab versus Everolimus in pretreated Advanced/Metastatic RCC

N=821

Key Inclusion Criteria
- Advanced/metastatic clear cell RCC
- 1 or 2 prior anti-angiogenic therapy regimens in advanced/metastatic setting
- No prior therapy with mTOR inhibitor
- Karnofsky PS ≥70%
- No CNS metastases

R 1:1

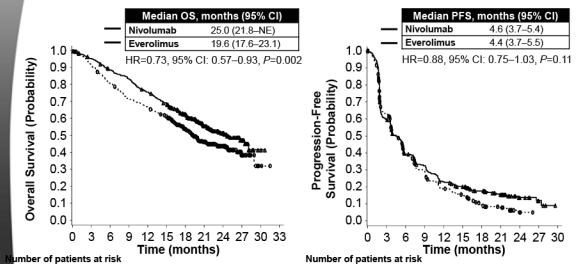
- Nivolumab 3 mg/kg q2w
- Everolimus 10 mg qd

Until progression, unacceptable toxicity, withdrawal of consent, or end of trial

Primary Outcome Measure: OS
Secondary Outcome Measures: PFS, ORR, duration of objective response, association between OS and PD-L1 status, safety, disease-related symptom progression rate, HRQoL

Motzer et al. New Engl J Med. 373:1803, 2015

CheckMate 025: OS and PFS (14-month follow-up)



Number of patients at risk

Nivolumab	410	389	359	337	305	275	213	139	73	29	3	0	
Everolimus	411	366	324	287	265	241	187	115	61	20	2	0	

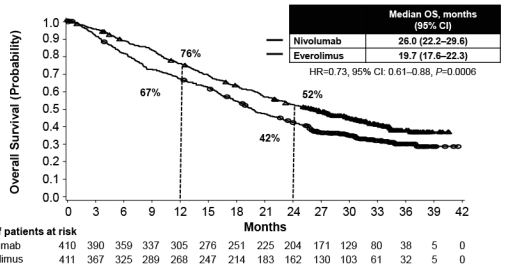
Number of patients at risk

Nivolumab	410	230	145	116	81	66	48	29	11	4	0			
Everolimus	411	227	129	97	61	47	25	16	3	0	0			

Based on data cut-off of June 2015.

Motzer et al. New Engl J Med. 373:1803, 2015

CheckMate 025: OS 26-month Follow-up



No. of patients at risk

Nivolumab	410	390	359	337	305	276	251	225	204	171	129	80	38	5	0
Everolimus	411	367	325	289	268	247	214	183	162	130	103	61	32	5	0

Adapted from Plimack et al, Kidney Cancer Symposium 2016.

Median OS benefit observed for nivolumab vs everolimus in patients with MSKCC intermediate risk (21.9 months versus 18.4 months) and poor risk (15.3 months versus 7.9 months)

Checkmate 025: Objective Response Rate

	14-Month Follow-up[1,2]		26-Month Follow-up[3]	
	Nivolumab n=410	Everolimus n=411	Nivolumab n=410	Everolimus n=411
Objective response rate, %	25	5	26	5
Best overall response, %				
Complete response	1	1	1	<1
Partial response	24	5	25	5
Stable disease	34	55	34	56
Progressive disease	35	28	35	27
Not evaluated/unable to determine	6	12	6	11
Median duration of response, months	12	12	12	12

1. Motzer RJ et al. *N Engl J Med*. 2015;373(19):1803-1813.
2. Motzer RJ et al. *N Engl J Med*. 2015;373(19):1803-1813 [supplementary appendix].
3. Plimack ER et al. Poster presentation at KCS 2016.

CheckMate 025: AEs (Top 10) (26-month follow-up)

	Nivolumab n=406		Everolimus n=397	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Treatment-related AEs	79	**20**	88	**37**
Fatigue	34	**2**	34	**3**
Nausea	15	**<1**	17	**1**
Diarrhea	14	**1**	21	**1**
Decreased appetite	12	**<1**	20	**1**
Rash	10	**<1**	20	**1**
Cough	9	**0**	19	**0**
Anemia	8	**2**	24	**9**
Mucosal inflammation	3	**0**	19	**3**
Stomatitis	2	**0**	29	**4**
Hypertriglyceridemia	1	**0**	16	**5**

Adapted from Plimack et al, 2016.

No deaths from study-drug toxicity were reported in the nivolumab group

Two deaths were reported in the everolimus group (one from septic shock and one from bowel ischemia)

NIVOREN-GETUG AFU 26 study (F), NCT03013335
safety and efficacy of Nivolumab in a 'real world setting'

Summary of the findings

	CheckMate 025	GETUG- AFU 26 NIVOREN
n	406	**720**
Median FUp	14 mo (minimum Fup)	**23.9 mo**
Median PFS	4.6 mo	**3.7 mo**
Median OS	25.0 mo	**24.5 mo**
ORR SD PD	25% 34% 35%	**21.0%** **31.1%** **47.9%**
Ttt beyond progression	44%	**47.0%**
Grade ≥3 TRAEs	19%	**17.9%**

PRESENTED AT: **2019 Genitourinary Cancers Symposium | #GU19**

Presented by: Laurence Albiges, MD PhD

VUmc CheckMate 214

CheckMate 214: Study Design

Patients

- Treatment-naïve clear-cell aRCC
- Measurable disease
- KPS ≥70%
- Tumor tissue available for PD-L1 testing

Randomize 1:1

Stratified by
- IMDC prognostic score
  - 0 (favorable risk)
  - 1 or 2 (intermediate risk)
  - 3 to 6 (poor risk)
- Region
  - US
  - Canada/Europe
  - Rest of world

Treatment

Arm A
NIVO 3 mg/kg + IPI 1 mg/kg every 3 weeks for 4 doses then NIVO 3 mg/kg every 2 weeks

Patients receiving NIVO monotherapy could to switch to NIVO 240mg flat dosing[a]

Arm B
SUN 50 mg once daily for 4 weeks on, 2 weeks off (6-week cycles)

Crossover from SUN to NIVO+IPI was permitted[b]

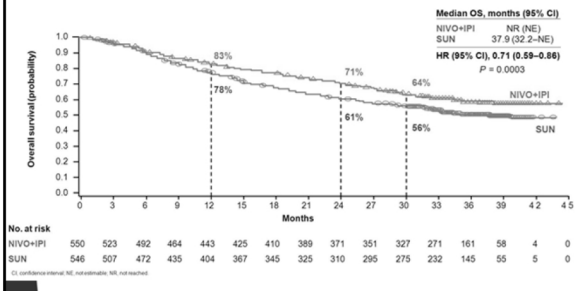
Treatment until progression or unacceptable toxicity

Patients could discontinue after 2 years of study treatment[c]

[a]As of a November 2017 protocol amendment.
IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; KPS, Karnofsky performance status; PD-L1, programmed death ligand 1.

VUmc CheckMate 214

Overall Survival: ITT Patients



No. at risk																
NIVO+IPI	550	523	492	464	443	425	410	389	371	351	327	271	161	58	4	0
SUN	546	507	472	435	404	367	345	325	310	295	275	232	145	55	5	0

CI, confidence interval; NE, not estimable; NR, not reached.

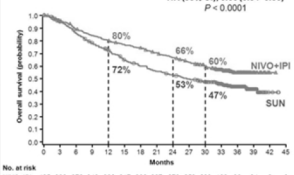
Presented By Nizar Tannir at 2019 Genitourinary Cancers Symposium

VUmc CheckMate 214

Overall Survival: by IMDC Risk

Intermediate/poor risk

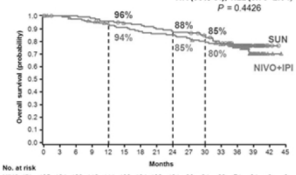
Median OS, months (95% CI)
NIVO+IPI NR (35.6–NE)
SUN 26.6 (22.1–33.4)
HR (95% CI), 0.66 (0.54–0.80)
P < 0.0001



No. at risk														
NIVO+IPI	425	399	372	348	332	317	306	287	270	253	233	183	90	34	2	0
SUN	422	388	353	318	290	257	236	220	207	194	179	144	75	29	3	0

Favorable risk

Median OS, months (95% CI)
NIVO+IPI NR (NE)
SUN NR (NE)
HR (95% CI), 1.22 (0.73–2.04)
P = 0.4426

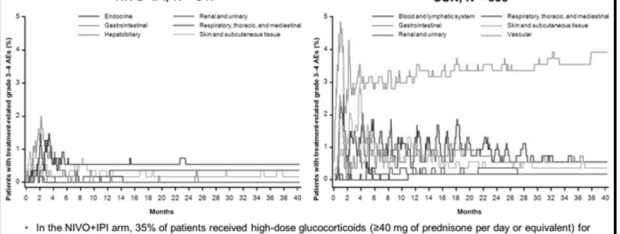


No. at risk														
NIVO+IPI	125	124	120	116	111	108	104	102	101	98	94	88	71	24	2	0
SUN	124	119	119	117	114	110	109	105	103	101	96	88	70	26	2	0

Presented By Nizar Tannir at 2019 Genitourinary Cancers Symposium

VUmc CheckMate 214

Treatment-Related AEs Over Time by Most Common System Organ Class (All Treated Patients)



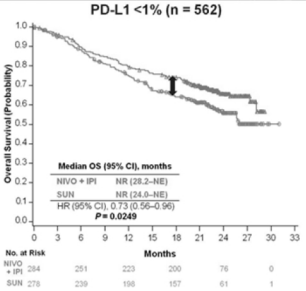
- In the NIVO+IPI arm, 35% of patients received high-dose glucocorticoids (≥40 mg of prednisone per day or equivalent) for select treatment-related AE management
- No additional treatment-related deaths occurred

Presented By Nizar Tannir at 2019 Genitourinary Cancers Symposium

Motzer et al SITC 2017

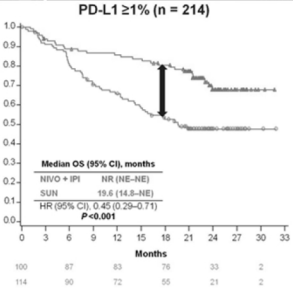
OS by tumor PD-L1 expression: IMDC intermediate/poor risk

PD-L1 <1% (n = 562)



No. at Risk						
NIVO + IPI	284	251	223	200	76	0
SUN	278	239	198	157	61	1

PD-L1 ≥1% (n = 214)



	100	87	83	76	33	2
	114	90	72	55	21	2

Presented By Cora Sternberg at 2018 Genitourinary Cancers Symposium: Translating Evidence to Multidisciplinary Care

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Drug Information Soundcast in Clinical Oncology (D.I.S.C.O.)

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FDA approves nivolumab plus ipilimumab combination for intermediate or poor-risk advanced renal cell carcinoma

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On April 16, 2018, the Food and Drug Administration granted approvals to nivolumab and ipilimumab (Opdivo and Yervoy, Bristol-Myers Squibb Co.) in combination for the treatment of intermediate or poor risk, previously untreated advanced renal cell carcinoma.

The approvals were based on CheckMate 214 (NCT02231749), a randomized open-label trial. Patients with previously untreated advanced RCC received nivolumab (3 mg/kg) plus ipilimumab (1 mg/kg) every 3 weeks for 4 doses followed by nivolumab monotherapy (3 mg/kg) every 2 weeks, or sunitinib 50 mg daily for 4 weeks followed by 2 weeks off every cycle.

Efficacy was evaluated in intermediate or poor-risk patients (n=847). The trial demonstrated statistically significant improvements in overall survival (OS) and objective response rate (ORR) for patients receiving the combination (n=425) compared with those receiving sunitinib (n=422). Estimated median OS was not estimable in the combination arm compared with 25.9 months in the sunitinib arm (hazard ratio 0.63, 95% CI: 0.44, 0.89; p<0.0001). The ORR was 41.6% (95% CI: 36.9, 46.5) for the combination versus 26.5% (95% CI: 22.4, 31) in the sunitinib arm (p<0.0001). The efficacy of the combination in patients with previously untreated renal cell carcinoma with favorable-risk disease was not established.

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

15 November 2018
EMA/CHMP/788598/2018
Committee for Medicinal Products for Human Use (CHMP)

Renal Cell Carcinoma (RCC)

Opdivo as monotherapy is indicated for the treatment of advanced renal cell carcinoma after prior therapy in adults.

Opdivo in combination with ipilimumab is indicated for the first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma

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Rationale for angiogenesis inhibitors & immunotherapy

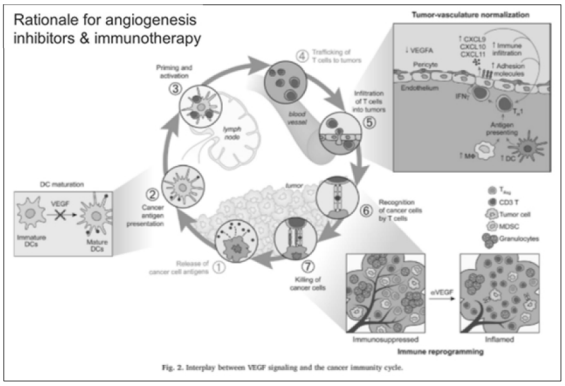

Fig. 2. Interplay between VEGF signaling and the cancer immunity cycle.

Hegde et al, Seminars Cancer Biol 52: 117, 2018

IMmotion 151: phase III study of atezolizumab in combination with bevacizumab versus sunitinib in untreated advanced RCC

Eligibility criteria:
- Locally advanced or mRCC with clear-cell and/or sarcomatoid component
- Previously untreated with any systemic therapy
- Karnofsky PS ≥70

N=830

RANDOMISATION

Atezolizumab 1200 mg IV Q3W + **bevacizumab** 15 mg/kg IV Q3W

Sunitinib 50 mg/day 4/2 schedule

www.clinicaltrials.gov (NCT02420821)

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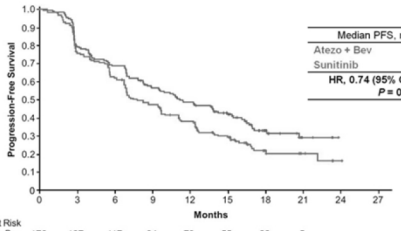
Progression-Free Survival in PD-L1+

Co-Primary Endpoint



Median PFS, mo (95% CI)	
Atezo + Bev	**11.2 (8.9, 15.0)**
Sunitinib	**7.7 (6.8, 9.7)**
HR, 0.74 (95% CI: 0.57, 0.96)	
***P* = 0.02**	

No. at Risk									
Atezo + Bev	178	137	117	94	79	55	22	5	
Sunitinib	184	135	110	83	64	44	15	7	1

PFS assessed by investigators. Minimum follow-up, 12 mo. Median follow-up, 15 mo.
The PFS analysis passed the pre-specified *P* value boundary of alpha = 0.04.

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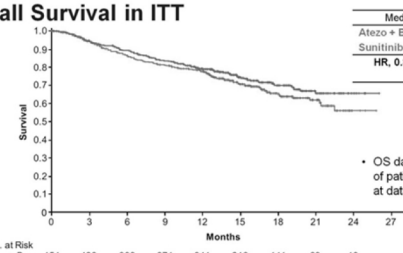
Overall Survival in ITT

Co-Primary Endpoint



Median OS, mo (95% CI)	
Atezo + Bev	**Not reached**
Sunitinib	**Not reached**
HR, 0.81 (95% CI: 0.63, 1.03)	
***P* = 0.09**	

- OS data are immature; 29% of patients had an OS event at data cutoff

No. at Risk									
Atezo + Bev	454	428	398	371	341	246	141	69	18
Sunitinib	461	422	384	357	331	227	126	65	15

Minimum follow-up, 12 mo. Median of follow-up, 15 mo. Event/patient ratio: 27% for atezo + bev, 31% for sunitinib.
The OS analysis did not pass the *P* value boundary of alpha = 0.0009 at the first interim analysis.

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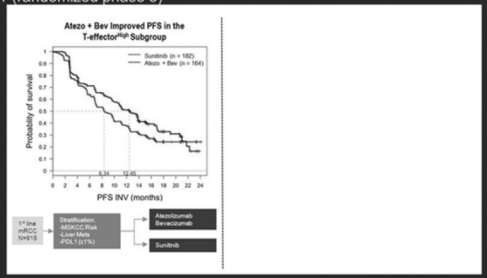
IMmotion151 (randomized phase 3)

Co-primary PFS / OS



Rini et al., EMSO 2018

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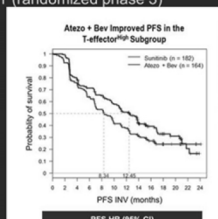
IMmotion151 (randomized phase 3)

Co-primary PFS / OS



PFS HR (95% CI)	
Atezo + bev vs sunitinib	0.76 (0.59, 0.99)

Gene Expression profiling:
--Angiogenesis signal
Positive: Atezo + Bev = Sunitinib
Negative: Atezo + Bev > Sunitinib

Rini et al., EMSO 2018

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JAVELIN Renal 101: study design

Key eligibility criteria:
- Treatment-naive aRCC with a clear cell component
- ≥ 1 measurable lesion as defined by RECIST v1.1
- Tumor tissue available for PD-L1 staining
- ECOG PS 0 or 1

Stratification:
- ECOG PS (0 vs 1)
- Geographic region (USA vs Canada/Western Europe vs ROW)

N = 886

R 1:1

Avelumab 10 mg/kg IV Q2W + Axitinib 5 mg PO BID (6-week cycle)

Sunitinib 50 mg PO QD (4 weeks on, 2 weeks off)

1º: PFS and OS in PDL1⁺ pts
2º: PFS and OS in overall pts

BID, twice per day; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **IV**, intravenous; **PO**, orally; **Q2W**, every 2 weeks; **QD**, once per day; **ROW**, rest of the world.

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Motzer et al, NEJM 2019, epub

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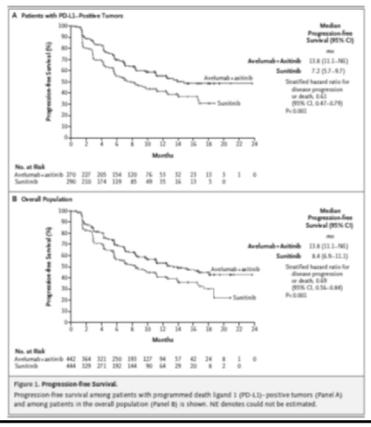

Figure 1. Progression-free Survival.
Progression-free survival among patients with programmed death ligand 1 (PD-L1)–positive tumors (Panel A) and among patients in the overall population (Panel B) is shown. NE denotes could not be estimated.

Motzer et al, NEJM 2019, epub

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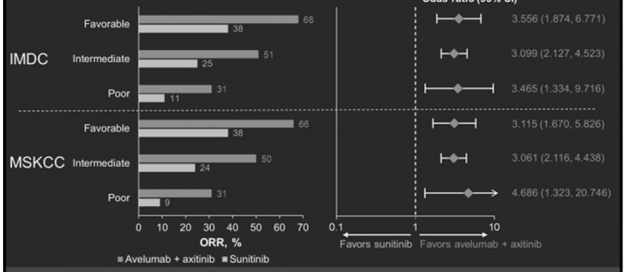
ORR per IRC in prognostic risk groups in the overall population



Presented by: Toni K. Choueiri, MD

IRC = independent review committee

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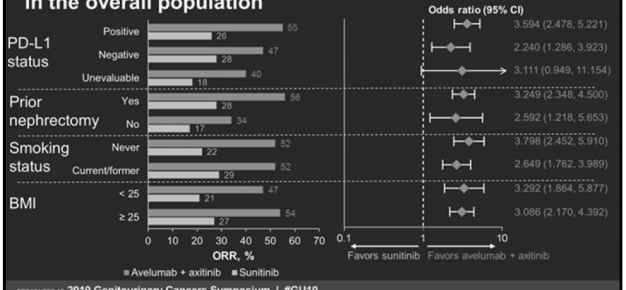
ORR per IRC in other key subgroups in the overall population



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KEYNOTE-426 Study Design

Key Eligibility Criteria
- Newly diagnosed or recurrent stage IV clear-cell RCC
- No previous systemic treatment for advanced disease
- Karnofsky performance status ≥70
- Measurable disease per RECIST v1.1
- Provision of a tumor sample for biomarker assessment
- Adequate organ function

Stratification Factors
- IMDC risk group (favorable vs intermediate vs poor)
- Geographic region (North America vs Western Europe vs ROW)

R (1:1)

N = 432: Pembrolizumab 200 mg IV Q3W for up to 35 cycles + Axitinib 5 mg orally twice daily[a]

N = 429: Sunitinib 50 mg orally once daily for first 4 wks of each 6-wk cycle[b]

End Points
- **Dual primary:** OS and PFS (RECIST v1.1, BICR) in ITT
- **Key secondary:** ORR (RECIST v1.1, BICR) in ITT
- **Other secondary:** DOR (RECIST v1.1), PROs, safety

[a]Axitinib dose could be increased to 7 mg, then 10 mg, twice daily if safety criteria were met; dose could be reduced to 3 mg, then 2 mg, twice daily to manage toxicity.
[b]Sunitinib dose could be decreased to 37.5 mg, then 25 mg, once daily for the first 4 wks of each 6-wk cycle to manage toxicity.
BICR, blinded independent central radiologic review; DOR, duration of response; PROs, patient-reported outcomes; ROW, rest of world.
KEYNOTE-426 is a randomized, open-label, phase 3 study (ClinicalTrials.gov identifier NCT02853331).

Rini et al, NEJM 2019, epub

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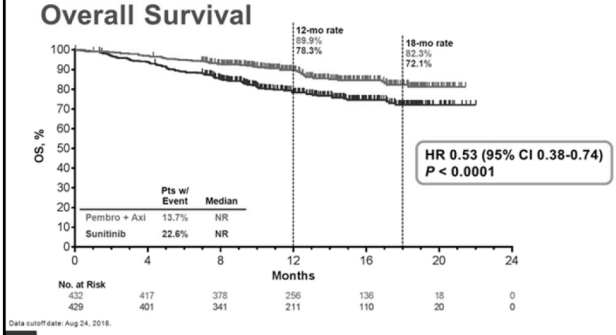
Overall Survival



Data cutoff date: Aug 24, 2018.

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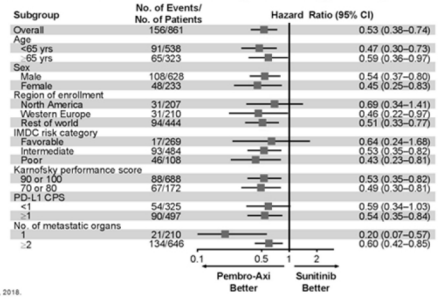
Overall Survival in Key Subgroups



Data cutoff date: Aug 24, 2018.

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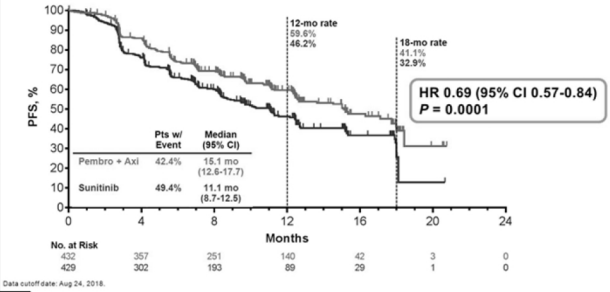
Progression-Free Survival



Data cutoff date: Aug 24, 2018.

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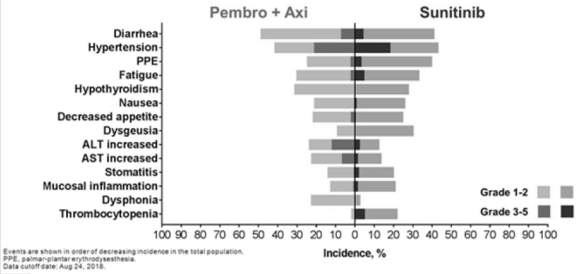
Treatment-Related Adverse Events: Incidence ≥20%



Events are shown in order of decreasing incidence in the total population.
PPE, palmar-plantar erythrodysesthesia.
Data cutoff date: Aug 24, 2018.

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Phase III IO-based Combinations in RCC-Current Status

Control	Comparator(s)	PFS (HR)	OS (HR)
Sunitinib	Nivolumab/Ipilimumab	Yes# (0.82)	Yes (0.63)
		No* (0.98)	Yes (0.68)
Sunitinib	Bevacizumab + Atezolizumab	Yes (0.88)	TE
Sunitinib	Axitinib + Avelumab	Yes (0.69)	TE (0.78)
Sunitinib	Axitinib + Pembrolizumab	Yes (today)	Yes (today)
Sunitinib	Lenvatinib + Everolimus *vs* Lenvatinib/Pembro	TE	TE
Sunitinib	Cabozantinib/Nivolumab	TE	TE

Median PFS is principal endpoint

for Intermediate and poor risk only

* ITT population

Presented By Michael Atkins at 2019 Genitourinary Cancers Symposium

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Choosing second line therapy

Determinants of therapy selection

Choices

PRESENTED AT: 2019 Genitourinary Cancers Symposium | #GU19

Presented by: @DrDanielHeng

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Post VEGF Inhibition: RCTs

Medication	Trial Comparator	Population	PFS Benefit	OS Benefit
Axitinib	Sorafenib	2nd line post VEGF/cytokines	Yes	No
Cabozantinib	Everolimus	2nd+ line post VEGF (prior nivolumab allowed)	Yes	Yes
Everolimus	Placebo	2nd+ line post VEGF	Yes	No
Lenvatinib + Everolimus	Everolimus (third arm Lenva)	2nd+ line post VEGF (prior CPI allowed)	Yes (PhII)	Yes (PhII)
Nivolumab	Everolimus	2nd or 3rd line post VEGF	No	Yes
Tivozanib	Sorafenib	3rd or 4th line post VEGF	Yes	Immature

Rini et al Lancet 2011, Choueiri et al NEJM 2015, Motzer et al Lancet 2008, Motzer et al Lancet Oncol 2016, Motzer et al NEJM 2015, Rini et al GU ASCO 2019

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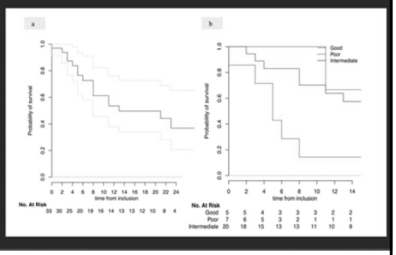
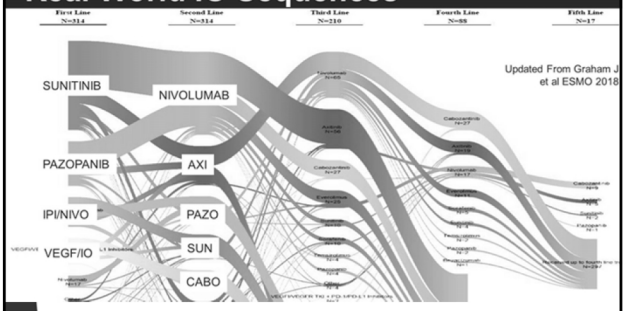
TKI Post Ipi/Nivo Retrospective Study

- Overall Response Rate 12/30 (36%)
- Median PFS: 8 months
- OS: 54% at 12 months
- Type of TKIs used:
  - Sunitinib (17)
  - Axitinib (8)
  - Pazopanib (6)
  - Cabozantinib (2)



Auvray et al, Eur J Cancer 108: 33, 2019

Real World IO Sequences



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Beyond First Line Therapy

	2nd LINE	3rd LINE
Post VEGF	• Cabozantinib (L1 OS) • Nivolumab (L1 OS) • Lenvatinib+Everolimus (L1 OS Ph2) • Axitinib (L1 PFS)	• Targeted therapy not previously used
Post Ipi/Nivo	• VEGF Targeted Therapy (L2) • E.g. cabozantinib, axitinib, sunitinib, pazopanib	• Targeted therapy not previously used
Post VEGF/PD(L)1	• VEGF Targeted Therapy (not previously used) (L2)	• Targeted therapy not previously used

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- Variety of second-line treatment options
  - Post IO: real world evidence and prospective trials should guide funding decisions
  - VEGF seem to be favored over mTOR post IO
- There are no biomarkers for therapy selection
- Rapid pace of change as new therapies emerge

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Several questions on optimization of the use of immune checkpoint inhibitors (ICI)

- What is the optimal stage of disease and sequence in which to use different therapeutic agents?
- In the adjuvant setting, what degree of cancer burden is required for an immune effect to occur?
- Should checkpoint inhibitors be given before surgical removal of the primary tumor and/or draining lymph nodes?
- Individualization of patient therapy by identification of predictive factors for response. Biomarkers?
- Optimal duration of therapy with ICIs?

Atkins et al, Annals of Oncology 28: 1484–1494, 2017

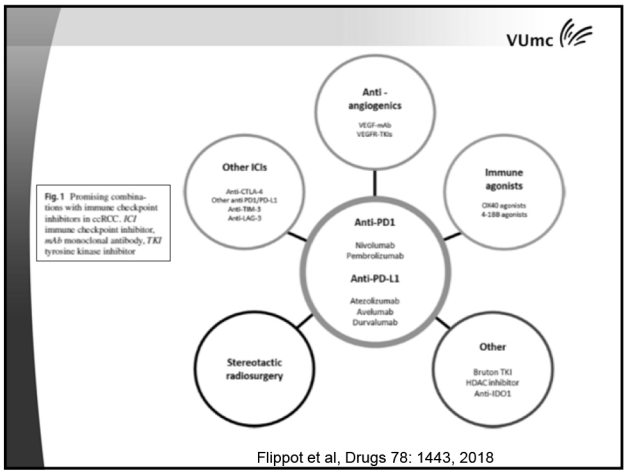


Fig. 1 Promising combinations with immune checkpoint inhibitors in ccRCC. *ICI* immune checkpoint inhibitor, *mAb* monoclonal antibody, *TKI* tyrosine kinase inhibitor

Flippot et al, Drugs 78: 1443, 2018

	First-line therapy	Second-line therapy	Third-line therapy
IMDC favourable-risk disease	Sunitinib or Pazopanib	Cabozantinib or nivolumab	Cabozantinib or nivolumab
IMDC intermediate- and -poor risk disease	Ipilimumab/ nivolumab	Cabozantinib or VEGF-targeted therapy	Cabozantinib or an alternative targeted therapy
	Cabozantinib, Sunitinib Pazopanib *	VEGF-targeted therapy or nivolumab	An alternative targeted therapy or nivolumab

Boxed categories represent strong recommendations

Ljungberg et al, Eur Urol 2019, epub

EAU Guidelines Recommendations on Bladder cancer

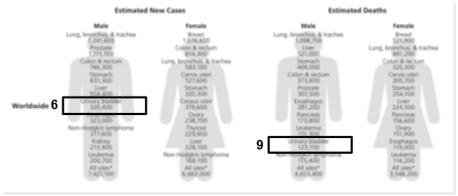
Steven Joniau, MD, PhD
Dept of Urology
University Hospitals Leuven
Belgium

Overview

1. Epidemiology
2. Diagnosis
3. Clinical staging
4. Primary treatment (TURBT +/- MMC)
5. Risk stratification
6. Bladder instillations: MMC / BCG
7. Management of BCG failure / resistance
8. Follow-up of patients with NMIBC
9. Management of patients with MIBC
10. Prognosis

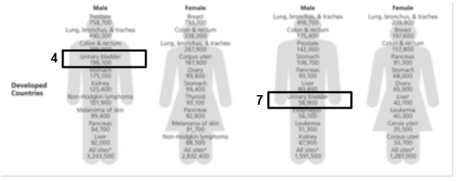
Epidemiology

Estimated new cases and deaths Worldwide, 2012



Torre LA, et al. CA Cancer J Clin 2015

Estimated new cases and deaths Developed World, 2012



Torre LA, et al. CA Cancer J Clin 2015

Summary of evidence and recommendations for epidemiology and risk factors

Summary of evidence	LE
Worldwide, bladder cancer is the 11th most commonly diagnosed cancer.	2a
Several risk factors connected with the risk of BC diagnosis have been identified.	3
Active and passive tobacco smoking continues to be the main risk factor, while the exposure-related incidence is decreasing.	2a
The increased risk of developing bladder cancer in patients undergoing external-beam radiotherapy (EBRT), brachytherapy (BT), or a combination of EBRT and BT, must be taken into account during patient follow-up. As bladder cancer requires time to develop, patients treated with radiation at a young age are at the greatest risk and should be followed up closely.	3

Recommendations	GR
The principal preventable risk factor for MIBC is active and passive smoking.	B
Notwithstanding stricter regulations, workers should be informed about the potential carcinogenic effects of a number of recognised substances, duration of exposure, and latency periods. Protective measures should be recommended.	A

Diagnosis

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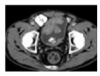
Diagnostic tests

- Urinalysis
- Urine cytology (voided urine or bladder wash)
  - False negative in low-grade tumors!

- Physical exam, bimanual palpation
- Cystoscopy

- Ultrasound



- CT

- MRI

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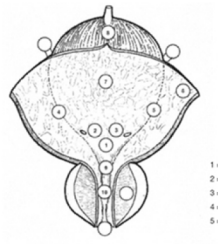
Cystoscopy



1 = Trigone
2 = Right ureteral orifice
3 = Left ureteral orifice
4 = Right wall
5 = Left wall
6 = Anterior wall
7 = Posterior wall
8 = Dome
9 = Neck
10 – Posterior urethra

9

Summary of evidence and guidelines for the primary assessment of non-muscle-invasive bladder cancer

Summary of evidence	LE
The diagnosis of bladder cancer depends on cystoscopy examination.	1
Urinary cytology has high sensitivity in high-grade tumours including carcinoma *in situ*.	2b

Recommendations	Strength rating
Take a patient history, focusing on urinary tract symptoms and haematuria.	Strong
Use renal and bladder ultrasound and/or computed tomography-intravenous urography (CT-IVU) during the initial work-up in patients with haematuria.	Strong
Once a bladder tumour has been detected, perform a CT urography in selected cases (e.g., tumours located in the trigone, multiple- or high-risk tumours).	Strong
Perform cystoscopy in patients with symptoms suggestive of bladder cancer or during surveillance. It cannot be replaced by cytology or by any other non-invasive test.	Strong
In men, use a flexible cystoscope, if available.	Strong
Describe all macroscopic features of the tumour (site, size, number and appearance) and mucosal abnormalities during cystoscopy. Use a bladder diagram (Figure 5.1).	Strong
Use voided urine cytology as an adjunct to cystoscopy to detect high-grade tumour.	Strong
Perform cytology on at least 25 mL fresh urine or urine with adequate fixation. Morning urine is not suitable because of the frequent presence of cytolysis.	Strong
Use the Paris system for cytology reporting.	Strong

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Clinical staging

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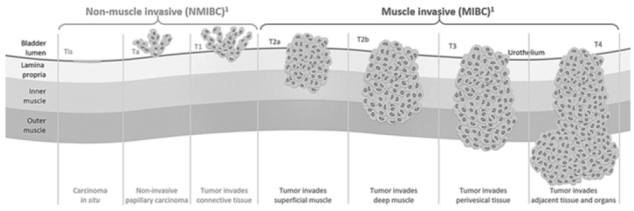
T-stage



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2017 TNM classification of urinary bladder cancer

T - Primary tumour		
TX	Primary tumour cannot be assessed	
T0	No evidence of primary tumour	
Ta	Non-invasive papillary carcinoma	
Tis	Carcinoma *in situ*: 'flat tumour'	
T1	Tumour invades subepithelial connective tissue	
T2	Tumour invades muscle	
	T2a	Tumour invades superficial muscle (inner half)
	T2b	Tumour invades deep muscle (outer half)
T3	Tumour invades perivesical tissue	
	T3a	Microscopically
	T3b	Macroscopically (extravesical mass)
T4	Tumour invades any of the following: prostate stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall	
	T4a	Tumour invades prostate stroma, seminal vesicles, uterus or vagina
	T4b	Tumour invades pelvic wall or abdominal wall

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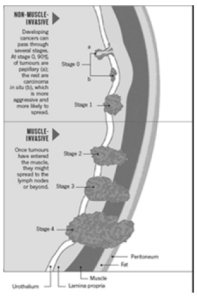

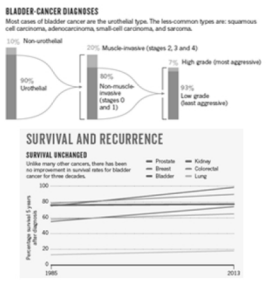

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2017 TNM classification of urinary bladder cancer

N – Regional lymph nodes		
NX	Regional lymph nodes cannot be assessed	
N0	No regional lymph node metastasis	
N1	Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral)	
N2	Metastasis in multiple regional lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)	
N3	Metastasis in common iliac lymph node(s)	
M - Distant metastasis		
M0	No distant metastasis	
	M1a	Non-regional lymph nodes
	M1b	Other distant metastases

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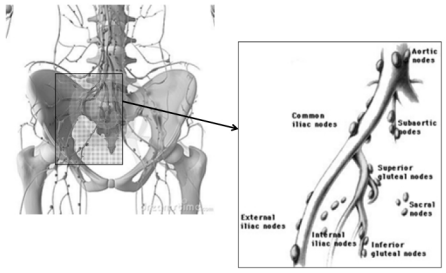
N-stage – Lymph node invasion



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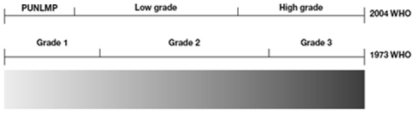
WHO grading in 1973 and in 2004

1973 WHO grading
Grade 1: well differentiated
Grade 2: moderately differentiated
Grade 3: poorly differentiated

2004 WHO grading system (papillary lesions)
Papillary urothelial neoplasm of low malignant potential (PUNLMP)
Low-grade (LG) papillary urothelial carcinoma
High-grade (HG) papillary urothelial carcinoma



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Summary of evidence and guidelines for bladder cancer classification

Summary of evidence	LE
The depth of invasion (staging) is classified according to the TNM classification.	2a
Papillary tumours confined to the mucosa and invading the lamina propria are classified as stage Ta and T1, respectively. Flat, high-grade tumours that are confined to the mucosa are classified as CIS (Tis).	2a
For histological classification of NMIBC, both the WHO 1973 and 2004 grading systems are used.	2a

Recommendations	Strength rating
Use the 2017 TNM system for classification of the depth of tumour invasion (staging).	Strong
Use both the 1973 and 2004/2016 WHO grading systems for histological classification.	Strong
Do not use the term 'superficial bladder cancer'.	Strong
Mention the tumour stage and grade whenever the terminology NMIBC is used in individual cases.	Strong

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Primary treatment
(TURBT +/- MMC)

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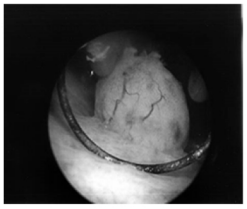
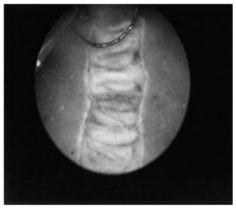
TURBT





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Summary of evidence and guidelines for transurethral resection of the bladder, biopsies and pathology report

Summary of evidence	LE
Transurethral resection of the bladder (TURB) followed by pathology investigation of the obtained specimen(s) is an essential step in the treatment of NMIBC.	1
The absence of detrusor muscle in the specimen is associated with a significantly higher risk of residual disease and tumour understaging (with the exception of TaLG tumours).	2b
In patients with a history of small TaLG/G1 tumours, fulguration of small papillary recurrences on an outpatient basis is feasible and safe.	3
A second TURB can detect residual tumours and tumour understaging, increase recurrence-free survival, improve outcomes after BCG treatment and provide prognostic information.	2

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Summary of evidence and guidelines for transurethral resection of the bladder, biopsies and pathology report

Recommendations	Strength rating
In patients suspected of having bladder cancer, perform a TURB followed by pathology investigation of the obtained specimen(s) as a diagnostic procedure and initial treatment step.	Strong
Outpatient fulguration or laser vaporisation of small papillary recurrences can be used in patients with a history of TaG1/LG tumours.	Weak
Perform TURB systematically in individual steps: • bimanual palpation under anaesthesia. This step may be omitted in case non-invasive or early treatment for invasive disease is planned; • insertion of the resectoscope, under visual control with inspection of the whole urethra; • inspection of the whole urothelial lining of the bladder; • biopsy from the prostatic urethra (if indicated); • cold-cup bladder biopsies (if indicated); • resection of the tumour; • recording of findings in the surgery report/record; • precise description of the specimen for pathology evaluation.	Strong

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Summary of evidence and guidelines for transurethral resection of the bladder, biopsies and pathology report

Performance of individual steps	
Perform *en-bloc* resection or resection in fractions (exophytic part of the tumour, the underlying bladder wall and the edges of the resection area). The presence of detrusor muscle in the specimen is required in all cases except for TaG1/LG tumours.	Strong
Avoid cauterisation as much as possible during TURB to avoid tissue deterioration.	Strong
Take biopsies from abnormal-looking urothelium. Biopsies from normal-looking mucosa (mapping biopsies from the trigone, bladder dome, right, left, anterior and posterior bladder wall) are recommended when cytology is positive, in case of a history of HG/G3 tumours and in tumours with non-papillary appearance. If equipment is available, perform fluorescence-guided (PDD) biopsies.	Strong
Take a biopsy of the prostatic urethra in cases of bladder neck tumour, when bladder carcinoma *in situ* is present or suspected, when there is positive cytology without evidence of tumour in the bladder, or when abnormalities of the prostatic urethra are visible. If biopsy is not performed during the initial procedure, it should be completed at the time of the second resection.	Strong
Take the biopsy from abnormal areas in the prostatic urethra and from the precollicular area (between the 5 and 7 o'clock position) using a resection loop. In primary non-muscle-invasive tumours when stromal invasion is not suspected, cold-cup biopsy with forceps can be used.	Weak

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Use methods to improve tumour visualization (fluorescence cystoscopy, narrow-band imaging) during TURB, if available.	Weak
Refer the specimens from different biopsies and resection fractions to the pathologist in separately labelled containers.	Weak
The TURB record must describe tumour location, appearance, size and multifocality, all steps of the procedure, as well as extent and completeness of resection.	Strong
In patients with positive cytology, but negative cystoscopy, exclude an upper tract urothelial carcinoma, CIS in the bladder (by mapping biopsies or PDD-guided biopsies) and tumour in the prostatic urethra (by prostatic urethra biopsy).	Strong
Perform a second TURB in the following situations: • after incomplete initial TURB, or in case of doubt about completeness of a TURB); • if there is no muscle in the specimen after initial resection, with the exception of TaLG/G1 tumours and primary CIS; • in T1 tumours.	Strong
If indicated, perform a second TURB within two-six weeks after initial resection. This second TURB should include resection of the primary tumour site.	Weak
Register the pathology results of a second TURB as it reflects the quality of the initial resection.	Weak
Inform the pathologist of prior treatments (intravesical therapy, radiotherapy, etc.).	Strong
The pathological report should specify tumour location, tumour grade and stage, lymphovascular invasion, unusual (variant) histology, presence of CIS and detrusor muscle.	Strong

24

Use methods to improve tumour visualization (fluorescence cystoscopy, narrow-band imaging) during TURB, if available.	Weak
Refer the specimens from different biopsies and resection fractions to the pathologist in separately labelled containers.	Weak
The TURB record must describe tumour location, appearance, size and multifocality, all steps of the procedure, as well as extent and completeness of resection.	Strong
In patients with positive cytology, but negative cystoscopy, exclude an upper tract urothelial carcinoma, CIS in the bladder (by mapping biopsies or PDD-guided biopsies) and tumour in the prostatic urethra (by prostatic urethra biopsy).	Strong
Perform a second TURB in the following situations: • after incomplete initial TURB, or in case of doubt about completeness of a TURB); • if there is no muscle in the specimen after initial resection, with the exception of TaLG/G1 tumours and primary CIS; • in T1 tumours.	Strong
If indicated, perform a second TURB within two-six weeks after initial resection. This second TURB should include resection of the primary tumour site.	Weak
Register the pathology results of a second TURB as it reflects the quality of the initial resection.	Weak
Inform the pathologist of prior treatments (intravesical therapy, radiotherapy, etc.).	Strong
The pathological report should specify tumour location, tumour grade and stage, lymphovascular invasion, unusual (variant) histology, presence of CIS and detrusor muscle.	Strong

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Risk stratification

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Risk stratification

EORTC

Predicts recurrence & progression in NMIBC patients

- Number of tumors
- Tumor size
- Prior recurrence rate
- T category
- Tumor grade
- Concomitant CIS

CUETO

Predicts recurrence & progression in NMIBC patients **treated with BCG**

- Sex
- Age
- Number of tumors
- Prior recurrence rate
- T category
- Tumor grade
- Associated CIS

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EORTC

Weighting used to calculate disease recurrence and progression scores

Factor	Recurrence	Progression
Number of tumours		
Single	0	0
2-7	3	3
≥ 8	6	3
Tumour diameter		
< 3 cm	0	0
≥ 3	3	3
Prior recurrence rate		
Primary	0	0
≤ 1 recurrence/year	2	2
> 1 recurrence/year	4	2
Category		
Ta	0	0
T1	1	4
Concurrent CIS		
No	0	0
Yes	1	6
Grade		
G1	0	0
G2	1	0
G3	2	5
Total Score	**0-17**	**0-23**

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EORTC

Probability of recurrence and disease progression according to total score

Recurrence score	Probability of recurrence at 1 year		Probability of recurrence at 5 years	
	%	(95% CI)	%	(95% CI)
0	15	(10-19)	31	(24-37)
1-4	24	(21-26)	46	(42-49)
5-9	38	(35-41)	62	(58-65)
10-17	61	(55-67)	78	(73-84)

Progression score	Probability of progression at 1 year		Probability of progression at 5 years	
	%	(95% CI)	%	(95% CI)
0	0.2	(0-0.7)	0.8	(0-1.7)
2-6	1	(0.4-1.6)	6	(5-8)
7-13	5	(4-7)	17	(14-20)
14-23	17	(10-24)	45	(35-55)

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NMIBC – Risk group stratification

Risk group stratification	Characteristics
Low-risk tumours	Primary, solitary, TaG1 (PUNLMP, LG*), < 3 cm, no CIS
Intermediate-risk tumours	All tumours not defined in the two adjacent categories (between the category of low- and high risk).
High-risk tumours	Any of the following: • T1 tumour • G3 (HG**) tumour • carcinoma *in situ* (CIS) • Multiple, recurrent and large (> 3 cm) TaG1G2 /LG tumours (all features must be present)*.
	Subgroup of highest risk tumours:
	T1G3/HG associated with concurrent bladder CIS, multiple and/or largeT1G3/HG and/or recurrent T1G3/HG,T1G3/HG with CIS in the prostatic urethra, some forms of variant histology of urothelial carcinoma, lymphovascular invasion.

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Summary of evidence and guidelines for stratification of non-muscle-invasive bladder cancer

Summary of evidence	LE
The EORTC scoring system and risk tables predict the short- and long-term risks of disease recurrence and progression in individual patients with non-muscle-invasive bladder cancer (NMIBC).	2a
Patients with Ta G1/G2 tumours receiving chemotherapy have been further stratified into three risk groups for recurrence, taking into account the history of recurrences, history of intravesical treatment, tumour grade, number of tumours and adjuvant chemotherapy.	2a-b
In patients treated with BCG, the CUETO scoring model predicts the short- and long-term risks of disease recurrence and progression.	2a
In patients receiving BCG maintenance; prior recurrence rate and number of tumours are the most important prognostic factors for disease recurrence.	2a
Stage and grade are the most important prognostic factors for disease progression and disease-specific survival.	2a
Patient age and grade are the most important prognostic factors for overall survival.	2a

Recommendations	Strength rating
Stratify patients into three risk groups according to Table 6.3.	Strong
Apply the EORTC risk tables and calculator for the prediction of the risk of tumour recurrence and progression in different intervals after transurethral resection of the bladder, in individual patients.	Strong
Use the CUETO risk tables and the EORTC risk groups for the prediction of the risk of tumour recurrence and progression in individual patients treated with bacillus Calmette-Guérin.	Strong

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Bladder instillations: MMC / BCG

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Adjuvant single instillation

Summary of evidence	LE
In patients with non-muscle-invasive bladder cancer and a prior low recurrence rate (to one recurrence per year) and in those with an EORTC recurrence score < 5, a single instillation (SI) significantly reduces the recurrence rate compared to transurethral resection of the bladder alone.	1a
Single instillation might have an impact on recurrence even when further adjuvant chemotherapy instillations are given.	3
Repeat chemotherapy instillations (with or without previous SI) improve recurrence-free survival in intermediate-risk patients.	2a

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Adjuvant single instillation

General recommendations	Strength rating
In patients with tumours presumed to be at low risk and in those presumed to be at intermediate risk with previous low recurrence rate (less than one recurrence per year) and expected EORTC recurrence score < 5, one immediate chemotherapy instillation is recommended.	Strong
Recommendations - technical aspects for treatment	
Intravesical chemotherapy	
If given, administer a single immediate instillation of chemotherapy within 24 hours after TURB.	Weak
Omit a single immediate instillation of chemotherapy in any case of overt or suspected bladder perforation or bleeding requiring bladder irrigation.	Strong
Give clear instructions to the nursing staff to control the free flow of the bladder catheter at the end of the immediate instillation.	Strong
The optimal schedule and duration of further intravesical chemotherapy instillation is not defined; however, it should not exceed one year.	Weak
If intravesical chemotherapy is given, use the drug at its optimal pH and maintain the concentration of the drug by reducing fluid intake before and during instillation.	Strong
The length of individual instillation should be one to two hours.	Weak

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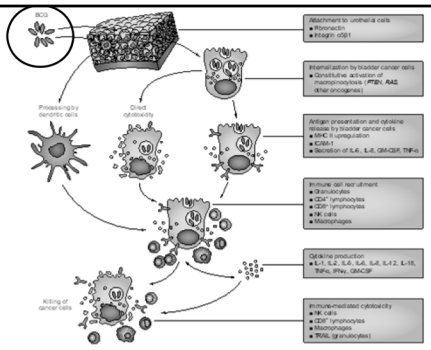

Redelman-Sidi et al, Nat Rev Urol 2014

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BCG & Treatment of CIS

Summary of evidence	LE
In patients with intermediate- and high-risk tumours, intravesical bacillus Calmette-Guérin (BCG) after TURB reduces the risk of tumour recurrence; it is more effective than TURB alone or TURB and intravesical chemotherapy.	1a
For optimal efficacy, BCG must be given in a maintenance schedule.	1a
Three-year maintenance is more effective than one year to prevent recurrence in patients with high-risk tumours, but not in patients with intermediate-risk tumours.	1a

Summary of evidence	LE
Carcinoma *in situ* (CIS) cannot be cured by an endoscopic procedure alone.	4
Compared to intravesical chemotherapy, bacillus Calmette-Guérin treatment of CIS increases the complete response rate, the overall percentage of patients who remain disease free, and reduces the risk of tumour progression.	1b

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Management options for local side effects (modified from the International Bladder Cancer Group)	
Symptoms of cystitis	Phenazopyridine, propantheline bromide, or non-steroidal anti-inflammatory drugs (NSAIDs)
	If symptoms improve within a few days: continue instillations
	If symptoms persist or worsen: a. Postpone the instillation b. Perform a urine culture c. Start empirical antibiotic treatment
	If symptoms persist even with antibiotic treatment: a. With positive culture: adjust antibiotic treatment according to sensitivity b. With negative culture: quinolones and potentially analgesic antiinflammatory instillations once daily for 5 days (repeat cycle if necessary) [241].
	If symptoms persist: anti-tuberculosis drugs and corticosteroids.
	If no response to treatment and/or contracted bladder: radical cystectomy.
Haematuria	Perform urine culture to exclude haemorrhagic cystitis, if other symptoms present.
	If haematuria persists, perform cystoscopy to evaluate presence of bladder tumour.
Symptomatic granulomatous prostatitis	Symptoms rarely present: perform urine culture.
	Quinolones.
	If quinolones are not effective: isoniazid (300 mg/day) and rifampicin (600 mg/day) for three months.
	Cessation of intravesical therapy.
Epididymo-orchitis [242]	Perform urine culture and administer quinolones.
	Cessation of intravesical therapy.
	Orchidectomy if abscess or no response to treatment.

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Management options for systemic side effects	
General malaise, fever	Generally resolve within 48 hours, with or without antipyretics.
Arthralgia and/or arthritis	Rare complication and considered autoimmune reaction.
	Arthralgia: treatment with NSAIDs.
	Arthritis: NSAIDs.
	If no/partial response, proceed to corticosteroids, high-dose quinolones or antituberculosis drugs [243].
Persistent high-grade fever (> 38.5°C for > 48 h)	Permanent discontinuation of BCG instillations.
	Immediate evaluation: urine culture, blood tests, chest X-ray.
	Prompt treatment with more than two antimicrobial agents while diagnostic evaluation is conducted.
	Consultation with an infectious diseases specialist.
BCG sepsis	Prevention: initiate BCG at least 2 weeks post-transurethral resection of the bladder (if no signs and symptoms of haematuria).
	Cessation of BCG.
	For severe infection: • High-dose quinolones or isoniazid, rifampicin and ethambutol 1.2 g daily for 6 months. • Early, high-dose corticosteroids as long as symptoms persist. • Consider an empirical non-specific antibiotic to cover Gram-negative bacteria and/or *Enterococcus*.
Allergic reactions	Antihistamines and anti-inflammatory agents.
	Consider high-dose quinolones or isoniazid and rifampicin for persistent symptoms.
	Delay therapy until reactions resolve.

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Treatment recommendations in TaT1 tumours and carcinoma *in situ* according to risk stratification

Risk category	Definition	Treatment recommendation
Low-risk tumours	Primary, solitary, TaG1 (PUNLMP, LG), < 3 cm, no CIS	One immediate instillation of intravesical chemotherapy after TURB.
Intermediate-risk tumours	All tumours not defined in the two adjacent categories (between the category of low and high risk).	In patients with previous low recurrence rate (less than or equal to one recurrence per year) and expected EORTC recurrence score < 5, one immediate instillation of intravesical chemotherapy after TURB. In all patients either one-year full-dose BCG treatment (induction plus three-weekly instillations at three, six and twelve months), or instillations of chemotherapy (the optimal schedule is not known) for a maximum of one year.
High-risk tumours	Any of the following: • T1 tumours; • G3 (HG) tumour; • CIS; • Multiple, recurrent and large (> 3 cm) TaG1/G2/LG tumours (all features must be present).	Intravesical full-dose BCG instillations for one to three years or radical cystectomy (in highest-risk tumours - *see below*).
	Subgroup of highest-risk tumours	
	T1G3/HG associated with concurrent bladder CIS, multiple and/or large T1G3/HG and/or recurrent T1G3/HG, T1G3/HG with CIS in the prostatic urethra, some forms of variant histology of urothelial carcinoma, LVI (see Sections 4.7 and 6.4).	Radical cystectomy should be considered. In those who refuse or are unfit for RC intravesical full-dose BCG instillations for one to three years.

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Guidelines for adjuvant therapy in TaT1 tumours and for therapy of carcinoma *in situ*

General recommendations	Strength rating
Counsel smokers with confirmed non-muscle-invasive bladder cancer (NMIBC) to stop smoking.	Strong
The type of further therapy after transurethral resection of the bladder (TURB) should be based on the risk groups shown in Table 6.3 and Section 7.6.	Strong
In patients with intermediate-risk tumours (with or without immediate instillation), one-year full-dose bacillus Calmette-Guérin (BCG) treatment (induction plus three-weekly instillations at 3, 6 and 12 months), or instillations of chemotherapy (the optimal schedule is not known) for a maximum of one year is recommended. The final choice should reflect the individual patient's risk of recurrence and progression as well as the efficacy and side effects of each treatment modality.	Strong
In patients with high-risk tumours, full-dose intravesical BCG for one to three years (induction plus three-weekly instillations at 3, 6, 12, 18, 24, 30 and 36 months), is indicated. The additional beneficial effect of the second and third years of maintenance should be weighed against its added costs and inconveniences.	Strong
Offer transurethral resection of the prostate, followed by intravesical instillation of BCG to patients with CIS in the epithelial lining of the prostatic urethra.	Weak

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Guidelines for adjuvant therapy in TaT1 tumours and for therapy of carcinoma *in situ*

General recommendations	Strength rating
Discuss immediate radical cystectomy (RC) with patients at the highest risk of tumour progression (see Section 7.6).	Strong
Offer a RC to patients with BCG failure (see Section 7.7).	Strong
Offer patients with BCG-refractory tumours, who are not candidates for RC due to comorbidities, preservation strategies (intravesical chemotherapy, chemotherapy and microwave-induced hyperthermia).	Weak

Recommendations - technical aspects for treatment	
BCG intravesical immunotherapy	
Absolute contraindications of BCG intravesical instillation are: • during the first two weeks after TURB; • in patients with visible haematuria; • after traumatic catheterisation; • in patients with symptomatic urinary tract infection.	Strong

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Management of BCG failure / resistance

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Categories of unsuccessful treatment with intravesical BCG

BCG failure
Whenever a MIBC is detected during follow-up.
BCG-refractory tumour: 1. If T1G3/HG, non-muscle-invasive papillary tumour is present at three months [265]. Further conservative treatment with BCG is associated with increased risk of progression [175, 266] (LE: 3). 2. If TaG3/HG or CIS (without concomitant papillary tumour) is present at both three and six months (after a second induction course or the first maintenance course of BCG). If patients with CIS present at three months, an additional BCG course can achieve a complete response in > 50% of cases [39] (LE: 3). 3. If high-grade tumour appears during BCG therapy*.
BCG relapsing tumour: 1.Recurrence of G3/HG (WHO 2004/1973) tumour after completion of BCG maintenance, despite an initial response [267] (LE: 3).
BCG unresponsive: 1.BCG refractory or T1Ta/HG BCG relapse within 6 months or development of CIS within 12 months of last BCG exposure [263].
BCG intolerance
Severe side effects that prevent further BCG instillation before completing treatment [240].

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Treatment options for bacillus Calmette-Guérin (BCG) failure

Category	Treatment options
BCG-unresponsive (BCG refractory or T1Ta/High-grade [HG] BCG relapse ≤ 6 months or CIS ≤ 12 months of last BCG exposure)	1. Radical cystectomy (RC) 2. Bladder-preserving strategies in patients unsuitable for RC
T1Ta/HG recurrence > 6 months or CIS > 12 months of last BCG exposure	1. Radical cystectomy or repeat BCG course according to individual situation 2. Bladder-preserving strategies
Non-HG recurrence after BCG for primary intermediate-risk tumour	1. Repeat BCG or intravesical chemotherapy 2. Radical cystectomy

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Follow-up of patients with NMIBC

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Recommendations	Strength rating
Base follow-up of TaT1 tumours and carcinoma *in situ* (CIS) on regular cystoscopy.	Strong
Patients with low-risk Ta tumours should undergo cystoscopy at three months. If negative, subsequent cystoscopy is advised nine months later, and then yearly for five years.	Weak
Patients with high-risk tumours should undergo cystoscopy and urinary cytology at three months. If negative, subsequent cystoscopy and cytology should be repeated every three months for a period of two years, and every six months thereafter until five years, and then yearly.	Weak
Patients with intermediate-risk Ta tumours should have an in-between (individualised) follow-up scheme using cystoscopy.	Weak
Regular (yearly) upper tract imaging (computed tomography-intravenous urography [CT-IVU] or IVU) is recommended for high-risk tumours.	Weak
Endoscopy under anaesthesia and bladder biopsies should be performed when office cystoscopy shows suspicious findings or if urinary cytology is positive.	Strong
During follow-up in patients with positive cytology and no visible tumour in the bladder, mapping-biopsies or PDD-guided biopsies (if equipment is available) and investigation of extravesical locations (CT urography, prostatic urethra biopsy) are recommended.	Strong
In patients initially diagnosed with TaLG/G1-2 bladder cancer, use ultrasound of the bladder during surveillance in case cystoscopy is not possible or refused by the patient.	Weak

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Management of patients with MIBC

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Neoadjuvant therapies

Recommendations	Strength rating
Offer neoadjuvant chemotherapy (NAC) for T2-T4a, cN0M0 bladder cancer. In this case, always use cisplatin-based combination therapy.	Strong
Do not offer NAC to patients who are ineligible for cisplatin-based combination chemotherapy.	Strong
Only offer neoadjuvant immunotherapy to patients within a clinical trial setting.	Strong

Recommendations	Strength rating
Do not offer pre-operative radiotherapy (RT) for operable MIBC since it will only result in downstaging, but will not improve survival.	Strong
Do not offer pre-operative RT when subsequent radical cystectomy with urinary diversion is planned.	Strong

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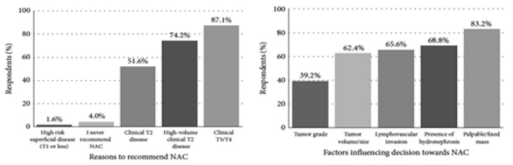
Neoadjuvant Chemotherapy Use in Bladder Cancer: A Survey of Current Practice and Opinions

A 20 questions survey to members of the SUO
Patients receiving NAC: 30-57%



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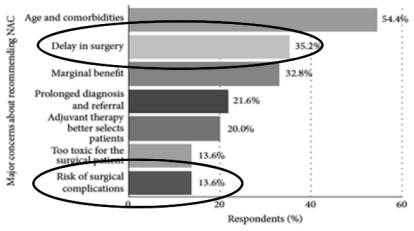
Gowan et al, Advances in Urol 2014

Neoadjuvant Chemotherapy Use in Bladder Cancer: A Survey of Current Practice and Opinions



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Gowan et al, Advances in Urol 2014

Articles

Neoadjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis

European Urology

European Urology 48 (2005) 202–206

Review—Bladder Cancer

Neoadjuvant Chemotherapy in Invasive Bladder Cancer: Update of a Systematic Review and Meta-Analysis of Individual Patient Data

Advanced Bladder Cancer (ABC) Meta-analysis Collaboration

Meta-analysis Group, Medical Research Council Clinical Trials Unit, 222 Euston Road, London NW1 2DA, UK

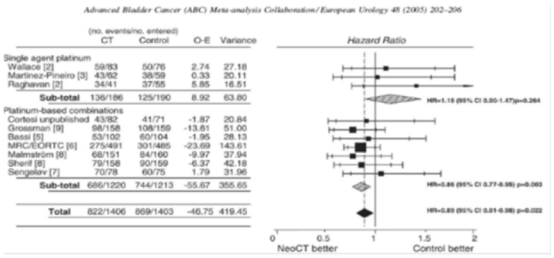
Accepted 6 April 2005

Available online 21 April 2005

51

Vale CL et al, Lancet 2003 & Eur Urol 2005

NAC – global survival



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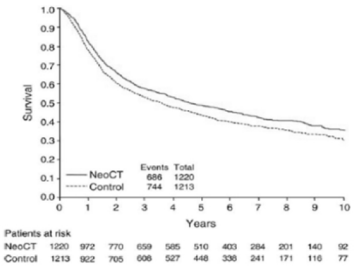
Vale CL et al, Eur Urol 2005

NAC – global survival



- 9% improvement in disease-free survival
- 5% improvement of survival at 5 years

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NAC – pros

- It determines chemosensitivity
- Better tolerated by the patient
- Early treatment of micrometastases
- Possibility of ↓tumour stage of unresectable tumours
- Possibility of bladder preservation according to response to chemotherapy (?)
- Assess the response to chemotherapy as a prognostic factor

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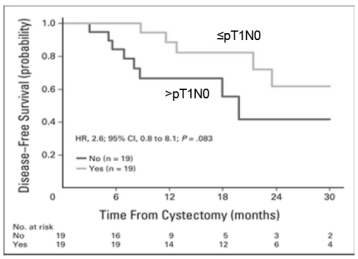
Association between pathologic response and disease-free survival



Choueiri TK et al, JCO 2014

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NAC – cons

- Exposure of the patients to unnecessary chemo: 20 patients are treated to improve outcome in 1
- Incorrect clinical staging: 30-50%
- Possibility of progression during treatment
- Delay in the start of the treatment
  - Chemo : 9 - 16 weeks
  - > 3 months: worse pathology, decreased survival

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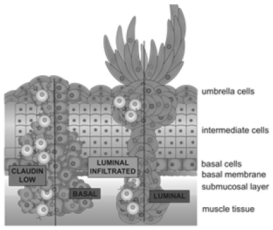
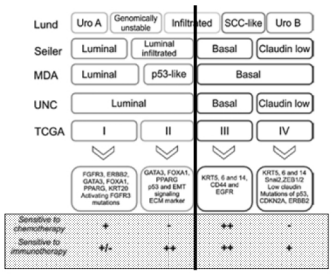
Molecular Subtyping





Seiler et al., EAU abstract 901, 2017

Wezel et al., TAU, 2017

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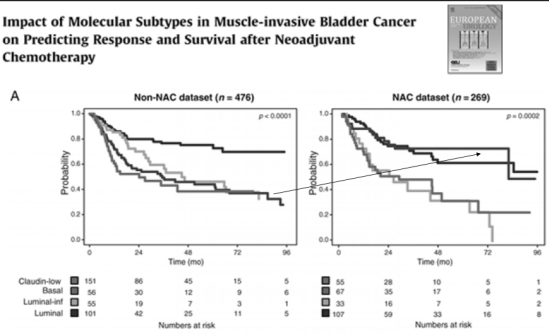
Impact of Molecular Subtypes in Muscle-invasive Bladder Cancer on Predicting Response and Survival after Neoadjuvant Chemotherapy



Seiler et al., Eur Urol, 2017

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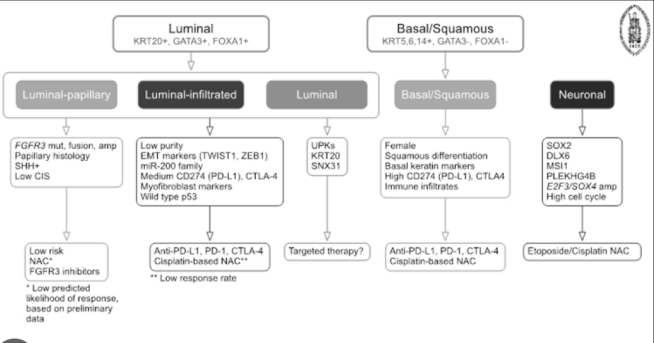

Robertson et al., Cell 2017

59

Molecular subtyping – which therapy

In MIBC:

- Neoadjuvant chemotherapy → Basal
- Immune checkpoint → Basal / luminal infiltrated
- Novel therapies based on subtypes

Pre-clinical data:

- Basal: EGFR inhibitors[1] MVAC+bevacizumab[2]
- Luminal-papillary: FGFR3 and ERBB2/3 targeted drugs[3,4]

[1]Rebouissou S et al., Sci Transl Med 2014; [2]McConkey DJ et al., Hematol Oncol Clin North Am 2015; [3]Kim J et al., Clin Cancer Res, 2015; [4]McConkey DJ et al., Eur Urol, 2015

60

Adjuvant Chemotherapy for Invasive Bladder Cancer: A 2013 Updated Systematic Review and Meta-Analysis of Randomized Trials

945 patients included in 9 RCTs

Results:

Overall survival 0.77 (95% CI, 0.59-0.99; p=0.049)
Disease free survival 0.66 (95% CI, 0.45-0.91; p=0.014)

DFS more apparent among those with (+) nodal involvement (p=0.010)

61

Leow et al, Eur Urol 2013

Adjuvant Chemotherapy for Invasive Bladder Cancer: A 2013 Updated Systematic Review and Meta-Analysis of Randomized Trials

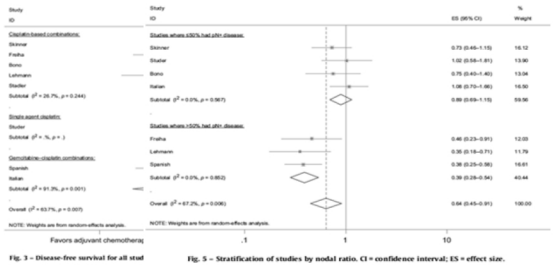

Fig. 3 – Disease-free survival for all stud

Fig. 5 – Stratification of studies by nodal ratio. CI = confidence interval; ES = effect size.

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Leow et al, Eur Urol 2013

A Systematic Review of Neoadjuvant and Adjuvant Chemotherapy for Muscle-invasive Bladder Cancer

Joshua J. Meeks[a], Joaquim Bellmunt[b], Bernard H. Bochner[a], Noel W. Clarke[c], Siamak Daneshmand[d], Matthew D. Galsky[e], Noah M. Hahn[f], Seth P. Lerner[g], Malcolm Mason[h], Thomas Powles[i], Cora N. Sternberg[j], Guru Sonpavde[kk,]*

One potential strategy would be to reserve NC to patients with more locally advanced cancer (≥cT3 disease). Patients with cT2N0 disease, especially those without LVI and downstaged to pT0 or non–muscle-invasive disease from transurethral resection, have excellent long-term outcomes with RC alone and would have been overtreated by cisplatin-based NC. In this context, it is worth remembering that cisplatin is sometimes characterized by persistent neuropathy or renal dysfunction. Unfortunately, it is not

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Meeks et al, Eur Urol 2012

Reality of NAC…

Urologists not really convinced!

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Pelvic organ-preserving RC

Recommendations	Strength rating
Do not offer sexual-preserving cystectomy to men as standard therapy for muscle-invasive bladder cancer.	Strong
Offer sexual-preserving techniques to men motivated to preserve their sexual function since the majority will benefit.	Strong
Select patients based on: • organ-confined disease; • absence of any kind of tumour at the level of the prostate, prostatic urethra or bladder neck.	Strong

Recommendations	Strength rating
Do not offer pelvic organ-preserving radical cystectomy to women as standard therapy for muscle-invasive bladder cancer.	Strong
Offer sexual-preserving techniques to women motivated to preserve their sexual function since the majority will benefit.	Weak
Select patients based on: • organ-confined disease; • absence of tumour in bladder neck or urethra.	Strong

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Minimally invasive RC

Summary of evidence	LE
Robot-assisted radical cystectomy (RARC) has longer operative time (1-1.5 hours) and major costs, but shorter length of hospital stay (1-1.5 days) and less blood loss compared to open radical cystectomy (ORC).	1
Robot-assisted radical cystectomy series suffer from a significant stage selection bias as compared to ORC.	1
Grade 3, 90-day complication rate is lower with RARC.	2
Most endpoints, if reported, including intermediate-term oncological endpoint and quality of life, are not different between RARC and ORC.	2
Surgeons experience and institutional volume are considered the key factor for outcome of both RARC and ORC, not the technique.	2
Recommendations on how to define challenging patients and an experienced RARC surgeon are still under discussion.	3
The use of neobladder after RARC still seems under-utilised, and functional results of intracorporeally constructed neobladders should be studied.	4

Recommendations	Strength rating
Inform the patient of the advantages and disadvantages of open radical cystectomy (ORC) and robot-assisted radical cystectomy (RARC) to allow selection of the proper procedure.	Strong
Select experienced centres, not specific techniques, both for RARC and ORC.	Strong

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RC & UD

Summary of evidence	LE
For MIBC, offer radical cystectomy (RC) the curative treatment of choice.	3
A higher case load reduces morbidity and mortality of cystectomy.	3
Radical cystectomy includes removal of regional lymph nodes.	3
There are data to support that extended lymph node dissection (LND) (vs. standard or limited LND) improves survival after RC.	3
Radical cystectomy in both sexes must not include removal of the entire urethra in all cases, which may then serve as the outlet for an orthotopic bladder substitution. The terminal ileum and colon are the intestinal segments of choice for urinary diversion.	3
The type of urinary diversion does not affect oncological outcome.	3
Laparoscopic cystectomy and robotic-assisted laparoscopic cystectomy are feasible but still investigational. Current best practice is open RC.	3
In patients aged > 80 years with MIBC, cystectomy is an option.	3
Surgical outcome is influenced by comorbidity, age, previous treatment for bladder cancer or other pelvic diseases, surgeon and hospital volumes of cystectomy, and type of urinary diversion.	2
Surgical complications of cystectomy and urinary diversion should be reported using a uniform grading system. Currently, the best-adapted grading system for cystectomy is the Clavien grading system.	2
No conclusive evidence exists as to the optimal extent of LND.	2a

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RC & UD

Recommendations	Strength rating
Do not delay radical cystectomy (RC) for > 3 months as it increases the risk of progression and cancer-specific mortality.	Strong
Before RC, fully inform the patient about the benefits and potential risks of all possible alternatives. The final decision should be based on a balanced discussion between the patient and the surgeon.	Strong
Do not offer an orthotopic bladder substitute diversion to patients who have a tumour in the urethra or at the level of urethral dissection.	Strong
Pre-operative bowel preparation is not mandatory. "Fast track" measurements may reduce the time to bowel recovery.	Strong
Offer RC in T2-T4a, N0M0, and high-risk non-MIBC.	Strong
Perform a lymph node dissection as an integral part of cystectomy.	Strong
Do not preserve the urethra if margins are positive.	Strong

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Prognosis

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Recurrence & prognosis

Site of recurrence	Summary of evidence	LE	Recommendation	Strength rating
Local recurrence	Poor prognosis. Treatment should be individualised depending on the local extent of tumour.	2b	Offer radiotherapy, chemotherapy and possibly surgery as options for treatment, either alone or in combination.	Strong
Distant recurrence	Poor prognosis.	2b	Offer chemotherapy as the first option, and consider metastasectomy in case of unique metastasis site.	Strong
Upper urinary tract recurrence	Risk factors are multifocal disease (NMIBC/CIS or positive ureteral margins).		See EAU Guidelines on Upper Urinary Tract Urothelial Carcinomas.	Strong
Secondary urethral tumour	Staging and treatment should be done as for primary urethral tumour.	3	See EAU Guidelines on Primary Urethral Carcinoma.	Strong

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How to optimize TURBT

Paolo Gontero

Chairmen Division of Urology
San Giovanni Battista Hospital
University of Studies of Torino
Torino, Italy

Belgrade, 12 Aprile 2019

DISCLOSURES

- Lecturer for
  - IPSEN
- Advisory board for
  - Janssen
  - Arquer
  - Astellas

The problem: Is WL TURBT adequate?

- TURBT remains the mainstay procedure for diagnosis and staging of BC
- In NMIBC, TURBT is also the first and probably most powerful treatment modality
- Any tumour unseen will likely persist even after intravesical therapy

EAU Guidelines NMIBC, 2015

- **A number of observations suggest that TURBT done under WL is inadequate**
- high rates of persistent disease at immediate re-TUR (even in low grade and stage NMIBC)
- uderdetection of concomitant CIS
- understaging of MIBC at the cystectomy specimen for clinical T1 disease

The problem: re-TUR studies show dramatic high rates of persistence disease

- re-TUR series
even in high risk

Variable
No residual tum
Ta
T1
CIS

Gontero

Tumor Type	No. Patients	Percent Pathology on Restaging TUR				
		pT0	pTaLG	pTaHG/CIS	pT1	pT2
pTaLG	215	49	46	5	0	0
pTaHG	396	35	0	50	10	5
pT1	701	22	0	23	25	30
Muscle	421	25	0	31	29	15
No muscle	280	20	0	15	20	45

LG: low-grade; HG: high-grade papillary tumors. Herr H, 2011

- In high risk NMIBC, re-TUR does NOT affect neither progression nor CSS if the muscle is appropriately sampled in primary TUR Gontero P, 2015
- re-TUR may be rendered obsolete with improvement in the accuracy of first TUR

The problem: Under-detection of CIS

- Concomitant CIS occurs in at least 50% of HR NMIBC but its rate in recent series does not exceed 10-20%. **Why?**

Author	Type of BC	% concomitant CIS	Multiple random biopsies
Algaba F, 2000	G1 G2 **G3**	8.2% 17.5% **66.2%**	yes
Palou J, Eur Urol 2012	**T1G3**	**50%**	yes
EORTC risk tables, 2006	All T1G3	4% 10%	no
Gontero P, 2015	T1G3	20%	no

- Optimal detection of CIS could occur through **multiple random biopsies** which are recommended ONLY in HRNMIBC, meaning an additional procedure is needed
- CIS is an independent prognostic factors of progression in BC, hence its detection can affects treatment decision making

The problem: Under-staging of MIBC and detrusor muscle

- Up to 50% of MIBC at cystectomy specimen down-staged at initial TURBT (T1 disease)

Author (year)	cT1 patients (n)	Upstaging ≥pT2 (%)	Positive nodes (%)	5-year DSS (%)	Ref.
Fritsche *et al.* (2010)	1136	51	16	70	[5]
Denzinger *et al.* (2008)	Early cystectomy: 54 Deferred cystectomy: 51	26 35	NR NR	78* 51*	[44]
Huguet *et al.* (2005)	31	27	NR	79	[47]
Wiesner *et al.* (2004)	188	34	16	NR	[48]
Amling *et al.* (1994)	166	30	7	NR	[49]
Freeman *et al.* (1995)	128	40	8*	83*	[50]

*10-year DSS.
†Including all cT2 patients.
cT1: Clinical T1; DSS: Disease-specific survival; NR: Not reported; pT1: Pathological T1.

(Fritsche HM, Eur Urol 2010

- Detrusor muscle (DM) (a proxy for GQ-WL TURBT) was absent in up to 20% of series from high quality centers (Mariappan P, BJU Int 2012)
- DM- seems more related to the morphology of the tumour (flat) rather than surgeon's experience (Capogrosso P, J Endourol 2015)

NEED TO SEE BETTER in order to do a BETTER RESECTION

Mechanism of action:

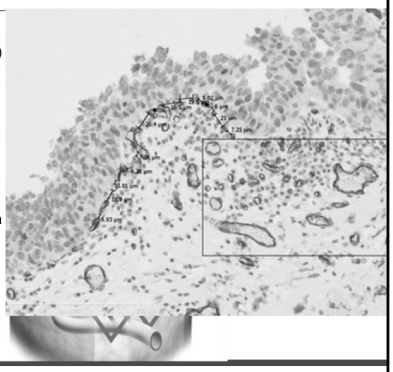
Narrow-Band Imaging (NBI)

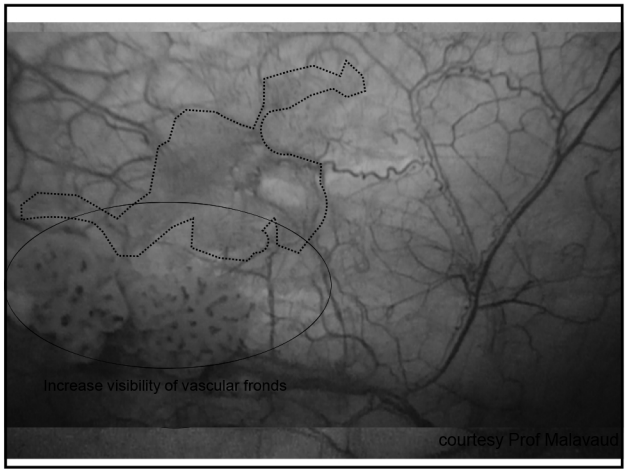
Microvascular density is increased in BC (10-fold in CIS!)

NBI designed to highlight the microvasculature

WL is filtered in 2 bands absorbed by hemoglobin:

- Blu (415 nm): absorbed by superficial vessels of the mucosa = shows up brownish-black
- Green (540 nm): absorbed by deep vessels = shows up green



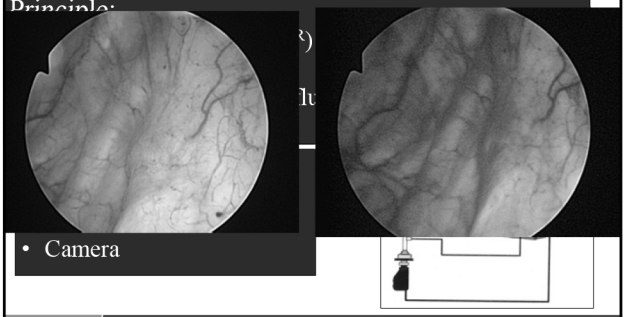


Mechanism of action:

Photodynamic diagnosis (PDD)

Principle:

- Camera



The evidence of PDD and NBI:

Tumour detection (CIS)

PDD

Tumour type	Both methods, *n* (%)	BL only, *n* (%)	WL only, *n* (%)	Total
Total Ta	1298 (80.1)	239 (14.7)	84 (5.2)	1621
Ta primary	495 (86.7)	64 (11.2)	12 (2.1)	571
Ta recurrent	803 (76.5)	175 (16.7)	72 (6.9)	1050
High risk	460 (77.3)	94 (15.8)	41 (6.9)	595
Intermediate risk	674 (79.9)	138 (16.4)	32 (3.8)	844
Low risk	164 (90.1)	7 (3.8)	11 (6.0)	182
Total T1	313 (84.1)	40 (10.8)	19 (5.1)	372
Primary	201 (84.5)	30 (12.6)	7 (2.9)	238
Recurrent	112 (83.6)	10 (7.5)	12 (9.0)	134
Total CIS	285 (54.1)	215 (40.8)	27 (5.1)	527
Primary	119 (54.6)	94 (43.1)	5 (2.3)	218
Recurrent	166 (53.7)	121 (39.2)	22 (7.1)	309

NBI

Additonal tumour detection (17% solely detected with NBI and 24% additionally detected with NBI) confirmed by 2 metanalyses

(Li k, Int J Urol 2013)

10-40% diagnostic gain for CIS lesions

Metanalysis of 6 studies: significant **additional** detection rates (over WL, within patients) for all stages of NMIBC, chiefly **+40%** in CIS

(Burger M, Metanalysis Eur Urol 2013)

Series	No. Cases	Cystoscopy	Sensitivity (%)	Specificity (%)
Herr and Donat [5]	67	WLI/NBI	83; 100	72; 76
Tatsugami [7]	30	WLI/NBI	50;90	83;75
Cauberg [6]	14	WLI/NBI	55;69	–
Shen [8]	11	WLI/NBI	68;77	82;77

(Herr H, Curr Urol Rep 2014)

The evidence of PDD and NBI:

Therapeutic effect? RECURRENCE

PDD

RECURRENCE RATE WL vs PDD

Controversial results of 2 RCT:

- UK study: no difference at 1y in 185 NMIBC
- German study: 551 NMIBC, 10% less RR with PDD at 9m, remained significant at longer follow up (55m)

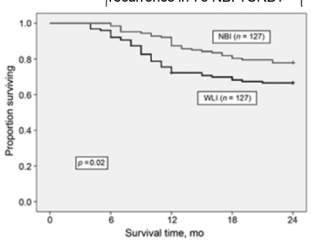
(O'Brien T, BJU Int 2013; Grossman HB, J Urol 2012)

RECURRENCE at re-TUR
3 times less persistence disease at standard re-TUR in high risk BC previously diagnosed with PDD

(Geavlete B, Urology 2010)

NBI

RCT showed 32% 1y recurrence in 76 NBI TURBT



-10% RECURRENCE RATE WITH EITHER PDD OR NBI

The evidence of PDD and NBI:

Therapeutic effect? PROGRESSION/SURVIVAL

PDD

SURVIVAL AT CYSTECTOMY AFTER HAL vs ALA vs WL TURBT

- Retrospective cohort (N=224)
- 66 pt previously undergone HAL-TURBT had better survival at cystectomy than 22 having ALA-TURBT and 135 undergone WL-TURBT
- Hypothesis generating study

(Gakis G, World J Urol 2015)

PROGRESSION TO MIBC
16 cases (6.1%) with WL vs 8 (3.1%) with PDD at a median of 55 months follow up (p=0.06)

(Grossman HB, J Urol 2012)

NBI

N.A.

NO STUDY SPECIFICALLY DESIGNED TO ADDRESS THIS END POINT

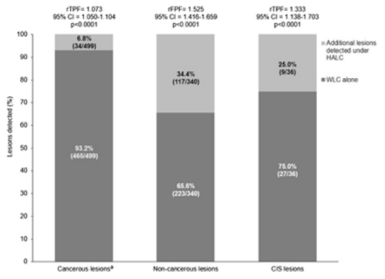
The evidence of PDD
Real life studies

OPTIC III *(German non-interventional study, Bach 2017)*

- May 2013 – April 2014, 30 German centers, 403 pts.
- 929 resections/biopsies
  - 62.2% Ta; 20.1% T1; 9.3% T2; 7.3% CIS
  - Blue light detected **6.8%** more cancer lesions and **25%** more CIS
    - In 10.0 % of pts, ≥1 additional lesion was detected with HAL
    - 2.2 % of NMIBC patients would have been missed with WL alone
- Conclusion
  - HAL significantly improves the detection of NMIBC in routine clinical practice in Germany.
  - Benefit across all types of NMIBC, but most relevant in CIS.

The evidence of PDD
Real life studies

OPTIC III *(German non-interventional study, Bach 2017)*



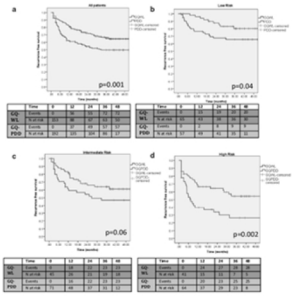
The evidence of PDD
Real life studies

Real life 3 year RR *(Gallagher 2017)*

- Comparison of good quality TUR with BL (2009/10) and WL (2007/8)
  - 345/808 new patients fullfiled good quality criteria (*)
  - 3 year RR BL: 57/146 = 39.0% versus WL 72/135 = 53.3%
    - Matched pair analysis **24.6% versus 50.0%**
  - Most benefit in high risk patients: 3 year RR 52.1% versus 80% (OR 0.27, 0.10-0.74)
- (*) Good quality criteria
  - TUR by or with close supervision of the consultant
  - Standardized with bladder mapping
  - Aim to complete resection
  - Detrusor obtained and histologically confirmed.

The evidence of PDD
Real life studies

Real life 3 year RR *(Gallagher 2017)*

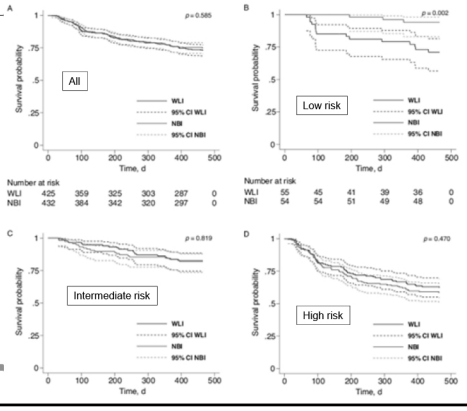


NBI *(CROES)*


The Clinical Research Office of the Endourological Society (CROES) Multicentre Randomised Trial of Narrow Band Imaging–Assisted Transurethral Resection of Bladder Tumour (TURBT) Versus Conventional White Light Imaging–Assisted TURBT in Primary Non–Muscle-invasive Bladder Cancer Patients: Trial Protocol and 1-year Results

- RCT: 481 WL vs. 484 NBI
- 294 and 303 completed 12 months FU
- TUR time WL: 35 min, vs 38.1 min with NBI
- Recurrence rates 27.1% (WL) vs. 25.4% (NBI), *p*=0.6 by ITT
  - Low risk group: RR 27.3% vs. 5.6%
- Possible explanations lack of difference
  - lack of uniformity of surgical resection
  - specific data regarding adjuvant intravesical instillation therapy
  - data on smoking status (RCT)
  - central pathology review (RCT)

NBI *(CROES)*



Limitations of PDD and NBI:
Are they relevant?

- **Observer bias**: both PDD and NBI are usually performed after first WL look
- NBI: 24% increased detection when surgeon blinded to the results of WL
- PDD: objective methodology

Cauberg ECC, Curr Op Urol 2009

The issue is not whether one modality is better than the other, but that NBI/PDD plus WL cystoscopy detects more tumors

- **False positive (FP)**: a substantial rate of FP lesions (lower specificity) occurs with both PDD and NBI

Under-detection rather than over-resection is an issue in TURBT

Costs of PDD and NBI:
Is the trouble cost-effective?

- **PDD**: potential cost savings by using PDD have been reported by several groups as a results of reduced need of repeat TURBT

Country, yr	Setting	Total cost per patient		Potential cost difference per patient (BLC vs WLC)	Basis of cost calculations
		WLC + TURBT	BLC + TURBT		
UK, 2008 [42]	Newly diagnosed NMIBC	NR	NR	−£455 (approximately −€553) over first year	• Includes costs of repeat TURBT and mitomycin C at 3 mo with WLC, reduced risk of recurrence leading to less intensive cystoscopic follow-up with BLC • Estimated overall net savings of £45 500 per 100 new cases of NMIBC

Witjes A, Eur Urol 2014

- **NBI**: a "cost free", repeatable mean to improve tumour detection

Geavlete B, J Med Life 2014

CONCLUSIONS:
Optical enhancement: why

- Cure rate of BC is highly dependent on correct diagnosis (high risk NMIBC, MIBC) and completeness of resection (NMIBC)
- Standard WL TURBT performance remains suboptimal at several levels
- Optical enhancement tools have clearly shown an improved detection rate particularly at the level of lesions that are poorly viewed with WL (CIS; small papillary tumours)
- This has so far translated into a small yet meaningful impact on recurrence rate (except in 1 study)
  and potentially to a change of management (CIS) or sparing of additional procedures like re-TUR (still to be demonstrated)
- Absence of proof of an impact on progression not to be viewed as a limitation (no study designed to address this end point so far)

CONCLUSIONS:
Optical enhancement: when

- **PDD**:
  - ideal setting: positive cytology and negative cystoscopy
  - to be strongly considered: all primary TURBT of BC
  - limitation: re-TUR, after instillation
- **NBI:**
- any time (light filter)
- **Goal**: less recurrences, less procedure, improved outcomes (better decision making)

If you can do 2 procedures in 1, do it!
It may cause some trouble, but the patient will thank you…

En Bloc Transurethral Resection of Bladder Tumors: A New Standard? JOURNAL OF ENDOUROLOGY Volume 31, Supplement 1, April 2017

Published evidence up to 2017:
- 16 studies (11 prospective & 3 RCT)
- 1000 cases

Issues (that limit standardization of technique)
- different resection techniques/equipment
- Several specimen retrieval methods
- Size limit?

Oncological outcomes

- Detrusor muscle presence:
  - 95% (vs 60% standard TUR)
- Residual disease (at re-TUR)
  - 1.5% (only 1 study)
- Recurrence
  - No difference with standard TUR (small RCTs)

Performance of individual steps	
Perform *en-bloc* resection or resection in fractions (exophytic part of the tumour, the underlying bladder wall and the edges of the resection area). The presence of detrusor muscle in the specimen is required in all cases except for TaG1/LG tumours.	Strong

RESTAGING TUR (RE-TUR)

- A **restaging TUR** accomplished after a macroscopically complete first TUR
- What it is NOT:
  - A «repeat resection» performed when a complete initial TUR cannot be accomplished

RE-TUR (SECOND RESECTION): WHY

5.12 Second resection

The significant risk of residual tumour after initial TURB of TaT1 lesions has been demonstrated [86] (LE: 2a). Persistent disease after resection of T1 tumours has been observed in 33-55% of patients, after resection of TaG3 tumour in 41.4% [121-124]. Moreover, the tumour is often understaged in the initial resection. The likelihood that muscle-invasive disease is detected by second resection of initially T1 tumour ranges from 1.3-25%, and increases to 45% if there was no muscle in the initial resection [109, 125-128]. This risk increased to 50% in some radical cystectomy (RC) series, although these studies only enrolled selected patients [129-131] (LE: 2a). Treatment of a TaT1 high-grade tumour and a T2 tumour is completely different; correct staging is therefore important. It has been demonstrated that a second TURB can increase recurrence-free survival [121, 122] (LE: 2a), improve outcomes after BCG treatment [132] (LE: 3) and provide prognostic information [127, 129, 133] (LE: 3).

EAU Guidelines, 2017

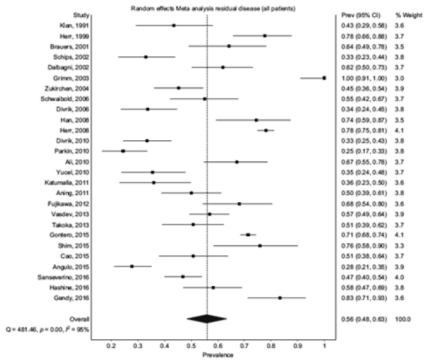
THE RATE OF INCOMPLETE RESECTION

Systematic Review & Metanalysis

N=3566 pt
(29 studies)

Residual tumour at re-TUR: 61%

- At best 25%
- No improvement over time



Naselli A, Eur Urol focus 2016

IS INCOMPLETE RESECTION ONLY A MATTER OF POOR QUALITY OF INITIAL TUR?

- Small tumours can be overlooked by experienced eyes
- CIS cannot always be seen
- Technical problems can sometimes make accurate resection impossible
  - Bladder spasm
  - Bleeding
  - Mucosal edema
  - Poor vision

This may occur also to experienced surgeons

Herr H, Sci W Journal 2011

DOES THE EXPERIENCE OF SURGEON MATTER?

- Wide variability of early recurrence across centers and interoperator first documented in pooled analysis of EORTC studies

  Brausi M, 2002
- Surgeons with experience less than 5 y or 10 y have less recurrencies

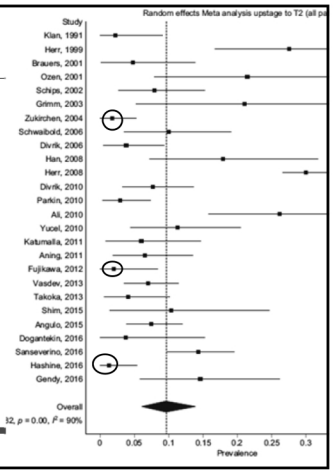
  Mariappan P, Eur Urol
  Han KS, J Endourol 2008
- Muscle in first TUR varies between 54 and 94% according to surgeon's experience

  Dalbagni G, BJU Int

As in most human tasks, experience matters…

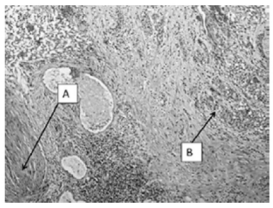
The most worring scenario: under-staging a MIBC

15% of T2 disease at re-TUR

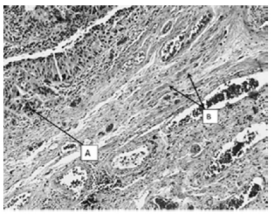


Naselli A, Eur Urol focus 2016

Risk of downstaging: A "pathologist factor"?



T1G3 (in B) far away from muscle layer that is well represented in A



T1G3 (in A) with only muscolaris mucosae represented in B but not muscolaris propria.

Muscolaris propria not always easy to be distinguished by muscolaris mucosae

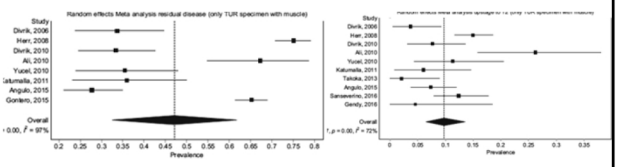
"DETRUSOR MUSCLE in TUR SPECIMEN"
The way out?

Detrusor muscle (DM) in TUR is considered a proxy for good quality TURBT

- Risk of downstaging is only 14% in T1 when muscle is present but 49% when it is absent *Herr H, J Urol 1999*
- 64% risk of downstaging when no muscle versus 30% when muscle is present *Dutta SC, j Urol 2001*

THE PROBLEM of
"THE PRESENCE OF DETRUSOR MUSCLE in TUR SPECIMEN"

Detrusor muscle (DM) was absent in up to 20% of series from high quality centers
(Mariappan P, BJU Int 2012)



High rate of residual disease (> 45%) and upstaging (10%) even when detrusor muscle is found in primary TUR specimen

Naselli A, Eur Urol focus 2016

RE-TUR (SECOND TUR):
FOR WHOM and WHEN

Perform a second TURB in the following situations: • after (suspicion of) incomplete initial TURB (in the case of any doubt about completeness of a TURB); • if there is no muscle in the specimen after initial resection, with the exception of TaLG/G1 tumours and primary CIS; • in T1 tumours.	A
If indicated, perform a second TURB within 2-6 weeks after initial resection. It should include the resection of primary tumour site.	C

Some non-T1 high risk NMIBC can be spared a re-TUR if the muscle has been adequately sampled

EAU Guidelines, 2018

RE-TUR (SECOND TUR):
NO MAJOR DIFFERENCES ACROSS MAIN GUIDELINES

Guideline body	Recommendation on suitable reTUR candidates	Level of evidence given	Major differences
EAU (European Association of Urology)	1. Incomplete initial TUR 2. No muscle in specimen with the exception of LG-Ta/G1 and primary CIS 3. T1 tumors.	All Grade A (Strong)	*Used as the reference standard*
AUA (American Urological Association)	1. Incomplete initial TUR 2. HG-Ta tumours 3. T1 tumours	1. Grade B (strong) 2. Grade C (moderate) 3. Grade B (strong)	No comment is made that HG-Ta tumours do not need reTUR if muscle is present in the initial TUR
NCCN (National Comprehensive Cancer Network)	1. Incomplete initial TUR 2. No muscle in initial TUR for HG disease 3. Large or multi-focal lesions 4. T1 tumours 5. Select HG-Ta especially if no muscle in initial TUR	All Strong	Include large or multi-focal lesions as a reason to re-resect. Doesn't specifically mention CIS
CUA (Canadian Urology Association)	1. Incomplete initial TUR 2. T1 tumour in absence of muscle 3. Any HG or T1 tumour with benign muscle	1. Grade A 2. Grade A 3. Grade C	Recommend reTUR in T1 or HG-Ta where muscle is present and not malignant.
NICE (Natioanl Institue for Clinical Excellence)	1. All high-risk non-muscle invasive bladder cancer	1. Low	Does not specify whether presence of muscle changes the approach.
ICUD (International Consultation on Bladder Cancer) 2012	1. T1 tumours (regardless of the presence of muscle)	1.Strong	Does not specify whether presence of muscle changes the approach. Does not discuss HG-Ta tumours.

Cumberback, Eur Urol 2018

re-TUR

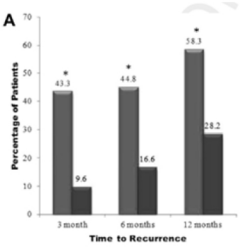
Does it affect clinical outcomes?

- Recurrence ?
- Progression ?
- Survival ?

IMPACT OF RE-TUR ON **RECURRENCE**

- 1021 NMIBC
  75% HG, 40% T1
  60% concomitant CIS
- 894 (87.5%) had re-TUR
- No re-TUR more likely to have high grade disease (= grups were NOT homogeneous)

All had BCG x 6



Re-TUR is associated with lower recurrence rate
Is this a valid end point to support the need for an additional TUR?

Sfakianos, JP, *J Urol 2014*

DOES RE-TUR IMPACT ON **CSS**?

- 210 T1NMIBC
- Randomised to receive:
  - re-TUR + MMC
  - MMC only
- FU: 54 months
- Upstaging at re-TUR: 8/105
- Progression:
  - Re-TUR: 6%
  - No re-TUR 23%

Table 4 – Multivariate analysis according to recurrence and progression

Variables	Recurrence		Progression	
	HR*	p	HR*	p
Age	0.990	0.363	0.985	0.451
Sex	0.821	0.582	1.365	0.620
No. of tumours (single vs multiple)	1.772	0.007	1.389	0.395
Tumour size (<3 cm vs ≥3 cm)	1.328	0.161	2.649	0.035
Grade (low vs high)	1.799	0.023	–	–
Second TUR (yes vs no)	2.482	0.001	3.487	0.007

HR = hazard ratio; TUR = transurethral resection.
* HR according to Cox regression analysis.

- The only level 1 evidence on re-TUR showed 5 death in re-TUR vs 11 in the no re-TUR arm
- The study is flowed by heavy biases (no intention to treat analysis reported)

Divrik RT, Eur Urol 2010

The impact of re-transurethral resection on clinical outcomes in a large multicentre cohort of patients with T1 high-grade/Grade 3 bladder cancer treated with bacille Calmette–Guérin

2451 T1G3, all treated with BCG
72% had muscle in the specimen

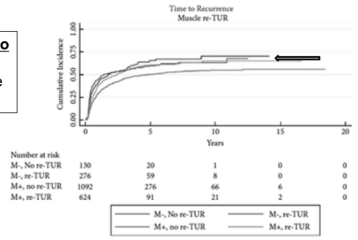
935 (41%) underwent re -TUR
Residual disease: 71%

Variable	No muscle, no re-TUR	No muscle, re-TUR	Muscle, o re-TUR	Muscle, re-TUR	Unknown	All patients
N	130	276	1092	624	329	2451
Pathology at re-staging TUR*						
No residual tumour	NA	39 (14.1)	NA	217 (34.8)	11 (3.3)	267 (10.9)
Ta	NA	126 (45.7)	NA	240 (38.5)	12 (3.6)	378 (15.4)
T1	NA	111 (40.2)	NA	166 (26.6)	12 (3.6)	289 (30.9)

Gontero P, Sylvester R et al, BJU Int 2015

The impact of re-transurethral resection on clinical outcomes in a large multicentre cohort of patients with T1 high-grade/Grade 3 bladder cancer treated with bacille Calmette–Guérin

Re-TUR and **time to recurrence** based on muscle +/- in the primary specimen

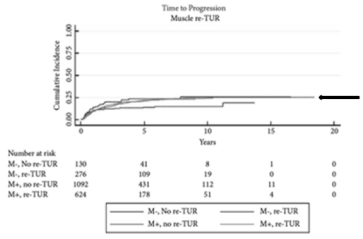


Re –TUR had an impact on **recurrence** ONLY when muscle was absent in the primary TUR
On multivarible analysis the **HR for re-TUR was 0.67 (p=0.08)** when muscle absent at first TUR

Gontero P, Sylvester R et al, BJU Int 2015

The impact of re-transurethral resection on clinical outcomes in a large multicentre cohort of patients with T1 high-grade/Grade 3 bladder cancer treated with bacille Calmette–Guérin

Re-TUR and **time to PROGRESSION** based on muscle +/- in the primary specimen

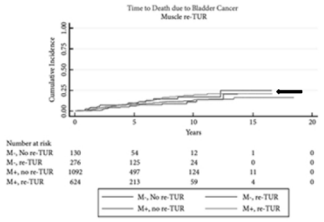


Re –TUR had an impact on **PROGRESSION** ONLY when muscle was absent in the primary TUR
On multivarible analysis the **HR for re-TUR was 0.46 (p=0.06)** when muscle absent at first TUR

Gontero P, Sylvester R et al, BJU Int 2015

The impact of re-transurethral resection on clinical outcomes in a large multicentre cohort of patients with T1 high-grade/Grade 3 bladder cancer treated with bacille Calmette–Guérin

Re-TUR and **time to DEATH FOR BC** based on muscle +/- in the primary specimen



Re –TUR had an impact on **CSS** ONLY when muscle was absent in the primary TUR
On multivarible analysis the **HR for re-TUR was 0.31 (p=0.07)** when muscle absent at first TUR

Gontero P, Sylvester R et al, BJU Int 2015

Repeat Transurethral Resection in Non–muscle-invasive Bladder Cancer: A Systematic Review

Marcus G.K. Cumberbatch[a,1,], Beat Foerster[b,c,1], James W.F. Catto[a], Ashish M. Kamat[d], Wassim Kassouf[e], Ibrahim Jubber[a], Shahrokh F. Shariat[b,f,g], Richard J. Sylvester[h], Paolo Gontero[i]*

EUROPEAN UROLOGY 73 (2018) 925–933

3.2.5. *T1 CSM*

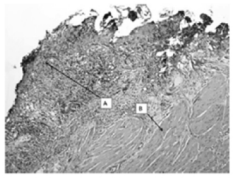
We found three studies reporting on 3593 persons of whom 1315 received a reTUR. Divrik et al [10] reported a survival benefit from reTUR (17% CSM in the reTUR arm vs 31% in the control arm), but the largest study [13] reported no survival benefit (10% CSM in the reTUR arm vs 9% in the control arm; Supplementary Table 7).

3.2.4. *Progression for T1 tumours (T1 ≥ T2)*

Eight studies reported progression from initial T1 tumours at reTUR. These reported on 4902 persons, 1954 of whom had a reTUR. A total of 410 cases progressed (by stage), which represents 21%. Out of 2117 controls (non-reTUR), 350 progressed by stage (17%). Average follow-up ranged from 26 to 66 mo. Six of the eight studies reported on a control population. Of these six studies, progression was higher in the non-reTUR groups in five studies. Only one RCT [10] reported a difference between groups of 6% in the reTUR group versus 24% in the control arm (Supplementary Table 6).

RE-TUR (SECOND TUR): HOW?

- Deep sampling of the old resection bed
- TUR loop resection of the old scar followed by a cold-cup biopsy of the base and resection edges of the old scar
- Each biopsy/specimen sent separately
- Limit excess cautery
  bypolar TUR loop helpful
- Add multiple biopsies (when indicated)



A = cautery artifacts; B = muscolaris propria

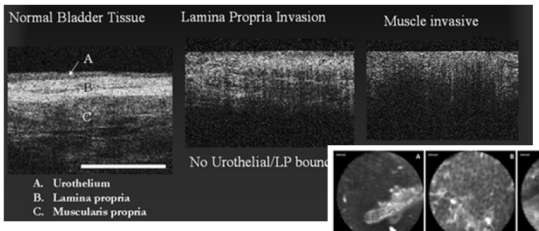
Ritch CR, Urol Clin N Am 2013

Re-TUR with multiple biopsies? (EAU guidelines 2018)

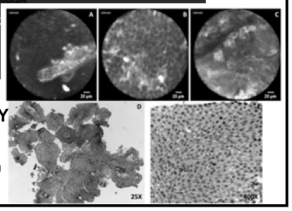
Take biopsies from abnormal-looking urothelium. Biopsies from normal-looking mucosa (trigone, bladder dome, and right, left, anterior and posterior bladder wall) are recommended when cytology is positive or when high-risk exophytic tumour is expected (non-papillary appearance). If equipment is available, perform fluorescence-guided (PDD) biopsies.	Strong
Take the biopsy from abnormal areas in the prostatic urethra and from the precollicular area (between the 5 and 7 o'clock position) using a resection loop. In primary non-muscle-invasive tumours when stromal invasion is not suspected, cold-cup biopsy with forceps can be used.	Weak

FUTURE DIAGNOSTIC TOOLS MAY ALLOW AN "IN-SITU PATHOLOGY

OPTICAL COHERENCE TOMOGRAPHY (OCT)



CONFOCAL LASER ENDOMICROSCOPY



Persistent T1 at re TUR
A so bad prognostic factor?

710 NMIBC (single center, retrosp)
All had re-TUR
All BCG after re-TUR

Re-staging TUR pathology	No. of patients	Tumour progression, n (%)
T0	278	25 (9)
TaG1	78	7 (9)
CIS	169	39 (23)
TaG3	105	17 (16)
T1	80	61 (76)

Herr H, BJU Int 2006

2450 T1G3 (multicenter, retrosp)
951 had re-TUR
All BCG after re-TUR
Median fu: 5.2y

5y CSS 86%
70% with native bladder

All patients submitted to Re-TUR

Re-TUR pathology	No. of patients	Tumour recurrence, n (%)	Tumour progression, n (%)
Not Done	1	1 (100)	0 (0)
No residual	267	112 (41.95)	38 (14.23)
Ta	378	193 (51.06)	55 (14.55)
T1	289	207 (71.63)	73 (25.26)
Total	935	513 (54.87)	166 (17.75)
Pearson chi2 (P)		*53.8132 (0,000)*	*16.2901 (0,001)*

Palou J, R Sylvester et al, unpublished data

CONCLUSIONS

Is re-TUR here to stay?

Today, yes (probably)

Will re-TUR remain the "gold standard" staging procedure in NMIBC?

The urological community should commit to integrate new technologies with high standard TUR in the setting of prospective trials to prove that re-TUR can be rendered obsolete,

rather than get stuck in the belief that it is an unavoidable procedure

VUmc

Are there alternatives for radical cystectomy?

Prof. dr. Jeroen van Moorselaar
Department of Urology
Amsterdam University Medical Centers, loc. VUmc
Amsterdam, NL

VUmc

I have no disclosures for this presentation

VUmc

Are there alternatives for radical cystectomy?

- TURBT alone
- Brachytherapy
- Trimodal therapy (TMT)

VUmc

0022-5347/98/1591-0095$03.00/0
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Vol. 159, 95-99, January 1998
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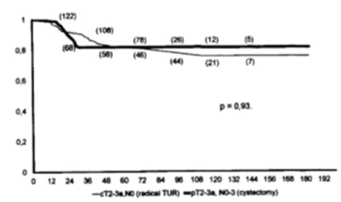
FEASIBILITY OF TRANSURETHRAL RESECTION FOR MUSCLE INFILTRATING CARCINOMA OF THE BLADDER: LONG-TERM FOLLOWUP OF A PROSPECTIVE STUDY

E. SOLSONA, I. IBORRA, J. V. RICÓS, J. L. MONRÓS, J. CASANOVA AND C. CALABUIG
From the Departments of Urology and Pathology, Instituto Valenciano de Oncología, Valencia, Spain



	%Cause-specific survival (95% confidence interval)	
Interval	cT2-3a, N0	pT2-3a, N0-3
12 ms.	96.5 (99.8-97.2)	96.5 (101.1-86.1)
24 ms.	91.7 (96.2-87.2)	89.4 (96.2-82.6)
36 ms.	88.7 (93.8-83.5)	81.5 (90.5-72.9)
48 ms.	83.4 (89.5-77.2)	81.5 (90.5-72.9)
60 ms	81.9 (88.3-75.5)	81.5 (90.5-72.9)
72 ms.	80.8 (87.4-74.2)	81.5 (90.1-72.9)
84 ms.	80.8 (87.4-74.2)	81.5 (90.1-72.9)
96 ms.	80.8 (87.4-74.2)	81.5 (90.1-72.9)
108 ms	80.8 (87.4-74.2)	81.5 (90.1-72.9)
120 ms	78.1 (86.5-69.7)	81.5 (90.1-72.9)
132 ms	78.1 (86.5-69.7)	81.5 (90.1-72.9)
144 ms.	78.1 (86.5-69.7)	81.5 (90.1-72.9)
156 ms	78.1 (86.5-69.7)	81.5 (90.1-72.9)

Comparison of cause specific survival of all patients (cT2–3a, N0) and controls (pT2–3a, N0–3). ***TUR*, transurethral resection**

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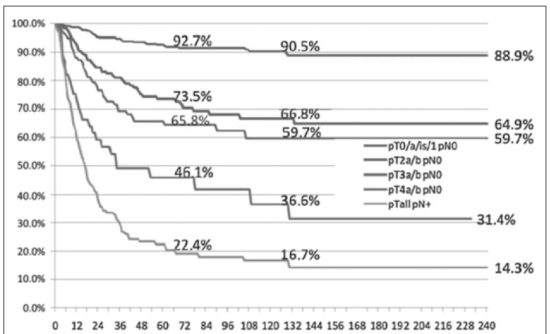

Fig. 2 – Disease-specific survival rates according to the tumor stage of the cystectomy specimen.

Hautmann et al, Eur Urol 61: 1039, 2012

VUmc

EUROPEAN UROLOGY 56 (2009) 113–122
available at www.sciencedirect.com
journal homepage: www.europeanurology.com
eau European Association of Urology
Bladder Cancer

External Beam Radiation Therapy Followed by Interstitial Radiotherapy with Iridium-192 for Solitary Bladder Tumours: Results of 111 Treated Patients

Ilze E.W. van Onna[a], Jorg R. Oddens[c], Esther T. Kok[a], R. Jeroen A. van Moorselaar[d], J.L.H. Ruud Bosch[a,], Jan J. Battermann[b]*

1988-2007
Solitary T1G3-T2G1-3
Tumour up to 5 cm
No CIS
M0

Table 1 – Patient and tumour characteristics

	No. of patients (total = 111)
Age (yr)	
Mean	58
Median	64
Sex	
Male	92
Female	19
T-stage[a]	
T1	13
T2	93
T3	5
Grade[b]	
G1	1
G2	35
G3	75
Adenocarcinoma	2
Squamous carcinoma	3

[a] Clinical T stage for most patients but the pathological stage for the nine patients who underwent a partial cystectomy.
[b] Grade was determined on the basis of transurethral resection (TUR) specimen or partial cystectomy.

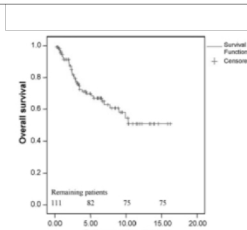

Fig. 1 – Overall survival rates for all treated patients (n = 111).

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EUROPEAN UROLOGY 74 (2018) 369–375

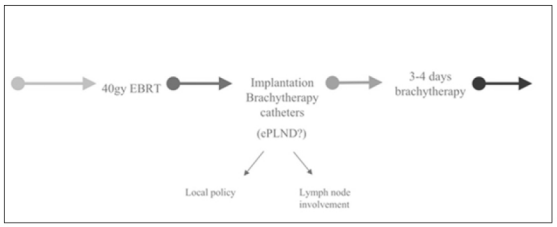
available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Surgery in Motion

Robot-assisted Laparoscopic Implantation of Brachytherapy Catheters in Bladder Cancer

Judith Bosschieter[a,], André N. Vis[a], Henk G. van der Poel[b], Luc M. Moonen[c], Simon Horenblas[b], Bas W.G. van Rhijn[b], Bradley R. Pieters[d], Jakko A. Nieuwenhuijzen[a], Kees Hendricksen[b]*



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Surgical steps

1. General anaesthesia, lithotomy position
2. Trocar placement
3. Robot installation + docking
4. Insertion cystoscope
5. Identification implantation area with simultaneous cystoscopy and laparoscopy
6. Placement of the needles and catheters implantation area
7. Guiding catheters outside of the patient
8. Mark the target field with Titanium clips
9. Remove needles, fix catheters, place transurethral catheter

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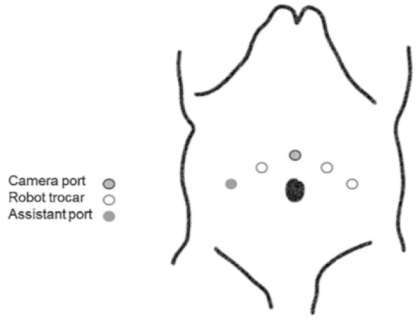

Fig. 1 – Schematic presentation of trocar placement.

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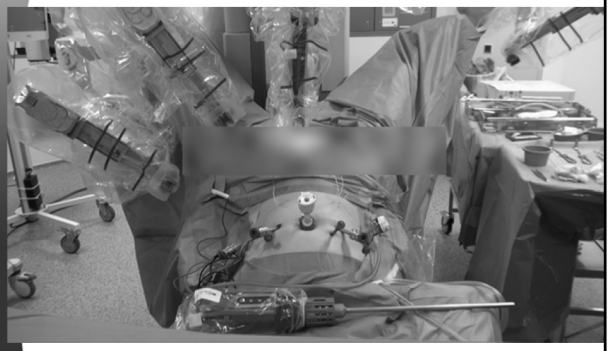

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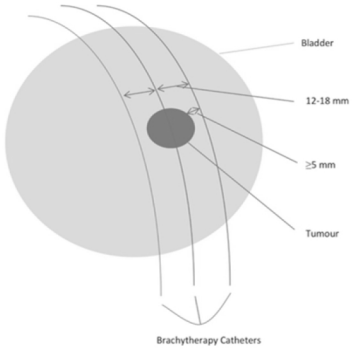

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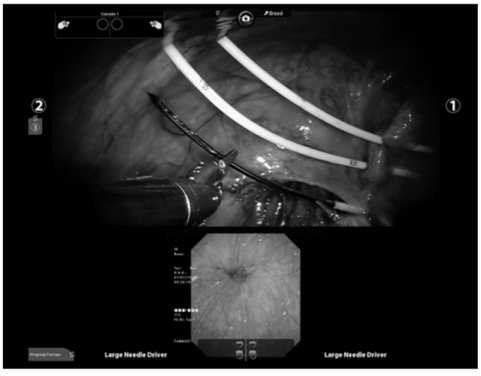
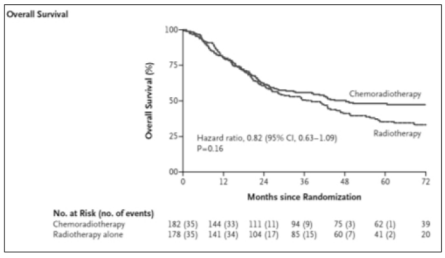


Trimodal Therapy

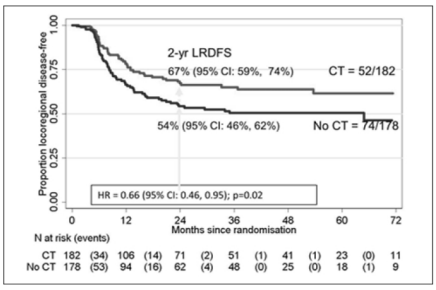
- TURBT
- Radiation therapy
- Chemotherapy



Radiotherapy 55 Gy in 20 fractions or 64 Gy in 32 fractions

5FU i.v during days 1-5 and 16-20 of radiotherapy
MMC i.v. day 1 of radiotherapy

James et al NEJM 366: 1477, 2012



James et al NEJM 366: 1477, 2012

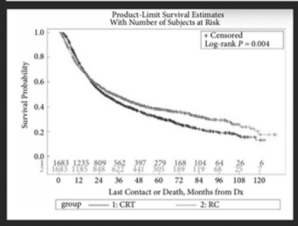
Presented By Jason A. Efstathiou at 2019 Genitourinary Cancers Symposium

RCT Data Free Zone

- No randomized controlled trial data exist comparing trimodal therapy with radical cystectomy
- Two single-center studies to date have noted comparable survival outcomes
  - Limitations include small number of patients and/or were derived from non-adjusted case-control series
- Comparative effectiveness research using cancer registry data with propensity score matching to control for selection bias and confounding is a reasonable approach

Presented By Michael Cookson at 2019 Genitourinary Cancers Symposium

Propensity matched comparative analysis of survival following chemoradiation or radical cystectomy for muscle-invasive bladder cancer



In a cohort of propensity matched patients undergoing RC and CRT, when controlling for known predictors of outcome, there is a survival advantage with RC at ≥2 years following treatment!

PRESENTED AT: 2019 Genitourinary Cancers Symposium | #GU19
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Ritch CR, et al: BJU Int 2018; 121: 745–751

Presented By Michael Cookson at 2019 Genitourinary Cancers Symposium

Comparative Effectiveness of Trimodal Therapy Versus Radical Cystectomy for Localized Muscle-invasive Urothelial Carcinoma of the Bladder

After 2 years, individuals treated with TMT were 1.40-fold more likely to die following presentation with localized muscle-invasive UCB.

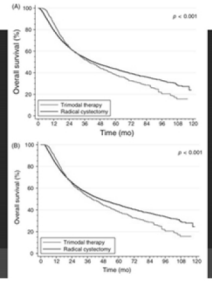

Fig. 1 – Inverse probability of treatment weighting (IPTW)–adjusted Kaplan-Meier analysis of overall survival (A) without and (B) with a 3-mo conditional landmark in patients who received trimodal therapy versus radical cystectomy for localized muscle-invasive urothelial carcinoma of the bladder. The *p* values were calculated using a χ^2 test from an IPTW-adjusted Cox regression model with a time-varying covariate for comparison of trimodal therapy versus radical cystectomy.

Seisen T, et al: European Urology 2017; 72: 483–487

PRESENTED AT: 2019 Genitourinary Cancers Symposium | #GU19
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Presented By Michael Cookson at 2019 Genitourinary Cancers Symposium

VUmc

Research

JAMA Surgery | Original Investigation

Comparing Survival Outcomes and Costs Associated With Radical Cystectomy and Trimodal Therapy for Older Adults With Muscle-Invasive Bladder Cancer

Stephen B. Williams, MD; Yong Shan, PhD; Usama Jazzar, BS; Hemalkumar B. Mehta, PhD; Jacques G. Baillargeon, PhD; Jinhai Huo, PhD; Anthony J. Senagore, MD; Eduardo Orihuela, MD; Douglas S. Tyler, MD; Todd A. Swanson, MD, PhD; Ashish M. Kamat, MD

Williams SB, et al: JAMA Surg 2018; 153: 881–9

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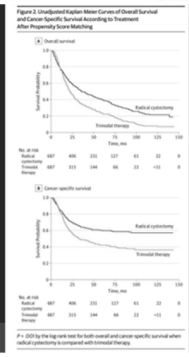
Oncologic Results

Table 2. Proportional Hazards Regression Model of Treatment for Overall Survival and Cancer-Specific Survival[a]

Covariate	Survival, HR (95% CI)
Cox Proportional Hazards Regression Overall Survival	
Treatment	
Radical cystectomy	1 [Reference]
Trimodal therapy	1.49 (1.31-1.69)
Competing Risk Regression Cancer-Specific Survival	
Treatment	
Radical cystectomy	1 [Reference]
Trimodal therapy	1.55 (1.32-1.83)

Abbreviation: HR, hazard ratio.

[a] All baseline covariates were well balanced in the propensity score–matched sample. Therefore, no covariates were controlled for in the outcome model.



Williams SB, et al: JAMA Surg 2018; 153: 881–9

PRESENTED AT: 2019 Genitourinary Cancers Symposium | #GU19

Presented By Jeanny Aragon-Ching at 2019 Genitourinary Cancers Symposium

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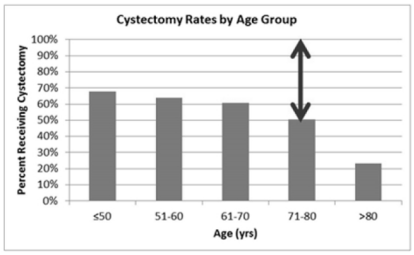
Cystectomy is not being performed in 50% of patients – huge unmet need, TMT can fill the gap

ACS / National Cancer Database (2004-2008)



Gray et al, Eur Urol 63: 823, 2013

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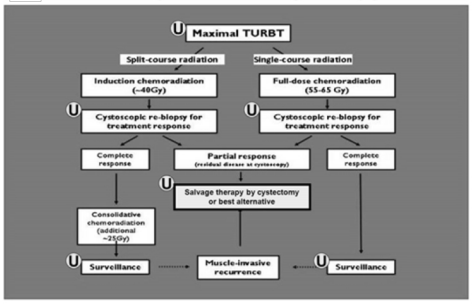
TMT is very much a surgical approach!



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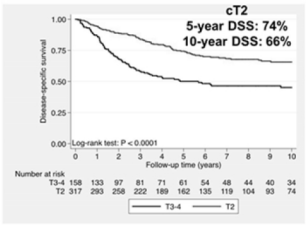
Long-term results of TMT are excellent and comparable to RC

MGH Experience 1986-2013 (cT2-T4, n=475, f/u 7.2yrs)



Giacalone et al, Eur Urol 71: 952, 2017

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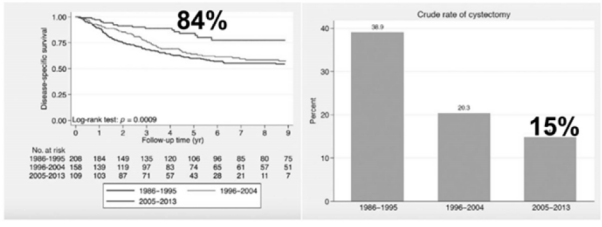
TMT Contemporary results 2005-2013



Giacalone et al, Eur Urol 71: 952, 2017

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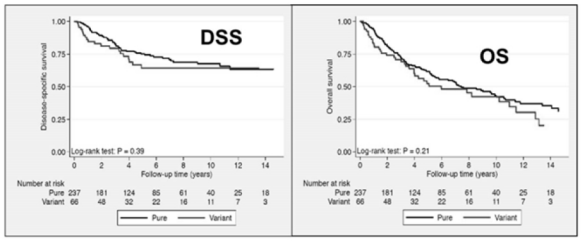
Mixed Histologic Variants treated by TMT

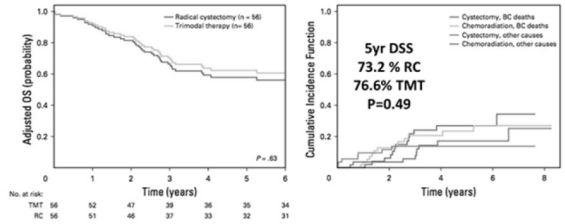


Krasnow et al, Eur Urol 72: 54, 2017

VUmc

Toronto TMT vs Cystectomy: 2008-2013

Propensity score matched analyses
n=112, median f/u 4.51 yrs

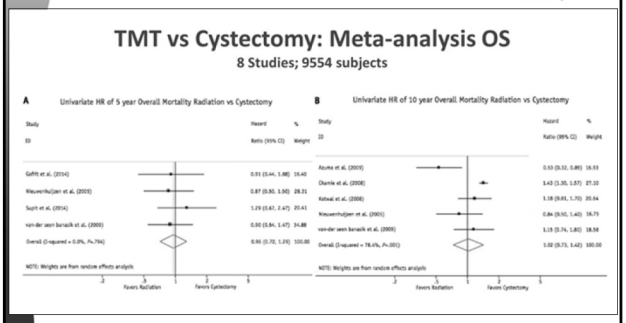


Kulkarni et al, J Clin Oncol. 35: 2299, 2017

VUmc

TMT vs Cystectomy: Meta-analysis OS

8 Studies; 9554 subjects

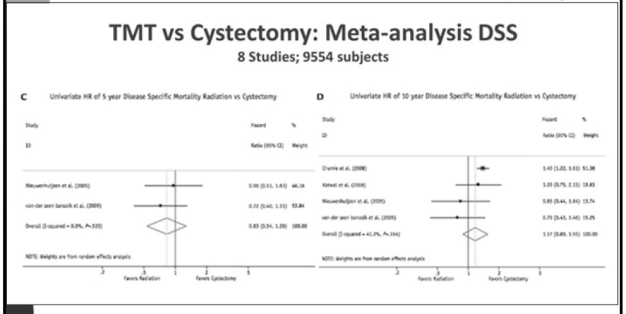


Vashistha et al, Int J Rad Oncol Biol Phys 97: 1002, 2017

VUmc

TMT vs Cystectomy: Meta-analysis DSS

8 Studies; 9554 subjects



Vashistha et al, Int J Rad Oncol Biol Phys 97: 1002, 2017

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Active radiosensitizing drugs

- Cisplatin
- Paclitaxel
- 5-FU
- Mitomycin C
- Gemcitabine (low dose)
- Carbogen/nicotinamide

Lots of options for non-cisplatin candidates

VUmc

In 2019, patients should be offered TMT

- **In clinically-matched patients, survival is comparable in modern era**
- **85% of contemporary patients keep their own bladder (better than continent diversion) and long-term QOL is good**
- **TMT is not a non-surgical treatment: maximal TURBT and salvage cystectomy are important components**
- **Supported by numerous guidelines (NCCN, AUA/ASTRO, EAU…)**
- **Need to advocate for multidisciplinary engagement**

EAU Guidelines 2018

VUmc

7.6.1.1 Guideline for transurethral resection of bladder tumour

Recommendation	Strength rating
Do not offer transurethral resection of bladder tumour alone as a curative treatment option as most patients will not benefit.	Strong

7.6.2.1 Summary of evidence and guideline for external beam radiotherapy

Summary of evidence	LE
External beam radiotherapy alone should only be considered as a therapeutic option when the patient is unfit for cystectomy or as part of a multimodality bladder-preserving approach.	3
Radiotherapy can also be used to stop bleeding from the tumour when local control cannot be achieved by transurethral manipulation because of extensive local tumour growth.	3

Recommendations	Strength rating
Do not offer radiotherapy alone as primary therapy for localised bladder cancer.	Strong

EAU Guidelines 2018

VUmc

7.6.3.1 Summary of evidence and guideline for chemotherapy for muscle-invasive bladder tumours

Summary of evidence	LE
Complete and partial local responses have been reported with cisplatin-based chemotherapy as primary therapy for locally advanced tumours in highly selected patients.	2b

Recommendations	Strength rating
Do not offer chemotherapy alone as primary therapy for localised bladder cancer.	Strong

7.6.4.1 Summary of evidence and guidelines for multimodality treatment in muscle-invasive bladder cancer

Summary of evidence	LE
In a highly selected patient population, long-term survival rates of multimodality treatment are comparable to those of early cystectomy.	2b

Recommendations	Strength rating
Offer surgical intervention or multimodality treatments (MMT) as primary curative therapeutic approaches since they are more effective than radiotherapy alone.	Strong
Offer MMT as an alternative in selected, well-informed and compliant patients, especially for whom cystectomy is not an option.	Strong

esu European School of Urology

TREATMENT OF LOCALIZED PROSTATE CANCER

Paolo Gontero
Chairmen Division of Urology
San Giovanni Battista Hospital
University of Studies of Torino
Torino, Italy

Belgrade, 12 Aprile 2019

AGENDA

- **RADICAL PROSTATECTOMY**
  - **Indications in localized disease**
  - **Different techniques and outcomes**
  - **Nerve sparing: when and how?**
  - **LAD: when?**
- **RADIOTHERAPY**
  - **Definitive external beam**
  - **Treatment by risk cathegory**
  - **Brachitherapy**
  - **Complications**
- **Comparative oncological outcomes RADIOTHERAPY vs SURGERY**
- **ACTIVE SURVEILLANCE**
- **ALTERNATIVE ABLATIVE THERAPIES & FOCAL THERAPY**

RADICAL PROSTATECTOMY (RP)

RP: INDICATIONS

6.2.1.4 Guidelines for the treatment of low-risk disease

Offer surgery and radiotherapy as alternatives to AS to patients suitable for such treatments and who accept a trade-off between toxicity and prevention of disease progression.	Weak

6.2.2.5 Guidelines for the treatment of intermediate-risk disease

Offer RP to patients with intermediate-risk disease and a life expectancy > ten years.	Strong

6.2.3.4 Guidelines for radical treatment of high-risk localised disease

Offer RP to patients with high-risk localised PCa and a life expectancy of > ten years only as part of multi-modal therapy.	Strong

European Association of Urology · ESTRO · SIOG

Sweden registry, 2000

LONG-TERM SURVIVAL IN A SWEDISH POPULATION-BASED COHORT OF MEN WITH PROSTATE CANCER

GABRIEL SANDBLOM, MONIKA DUFMATS, AND EBERHARD VARENHORST

Objectives. To study the long-term survival of patients with prostate cancer, determine the risk factors for prostate cancer death, and investigate the outcome of initially untreated localized prostate cancer and incidentally detected tumors.

Analysis of survival of 813 localised PCa patients (T1-T2) initially untreated

At 10, 15 and 20 yrs after diagnosis, CSS was 85%, 80%, and 62%

At 10 yrs, CSS among men treated with expectancy was 90% for grade 1 tumors, 74% for grade 2, and 59% for grade 3.

UROLOGY **56:** 442–447, 2000. © 2000, Elsevier Science Inc.

Sweden registry, 2000

TABLE I. *Distribution of treatment to all patients in the study, all with localized tumors, and those with localized tumors who were younger than 70 years*

	All Patients		Localized Tumors, All Patients		Localized Tumors, Patients <70 yr	
	n	Mean Age (yr)	n	Mean Age (yr)	n	Mean Age (yr)
Watchful waiting	274	74	235	74	73	65
Definitive treatment						
Radical prostatectomy	26	64	24	65	22	64
Radiotherapy	12	65	5	66	5	66
Neoadjuvant therapy plus radical prostatectomy	1	74				
Palliative treatment						
Bilateral orchiectomy	216	73	53	75	11	65
GnRH analogues	19	74	2	76		
Antiandrogen	13	72	3	70		
Estramustine phosphate	28	74				
Estrogen	192	73	45	72	17	64
Other palliative	14	73	9	73	3	60
Missing information	18	75	7	74	1	60
Total	813	73	383	73	132	65

Conclusions. Patients with localized tumors have a favorable prognosis, even without initial treatment. However, when deciding on therapy, the grade of malignancy should be taken into account, as it has a great influence on survival. We did not see a tendency toward increased mortality when the patients were followed up for longer than 10 years after diagnosis. UROLOGY **56:** 442–447, 2000. © 2000, Elsevier Science Inc.

UROLOGY **56:** 442–447, 2000. © 2000, Elsevier Science Inc.

SPCG-4, 2012

Results From the Scandinavian Prostate Cancer Group Trial Number 4: A Randomized Controlled Trial of Radical Prostatectomy Versus Watchful Waiting

347 men with localised PCa (T1-T2, PSA <50, well to moderately-well differentiated PCa) randomly assigned to RP and 348 to WW

At 15 yrs, the absolute risk reduction of dying from PCa was 6.1% in favor of RP

17 need to be randomized to RP to avert one death

Death from any cause and distant metastases significantly reduced in low-risk PCa at 18 yrs for RP compared to WW

SPCG-4, 2018

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Radical Prostatectomy or Watchful Waiting in Prostate Cancer — 29-Year Follow-up

CONCLUSIONS

Men with clinically detected, localized prostate cancer and a long life expectancy benefited from radical prostatectomy, with a mean of 2.9 years of life gained. A high Gleason score and the presence of extracapsular extension in the radical prostatectomy specimens were highly predictive of death from prostate cancer. (Funded by the Swedish Cancer Society and others.)

SPCG-4, 2018

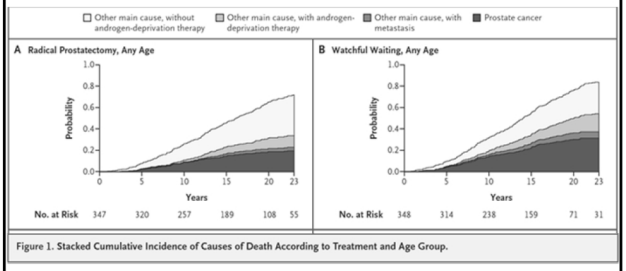


Figure 1. Stacked Cumulative Incidence of Causes of Death According to Treatment and Age Group.

ProtecT, 2016

The NEW ENGLAND JOURNAL of MEDICINE

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

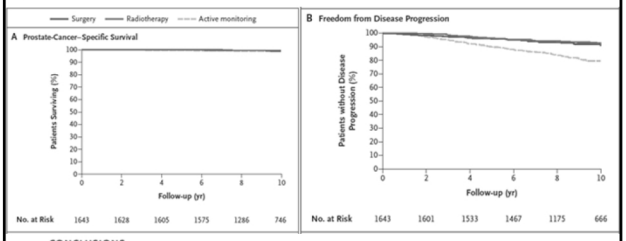
10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer

1643 patients with localised disease (PSA <20, >75% T1c or GS 6) randomised to active monitoring (545), RP (553), RT (545)

Benefit for MFS and PFS, but neither CSS nor OS, was seen for RP compared to AM or RT

THE DECISION TO OFFER RP IN LOW RISKS SHOULD BE BASED UPON THE PROBABILITIES OF CLINICAL PROGRESSION, SIDE-EFFECTS AND POTENTIAL BENEFITS TO SURVIVAL

ProtecT, 2016



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.)

PIVOT, 2017

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

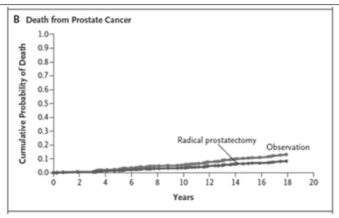
Follow-up of Prostatectomy versus Observation for Early Prostate Cancer

731 patients with localised disease (T1-T2, PSA <50) randomised to RP (364) or observation (367)

Surgery may have been associated with lower all-cause mortality (HR 0.69) than observation in intermediate risks (*not death from PCa*), but not in low- or high risks.

Treatment for disease progression was less frequent with surgery than with observation.

PIVOT, 2017



CONCLUSIONS

After nearly 20 years of follow-up among men with localized prostate cancer, surgery was not associated with significantly lower all-cause or prostate-cancer mortality than observation. Surgery was associated with a higher frequency of adverse events than observation but a lower frequency of treatment for disease progression, mostly for asymptomatic, local, or biochemical progression. (Funded by the Department of Veterans Affairs and others; PIVOT ClinicalTrials.gov number, NCT00007644.)

RP: TECHNIQUES

-OPEN / LAPAROSCOPIC / ROBOTIC

-TRANSPERITONEAL / EXTRAPERITONEAL

-If robotic: STANDARD TECHNIQUE / LATERAL APPROACH / RETZIUS SPARING

Is one technique superior to the other?

RP – functional outcomes across surgical techniques

Urinary Incontinence and Erectile Dysfunction After Robotic Versus Open Radical Prostatectomy: A Prospective, Controlled, Nonrandomised Trial

Characteristic	Open retropubic radical prostatectomy (n = 778)	Robot-assisted laparoscopic radical prostatectomy (n = 1847)	p value
Neurovascular bundle preservation, no. (%)			
No neurovascular dissection	246 (32)	287 (16)	<0.001
Lymph node dissection			
No	553 (73)	1604 (87)	<0.001
Yes	206 (27)	235 (13)	
Surgical margin status			
Negative	585 (77)	1 399 (77)	0.15
Positive	154 (20)	399 (22)	

Definition of urinary incontinence	Open surgery, n (%)	Robot-assisted surgery, n (%)	Adjusted A, OR (95% CI)	Adjusted B, OR (95% CI)	Adjusted C, OR (95% CI)
Change of pad ‡ at least once per 24 h (primary end point)	144 (20)	366 (21)	1.21 (0.96–1.54)	1.24 (0.96–1.60)	1.31 (1.01–1.70)

Definition of erectile dysfunction	Open surgery, n (%)	Robot-assisted surgery, n (%)	Adjusted A, OR (95% CI)	Adjusted B, OR (95% CI)	Adjusted C, OR (95% CI)
IIEF score §	531 (75)	1200 (70)	0.80 (0.64–1.00)	0.79 (0.63–1.00)	0.73 (0.58–0.93)

RP – functional outcomes across surgical techniques

Robot-assisted laparoscopic prostatectomy versus open radical retropubic prostatectomy: early outcomes from a randomised controlled phase 3 study

	Range	Baseline			6 weeks			12 weeks		
		Radical retropubic prostatectomy (n=152)	Robot-assisted laparoscopic prostatectomy (n=153)	p value	Radical retropubic prostatectomy (n=136)	Robot-assisted laparoscopic prostatectomy (n=131)	p value	Radical retropubic prostatectomy (n=119)	Robot-assisted laparoscopic prostatectomy (n=129)	p value
Primary										
Urinary function										
EPIC—urinary domain	0–100	88·79 (86·74–90·85)	88·50 (86·59–90·40)	0·83	74·50 (72·77–77·17)	71·10 (68·26–73·95)	0·09	83·80 (81·33–86·17)	82·50 (80·23–84·86)	0·48
Sexual function										
EPIC—sexual domain	0–100	59·80 (55·66–63·92)	63·05 (59·32–66·78)	0·25	30·75 (27·18–34·21)	32·78 (28·67–36·79)	0·45	35·00 (30·94–39·06)	38·90 (34·83–42·96)	0·18
Domain-specific QoL—IIEF total	0–75	43·96 (40·35–47·58)	46·65 (43·07–50·23)	0·30	23·75 (21·03–26·47)	25·63 (22·35–28·92)	0·38	27·56 (24·30–30·81)	30·14 (26·46–30·81)	0·31

RP – functional outcomes across surgical techniques

Radical prostatectomy performed via robotic, transperitoneal and extraperitoneoscopic approaches: functional and early oncological outcomes

	Total, n = 231	TPRP, n = 75	RARP, n = 90	ERP, n = 63	P value
Age, years	63.0 (60.0–67.0)	65.0 (62.0–68.0)	63.0 (59.0–67.0)	64.0 (61.0–67.0)	0.075
Body mass index, kg/m²	28.0 (26.26–30.0)	27.78 (26.0–30.1)	28.0 (26.0–30.0)	28.94 (27.76–29.86)	0.070
TRUS prostate volume, cm³	36.00 (27.0–50.0)	42.0 (27.0–56.0)	33.5 (27.0–40.0)	30.5 (28.0–50.0)	0.120
Procedure time, min	180.0 (145.0–205.0)	180.0 (130.0–235.0)	200.0 (180.0–210.0)	147.5 (120.0–160.0)	<0.001
Blood loss, mL	200.00 (100.0–300.0)	200.00 (150.0–400.0)	200.00 (100.0–300.0)	200.00 (150.0–300.0)	0.017
Nerve sparing, %					
– bilateral	66.2	13.7	56.9	29.4	<0.001
– none	33.8	69.2	3.8	26.9	
Lymph node dissection, %					
– extended	50.6	60.0	63.3	27.7	<0.001
– none	49.4	40.0	37.7	73.3	
Cathether removal, day	8.0 (8.0–9.0)	8.0 (8.0–10.0)	8.0 (7.0–9.0)	8.0 (8.0–8.0)	0.001
Pad-test	0.0 (0.0–1.0)	1.0 (0–1.0)	0 (0.0–0.0)	0.0 (0.0–1.0)	<0.001
ICIQ–score SF					
– 3 months	13.0 (5.0–15.0)	6.0 (0–9.0)	10.0 (0–14.0)	13.5(10.0–15.0)	<0.001
– 12 months	3.0 (0.0–8.0)	1.0 (0–1.0)	0.0 (0–6.0)	4.0 (3.0–7.0)	<0.001
Continence, %	72.7	52.0	83.3	81.8	<0.001
IIEF–5 score					
– Preoperative	20.0* (19.0–21.0)	19.0 (19.0–20.0)	20.0 (19.0–20.0)	21.0 (20.0–21.0)	0.020
– 12 months*	5.0 (0–19.0)	3.0 (0–8.0)	19.0 (8.0–21.0)	5.0 (5.0–5.0)	0.001

RP – functional outcomes across surgical techniques

A comparative study of robot-assisted and open radical prostatectomy in 10,790 men treated by highly trained surgeons for both procedures

[1]Martini-Klinik Prostate Cancer Center, University Hospital Hamburg-Eppendorf, Hamburg,

Comparison between ORP (n=7007) or RARP (n=3783)

- No difference regarding oncological outcome
- One-week continence higher in ORP (26% vs 22%)
- 1-yr continence modestly higher in RARP (90.3% vs 88.8%)
- 1-yr potency similar between groups
- Operative time shorter in ORP
- Blood loss, transfusions and time to catheter removal lower in RARP

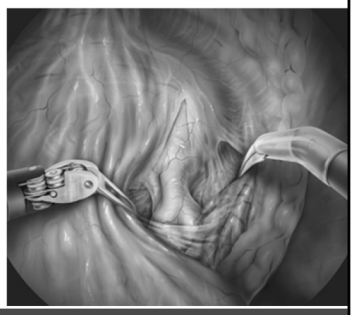
doi: 10.1111/bju.14760

RARP: lateral approach

Anastasios D. Asimakopoulos*†, Camille Mugnier*, Jean-Luc Hoepffner*, Thierry Piechaud* and Richard Gaston*

Possible option to obtain a complete preservation of the bladder neck

Immediate access to the neurovascular bundle



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RARP: Retzius sparing

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

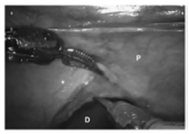
EUROPEAN

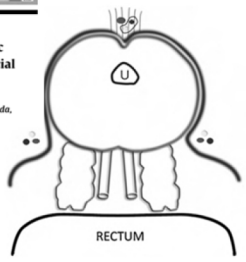
eau European Association of Urology

Case Series of the Month

A New Anatomic Approach for Robot-Assisted Laparoscopic Prostatectomy: A Feasibility Study for Completely Intrafascial Surgery

*Antonio Galfano *, Assunta Ascione, Salvatore Grimaldi, Giovanni Petralia, Elena Strada, Aldo Massimo Bocciardi*





EUROPEAN UROLOGY 58 (2010) 457–461

RARP: Retzius sparing

Retzius-sparing versus standard robot-assisted radical prostatectomy: a prospective randomized comparison on immediate continence rates

Anastasios D. Asimakopoulos[1,2] · Luca Topazio[1] · Michele De Angelis[1] · Enrico Finazzi Agrò[2] · Antonio Luigi Pastore[3] · Andrea Fuschi[1,3] · Filippo Annino[1]

102 pts randomised to RARP vs RS-RARP

Immediate continence 30% (RARP) vs 51% (RS-RARP)

Median time to continence 21d vs 1d

Age and Retzius sparing approach significantly associated to earlier continence recovery

Surgical Endoscopy
https://doi.org/10.1007/s00464-018-6499-z

RP: NERVE SPARING

Offer nerve-sparing surgery to patients with a low risk of extracapsular disease (refer to nomograms).	Strong

eau European Association of Urology ESTRO SIOG

WHEN?

6.1.2.1.3 Nerve-sparing surgery

Nerve-sparing RP can be performed safely in most men with localised PCa [358, 359]. Clear contraindications are patients in whom there is a high risk of extracapsular disease, such as any cT2c or cT3 PCa, any GS > 7 on biopsy. An externally validated nomogram predicting side-specific extracapsular extension can help guide decision making [360, 361]. If any doubt remains regarding residual tumour, the surgeon should remove the neurovascular bundle (NVB). Alternatively, the use of intra-operative frozen-section analysis can help guide these decisions [362].

mpMRI is essential when planning a nerve-sparing

RP: NERVE SPARING

HOW?

- **Interfascial**
- **Intrafascial**

- **Avoid thermal damage**
- **Use of metallic clips or Hemoloks**

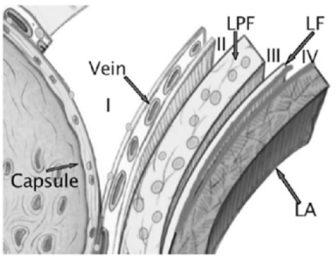
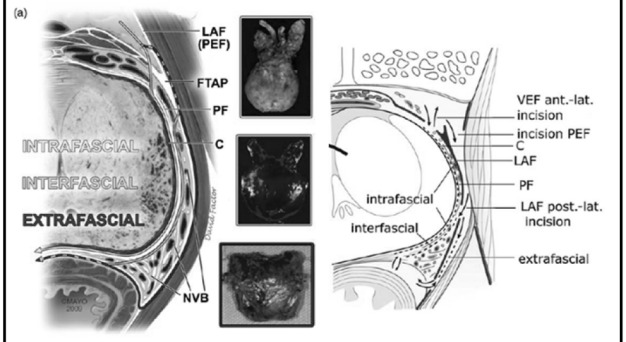


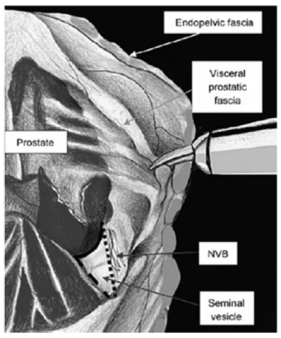
Fig. 3 – Layers of fascia enveloping prostatic capsule, demonstrating the planes of dissection for differing grades (1–4) of nerve sparing. LPF = lateral pelvic fascia; LF = levator fascia; LA = levator ani. (From [13,14].)

RP: NERVE SPARING



EUROPEAN UROLOGY 57 (2010) 179–192

Nerve sparing: anatomy



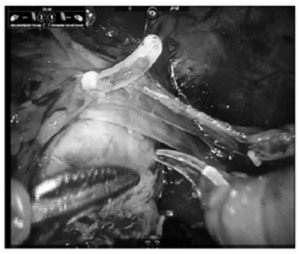


Figure 3. The three-layer structure of the lateral prostatic fascia is demonstrated.

EUROPEAN UROLOGY 58 (2010) 407–417

Ther Adv Urol
2019, Vol. 11: 1–7

Nerve sparing: options

A matched and controlled longitudinal cohort study of dehydrated human amniotic membrane allograft sheet used as a wraparound nerve bundles in robotic-assisted laparoscopic radical prostatectomy: a puissant adjunct for enhanced potency outcomes

Sanjay Razdan[1,5] · Rajesh Raj Bajpai[2] · Shirin Razdan[3] · Marcos A. Sanchez[4]

DEHYDRATED HUMAN AMNIOTIC MEMBRANE
1400 RARP with full bilateral nerve sparing
700 with allograft around the bundles VS 700 without
First erection sufficient for penetrative intercourse earlier
Allograft was significant predictor of achieving potency at 1 yr
BALANCE WITH COSTS!

Journal of Robotic Surgery
https://doi.org/10.1007/s11701-018-0873-7

RP: PLND, yes or no?

Perform an ePLND in intermediate-risk disease if the estimated risk for positive lymph nodes exceeds 5%.	Strong
Perform an ePLND in high-risk disease.	Strong
Do not perform a frozen section of nodes during RP to decide whether to proceed with, or abandon, the procedure.	Strong

European Association of Urology · ESTRO · SIOG

RP: PLND, how far?

Prostate Cancer

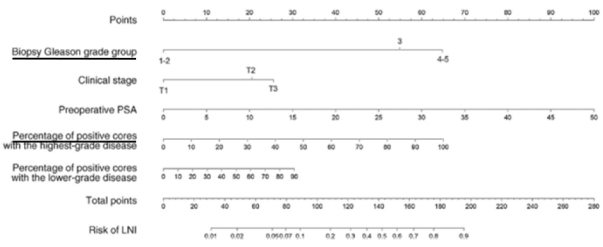
Development and Internal Validation of a Novel Model to Identify the Candidates for Extended Pelvic Lymph Node Dissection in Prostate Cancer

- Proposal of a **refined nomogram** that accounts for:
  - Biopsy GS group (taking into account intratumour grading heterogeneity)
  - Percentage of biopsy cores with highest GS
- **Methodology of development**:
  - 682 PC undergone ePLND, single institution
  - Variables found predictors in MVA fitted in a nomogram model
  - AUC = 90%
- **Interpretation**
  - Current Guidelines cut off for proceeding to PLND is 5% (based on existing nomograms)
  - Using the 7% probability of LNI to undergo ePLND would spare more ePLND (70%) and miss the same rate of N+ (1.5%)

Gandaglia G et al, Eur Urol 2017

Prostate Cancer

Development and Internal Validation of a Novel Model to Identify the Candidates for Extended Pelvic Lymph Node Dissection in Prostate Cancer



Gandaglia G et al, Eur Urol 2017

PLND: if you do it, do it properly

- Obturator fossa restricted LND highly inadequate and no longer acceptable (IPLND)
- LND limited to the **external iliac** and **obturator** location will include only 38% of prostate draining nodes (sPLND)
- To remove 75% of potentially cancer-bearing nodes LND should include **internal** and common **iliac vessels** (up to the crossing of ureter): ePLND

La Rochelle JC, Urol Clin North Am, 2011

DO & DONT'S IN PLND IN PC

- **Do not perform PLND in all patients:**
  - Lack of solid evidence of its oncological efficacy
  - Significant more complications (lymphoceles, mortality)
- **Do not avoid ePLND in all patients**
  - Staging accuracy
  - Use predictive models to balance the risk/benefit ratio
- **Do PLND no more than when indicated**
  - Avoid in low risk
  - Intermediate risk when risk of N+ > 5% (or 7% with updated nomogram)
  - All high risk

Fossati N, Eur Urol 2017

WHICH PCa SHOULD RECEIVE PLND?

9.1. Pelvic lymph node dissection

The individual risk of finding positive lymph nodes can be estimated using externally validated preoperative nomograms such as that described by Brigant~~i [49]. A risk of nodal~~ metastases >5% is an indication to perform an extended nodal dissection (ePLND). This includes removal of the nodes overlying the external iliac artery and vein, the nodes within the obturator fossa located cranially and caudally to the obturator nerve, the nodes medial and lateral to the internal iliac artery, and the nodes overlying the common iliac artery and vein up to the ureteral crossing. It is recommended that for each region the nodes should be sent separately for pathologic analysis. With this template, 75% of all anatomic landing sites are cleared, resulting in improved pathological staging compared with a limited pelvic lymph node dissection, but at the cost of three-fold higher complication rates (19.8% vs 8.2%), mainly related to significant lymphoceles [50].

EAU, ESMO & SIUG Guidelines 2017

RADIOTHERAPY

EBRT

Intensity-modulated radiotherapy (IMRT), with or without image-guided radiotherapy (IGRT), is the gold standard for EBRT.

- **IMRT** and **volumetric arc EBRT** employ dynamic multileaf collimators, which automatically and continuously adapt to the contours of the target volume seen by each beam
- With dose escalation using IMRT, organ movement becomes critical: IMRT is combined with **IGRT** to allow for corrections.
- **Tomotherapy** is another technique for the delivery of IMRT, using a linear accelerator mounted on a ring gantry that rotates as the patient is delivered thorugh the centre of the ring.

Dose escalation

Several RCT have shown that dose escalation **(74-80 Gy)** has a significant impact on 5-yr BCR.

The best evidence comes from a non-randomised propensity matched retrospective analysis of the US Nat Canc DB covering 42.481 patients.

In everyday practice, a minimum dose of **≥74 Gy** is recommended for EBRT.

Brachytherapy boost

High dose rate applications, delivered using multiple fractions with **temporary** applicator placement and remote after loading with **Iridium**.

Very high doses delivered to the prostate, with low doses to the surrounding normal tissues, and the ability to overcome the problem of organ motion.

The dose to peri-prostatic tissues, which may harbor microscopic disease, may be **insufficient**, and therefore it is usually used with **EBRT** for men with *intermediate or higher risk* features.

Not all men have suitable anatomy, and those with high IPSS scores are at higher risk of genitourinary toxicity.

Brachytherapy boost

Brachytherapy versus external beam radiotherapy boost for prostate cancer: Systematic review with meta-analysis of randomized trials

Daniel Lam Cham Kee[a], Jocelyn Gal[b], Alexander T. Falk[a], Renaud Schiappa[b], Marie-Eve Chand[a], Mathieu Gautier[a], Jérôme Doyen[a], Jean-Michel Hannoun-levi[a,*]

Background: Brachytherapy boost after external beam radiotherapy for intermediate and high-risk prostate cancer is presented as an attractive technique in numerous retrospective and prospective studies. Currently, three randomized controlled trials comparing brachytherapy versus external beam radiotherapy boost used non-homogenous irradiation features. Therefore, we analyzed the oncological outcomes by a systematic review with meta-analysis of the randomized controlled trials.

Methods: We performed a systematic literature review of MEDLINE and COCHRANE databases up to 30/04/10 and we considered all published randomized controlled trials comparing brachytherapy versus external beam radiotherapy boost for intermediate and high-risk prostate cancer according to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement. The review was assessed using Assessing the Methodological Quality of Systematic Reviews (AMSTAR) tool and the identified reports were reviewed according to the Consolidated Standards of Reporting Trials (CONSORT). Eight publications from 3 RCTs were selected.

Results: There was a significant benefit in 5-year biochemical-progression-free survival in favor of BT versus EBRT boost (HR: 0.49 [95% CI, 0.37–0.66], $p < 0.01$). There was no difference at 5 years in overall survival (HR: 0.92 [95% CI, 0.64–1.33], $p = 0.65$). ≥ grade 3 late genito-urinary (RR: 2.19 [95%CI, 0.76–6.30], $p = 0.15$) and late gastro-intestinal toxicities (RR: 1.85 [95%CI, 1.00–3.41] $p = 0.05$).

Conclusion: This meta-analysis provides further evidence in favor of BT boost for intermediate and high-risk prostate cancer in terms of b-PFS improvement, leading to suggest BT boost as level I and grade A recommendation. However, the risk of grade ≥ 3 late toxicity must be carefully investigated.

Hypofractionation (HFX)

- **Slowly proliferating cells (such as PCa) are very sensitive to an increased dose per fraction**
- HFX more effective? Metanalysis including 14.000 pts
- HFX more convenient for the patient, cheaper for the health care system

Extreme HFX

- **>3.4 Gy per fraction (6-9 Gy)**: requires **IGRT** and **SBRT**
- Short term biochemical control comparable to standard fractions
- GU and rectal toxicity?
- Insufficient FU for mature oncological outcomes

Whole pelvis RT?

Table 7 Whole pelvic radiotherapy

	Participants	Control	Experimental	ADT	Endpoints	Median f/u	Results
RTOG 7706 [7]	T1b–2N0M0 (nodes staged lymphangiography)	64.8 in Gy in 36 fractions prostate bed	WPRT to 45 Gy in 25 Boost to prostate to 64.8 Gy			7 years	No difference in local control, disease-free survival or overall survival
RTOG 9413 [88]	1995–1999 *n* = 1292 LNI risk > 15% (Roach), PSA ≤ 100 ng/mL 73% GS ≥ 7	4 field box, urethrogram to localize prostate 70.2 Gy in 39 fractions limit field size < 11 cm × 11cm	4 field box WPRT to 50.4 Gy in 28 fractions superior limit L5/S1 Boost to prostate/SV of 19.8 Gy in 11 fractions	2 × 2 design: all 4 months of total androgen suppression (goserelin or leuprolide + flutamide) Randomized to neoadjuvant or adjuvant	Powered for comparison NHT vs ADT and PORT with WPRT Primary endpoint: progression-free survival (PFS) = BF (ASTRO and Phoenix)	12 years	No significant difference in PFS comparing WP with PORT or NHT with ADT Suggested interactions between field size and use of NHT vs ADT—less clear with longer follow-up No significant difference in late ≥ G3 GU toxicity Increased late ≥ G3 GI toxicity in WP/NHT (5% WPRT/NHT vs 1% PO/NHT, 2% WPRT-AHT, 2% PORT/AHT)
GETUG-01 [121]	1998–2004 *n* = 444 T1b–3N0pN × M0 stratified by risk (low risk: cT1c–2c, GS ≤ 6, PSA < 3 × ULN; high risk cT3, GS ≥ 7, PSA > 3 × ULN) ~ 50% GS 6 > 50% LNI risk < 15% (Roach)	3DCRT, 4 field prostate to 66 Gy (increased to 70 Gy after 2000) Mean total dose 68 Gy Seminal vesicle to 46 Gy in uninvolved, 60 Gy if involved (other fractionation permitted 1.8–2.25 Gy/f)	3DCRT 4 field WPRT to 46 Gy; superior limit at S1/2 Boost to prostate/SV to same dose as control	Permitted high risk—4-8 months neoadjuvant and concomitant	Primary: event free survival (BF (ASTRO) or local or distant progression)	11.4 years	No difference in 10-year EFS or OS Post hoc analysis suggested benefit of WPRT in low-risk group, not receiving ADT No significant differences in toxicity

RP vs RT

RP vs RT (PCOS, 2013)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Long-Term Functional Outcomes after Treatment for Localized Prostate Cancer

RESULTS

Patients undergoing prostatectomy were more likely to have urinary incontinence than were those undergoing radiotherapy at 2 years (odds ratio, 6.22; 95% confidence interval [CI], 1.92 to 20.29) and 5 years (odds ratio, 5.10; 95% CI, 2.29 to 11.36). However, no significant between-group difference in the odds of urinary incontinence was noted at 15 years. Similarly, although patients undergoing prostatectomy were more likely to have erectile dysfunction at 2 years (odds ratio, 3.46; 95% CI, 1.93 to 6.17) and 5 years (odds ratio, 1.96; 95% CI, 1.05 to 3.63), no significant between-group difference was noted at 15 years. Patients undergoing prostatectomy were less likely to have bowel urgency at 2 years (odds ratio, 0.39; 95% CI, 0.22 to 0.68) and 5 years (odds ratio, 0.47; 95% CI, 0.26 to 0.84), again with no significant between-group difference in the odds of bowel urgency at 15 years.

RP vs RT (PCOS, 2013)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Long-Term Functional Outcomes after Treatment for Localized Prostate Cancer

CONCLUSIONS

At 15 years, no significant relative differences in disease-specific functional outcomes were observed among men undergoing prostatectomy or radiotherapy. Nonetheless, men treated for localized prostate cancer commonly had declines in all functional domains during 15 years of follow-up. (Funded by the National Cancer Institute.)

RP vs RT (Sweden, 2014)

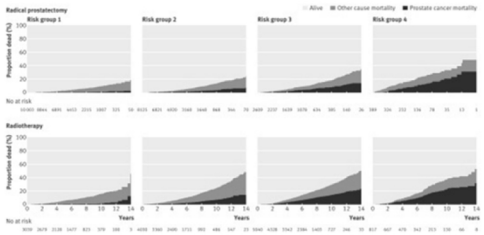
Comparative effectiveness of radical prostatectomy and radiotherapy in prostate cancer: observational study of mortality outcomes

Prasanna Sooriakumaran, assistant professor and senior clinical researcher,[1,2] Tommy Nyberg, statistician,[3] Olof Akre, associate professor,[4] Leif Haendler, consultant,[1] Inge Heus, statistician,[5] Mats Olsson, consultant,[1] Stefan Carlsson, consultant,[1] Monique J Roobol, associate professor,[5] Gunnar Steineck, professor,[3,6] and Peter Wiklund, professor[1]

34.515 men treated with RP (21.533) vs RT (12.982), FU 15 yrs

Results Prostate cancer mortality became a larger proportion of overall mortality as risk group increased for both the surgery and the radiotherapy cohorts. Among patients with non-metastatic prostate cancer the adjusted subdistribution hazard ratio for prostate cancer mortality favoured surgery (1.76, 95% confidence interval 1.49 to 2.08, for radiotherapy *v* prostatectomy), whereas there was no discernible difference in treatment effect among men with metastatic disease. Subgroup analyses indicated more clear benefits of surgery among younger and fitter men with intermediate and high risk disease. Sensitivity analyses confirmed the main findings.

RP vs RT (Sweden, 2014)



Conclusions This large observational study with follow-up to 15 years suggests that for most men with non-metastatic prostate cancer, surgery leads to better survival than does radiotherapy. Younger men and those with less comorbidity who have intermediate or high risk localised prostate cancer might have a greater benefit from surgery.

RP vs RT (Japan, 2015)

Radical Prostatectomy versus External Beam Radiotherapy for cT1-4N0M0 Prostate Cancer: Comparison of Patient Outcomes Including Mortality

Retrospective analysis of 891 cT1-4N0 Pca who underwent RP (569) or EBRT (322). Median FU 53 and 45 mo.

- No death from PCa in low- and intermediate risks
- More high-risk patients died from PCa in the EBRT group: RP independent prognostic factor for better CSS

Conclusions

Mortality outcomes of both RP and EBRT were generally favorable in low and intermediate risk patients. Improvement of CSS in high risk patients was seen in patients receiving RP over those receiving EBRT.

RP vs RT (ProtecT 2016)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Patient-Reported Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer

BACKGROUND

Robust data on patient-reported outcome measures comparing treatments for clinically localized prostate cancer are lacking. We investigated the effects of active monitoring, radical prostatectomy, and radical radiotherapy with hormones on patient-reported outcomes.

RP vs RT (ProCaSP 2015)

RESEARCH ARTICLE Open Access

The ProCaSP study: quality of life outcomes of prostate cancer patients after radiotherapy or radical prostatectomy in a cohort study

Nora Eisemann[1*], Sandra Nolte[2,3], Maike Schnoor[4], Alexander Katalinic[1,4], Volker Rohde[5,6] and Annika Waldmann[4]

Background: This study describes and compares health-related quality of life (HRQOL) of prostate cancer patients who received either radical prostatectomy (nerve-sparing, nsRP, or non-nerve-sparing, nnsRP) or radiotherapy (external RT, brachytherapy, or both combined) for treatment of localised prostate cancer.

Conclusions: Findings from previous research were reproduced in a specific setting of a patient cohort in the German health care system. According to the principle of evidence-based medicine, this strengthens the messages regarding treatment in prostate cancer and its impacts on patients' health-related quality of life. After adjustment for baseline HRQOL and other covariates, RT patients reported increased symptoms of diarrhoea, and nnsRP patients decreased prostate-specific HRQOL. RP patients experienced considerable impairment in sexual functioning. These differences should be taken into account by physicians when choosing the best therapy for a patient.

RP vs RT (ProtecT, 2016)

1643 men in ProtecT trial evaluated with validated questionnaires

- **RP:** had the greatest negative effect on sexual function and urinary continence; although there was some recovery, these outcomes remained worse in this group
- **RT**: greatest negative effect on sexual function at 6 months, little effect on urinary continence. Worse bowel function, urinary voiding and nocturia (the latter improved)
- **AM**: sexual and urinary function declined gradually

No differences among groups in terms of anxiety, depression, general health-related or cancer-related QoL

N ENGL J MED 375;15 NEJM.ORG OCTOBER 13, 2016

RP vs RT (NCDB, 2017)

Survival Outcomes of Radical Prostatectomy Versus Radiotherapy in Intermediate-Risk Prostate Cancer: A NCDB Study

268.387 intermediate-risk PCa (NCDB)

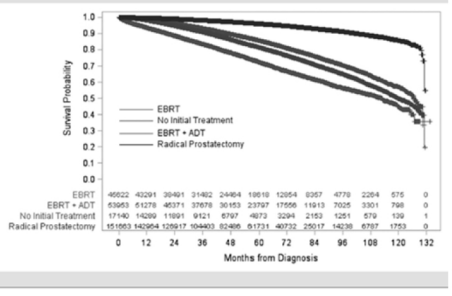
- Men receiving no initial treatment averaged greater adjusted mortality risk than men receiving EBRT (HR 1.7), EBRT+ADT (HR 1.7), or RP (HR 4.1)
- Men undergoing RP had significantly lower adjusted mortality risk than men receiving either EBRT

between men receiving EBRT or EBRT + ADT (HR, 1.01; 95% CI 0.97-1.05; *P* = .624). **Conclusion:** Men treated with RP experienced significantly lower overall mortality risk than EBRT with or without ADT and no treatment patients, regardless of patient, demographic, or facility characteristics. The results are limited by the lack of cancer-specific mortality in this database.

Clinical Genitourinary Cancer, Vol. 16, No. 1, e39-46 © 2017

RP vs RT (NCDB, 2017)

Figure 2 Kaplan-Meier Survival Curve by Treatment Cohort



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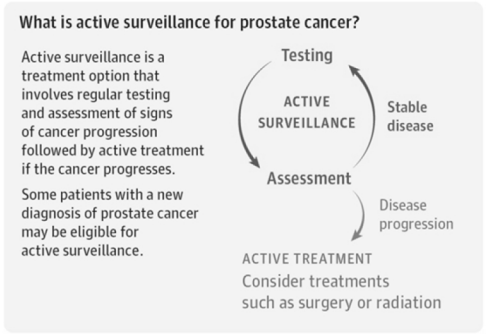
ACTIVE SURVEILLANCE

active surveillance



JAMA. 2017;318(21):2152

active surveillance - history

first desribed in 2002

initied in novembre 1995, accrued 206 patients

Choo R, Klotz L, Danjoux C, et al. Feasibility study: watchful waiting for localized low to intermediate grade prostate carcinoma with selective delayed intervention based on prostate specific antigen, histological and/or clinical progression. J Urol. 2002;167:1664-9.

active surveillance - history

Data from the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) registry demonstrates the increase in the use of active surveillance for patients with low-risk prostate cancer—from a low of 6.7% in the years from 1990 to 2009, to 40.4% in the period 2010 to 2013.

Tosoian JJ, Carter HB, Lepor A, Loeb S. Active surveillance for prostate cancer: current evidence and contemporary state of practice. Nat Rev Urol. 2016;13:205-15.

active surveillance - rationale

comparing tissue obtained during autopsy from prostate glands in both a Caucasian and an Asian population, Prostate cancer was found in a similar proportion (35%) of men in both groups.

Gleason patterns 3 and 4 are dramatically different genetically

solid molecular evidence suggests that Gleason pattern 3 (or Gleason 3+3=6) disease lacks the hallmarks of cancer, as defined in terms of gene expression abnormalities

Oncology (Williston Park). 2017 May 15;31(5):333-40, 345

active surveillance - rationale

A number of large surgical series have reported a rate of metastasis that approximates zero in surgically confirmed Gleason 6 prostate cancer

Eggener conducted a multicenter study of 24,000 men with long-term follow-up. Of those men, 12,000 had confirmed Gleason 6 disease. The 15-year prostate cancer–specific mortality rate for pathologic Gleason 6 disease was 0.2%. Only 1 patient in the cohort died of prostate cancer; a pathology review reported Gleason 4+3 disease in this man

J Urol. 2011;185:869-75.

selection criteria for active surveillance

Klotz L, Vesprini D, Sethukavalan P, et al. Long-term follow-up of a large active surveillance cohort of patients with prostate cancer. J Clin Oncol. 2015;33:272-7 University of Toronto

Tosoian JJ, Mamawala M, Epstein JI, et al. Intermediate and longer-term outcomes from prospective active surveillance program for favorable-risk prostate cancer. J Clin Oncol. 2015;33:3379-85. Johns Hopkins

Bokhorst LP, Valdagni R, Rannikko A, et al. A decade of active surveillance in the PRIAS Study: an update and evaluation of the criteria used to recommend a switch to active treatment. Eur Urol. 2016;70:954-60. Multicenter European Study

Newcomb LF, Thompson IM Jr, Boyer HD, et al; Canary PASS Investigators. Outcomes of active surveillance for clinically localized prostate cancer in the prospective, multi-institutional Canary PASS Cohort. J Urol. 2016;195:313-20 Canary Collaboration

selection criteria for active surveillance

	clinical stage	PSA level	Gleason score on biopsy	PSA density	N of pos cores on biopsy
University of Toronto	T1c/T2a	≤ 10-15 ng/ml	≤ 3+3	not included	not included
Johns Hopkins	T1c	not included	≤ 3+3	< 0,15 ng/ml/cm^3	2
Multicenter European Study	T1c/T2a	≤ 10 ng/ml	≤ 3+3	< 0.2 ng/ml/cm^3	2
Canary Collaboration	T1/T2	any	≤ 7	Any	Any

active surveillance - outcomes

University of Toronto.

740 pts (GS ≤ 3+3 and PSA ≤ 10 ng/ml) + 253 pts (GS ≤ 3+4 or PSA ≤ 15)

median fu 6,4 y

low risk group: metastasis free surv @15 y 95%

intermediate risk group: metastasis free surv @15 y 82%

GS pattern 4 increased risk of mts by 3.75

J Clin Oncol. 2015;33:272-7

active surveillance - outcomes

Johns Hopkins

1298 pts (≤ 2 positive cores, < 50% core involvement, and PSA density < 0.15 ng/ml/cm^3)

median fu 5 y

low risk group: metastasis free surv @15 y 99,4%

J Clin Oncol. 2015;33:3379-85

active surveillance - outcomes

Prostate Cancer Research International Active Surveillance (PRIAS)

5302 pts (≤ 2 positive cores, GS ≤ 3+3, and PSA density ≤ 0.2 ng/ml/cm^3)

median fu not available

reclassification rate 22%-33%

73% of pts discontinued AS @10 y

1/3 of subsequent RP had sill favorable pathologic tumor features

Eur Urol. 2016;70:954-60

active surveillance - outcomes

Canary PASS Cohort

905 pts

median fu 28 months

reclassification rate 24%

73% of pts discontinued AS @10 y

66% of subsequent RP had sill favorable pathologic tumor features

J Urol. 2016;195:313-20

active surveillance – key points

Gleason pattern 3 does not metastasize.

In their molecular genetics, most Gleason pattern 3 cells resemble normal cells

High-volume pattern 3 disease is associated with an increased risk of coexistent higher-grade cancer

J Urol. 2016;195:313-20

active surveillance – open questions

Which intermediate-risk patients are candidates for surveillance?

What is the most efficient and cost-effective way to follow patients longitudinally? Is serial biopsy still required, and in whom?

Can risk stratification allow some patients to minimize the burden of follow up?

Can the widespread adoption of surveillance for low-risk disease rehabilitate prostate cancer screening?

Oncology (Williston Park). 2017 May 15;31(5):333-40, 345

FOCAL THERAPY

FOCAL THERAPY

The prostate remains the only solid organ with no organ sparing approaches available …

RATIONALE

- **Index lesion theory**

  Ahmed et al, NEJM

- **Pca diagnosis improvements (mpMRI)**

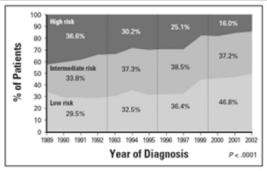
  PROMIS trial — Ahmed et al, Lancet Oncol
  PRECISION trial — Kasivisvanatan et al, NEJM
  MRI FIRST trial — Rouviere et al, Lancet Oncol
  4M trial — Van der Leest, Eur Urol

- **PSA = higher Pca incidence but same Pca mortality**

  Cooperberg et al, JCO

FOCAL THERAPY

RATIONALE



Cooperberg et al, JCO

- **Localized Pca RCT - Monitoring vs RP vs RT had 10ys same OS and CSS but higher progression and mets in monitoring group**

  ProTect trial – Hamdy et al, NEJM

- **Low risk = AS – same survival but QoL benefits**
- **High risk = Radical treatment**
- **Intermediat risk ? (now being offered the same treatment of high risk although different prognosis)**

FOCAL THERAPY

- **PROs (n=37 studies until 2017)**
  - **Recognized improvements in functional outcomes**
  - **Safe - low complications**

Valerio et al, Eur Urol, 2017

FOCAL THERAPY

- **PROs**
  - **Recognized improvements in functional outcomes**
    -92.6 – 100% pad-free
    -58-100% Preserved erections (vast majority >90%)
  - **Safe - low complications**

    -Fistula 0-2.1% (vast majority 0%)
    -UTI 0-16%
    -Urethral strictures 0-4%

Valerio et al, Eur Urol, 2019

FOCAL THERAPY

- **CONs**
- **mpMRI invisible lesions and diagnostic under-grading/staging**
- **Pca multifocal in 80%**
- **No intermediate/long term outcomes ?**
- **Salvage treatment after focal therapy jeopardize functional outcomes ?**
- **No RCTs with radical treatment ?**

FOCAL THERAPY

- **CONs**
- **mpMRI invisible lesions and diagnostic under-grading/staging**
- **Pca multifocal in 80%**
- **No intermediate/long term outcomes ?**
- **Salvage treatment after focal therapy jeopardize functional outcomes ?**
- **No RCTs with radical treatment ?**

FOCAL THERAPY – medium term outcomes

- 1032 men at 2 UK centers (HIFU hemi- or quadrant ablation)
- 11.9% T3 disease and 17% > 3+4 disease
- **96 months OS 97%**

Stabile et al, BJUI, 2019

FOCAL THERAPY – medium term outcomes

- **26.3% need of additional treatment BUT only 6.6% need of radical salvage treatment**
- **96 months re-treatment free survival 46% BUT 81% freedom from radical treatment**

Stabile et al, BJUI, 2019

FOCAL THERAPY – medium term outcomes

- **Learning curve** (technology, surgeon and patient selection improvements over the time)

Stabile et al, BJUI, 2019

FOCAL THERAPY – medium term outcomes

- n=122 focal cryotherapy
- Median f-up 27.8 mo
- 28.7% high risk - 71.3% intermediate
- 65.6% anterior ablation
- 0% pad use at 6mo - 16% erections insufficient for intercourse
- Clavien 3 1.6%

- **3 ys-FFS* 90.5%**

-84.7% in high risk
-93.3% in intermediate risk

- **3ys CSS 100%, OS 98% and MFS 96%**

*FFS: transition to radical, whole-gland, or systemic therapy, or metastases/death

Shah et al, Eur Urol, 2019

FOCAL THERAPY

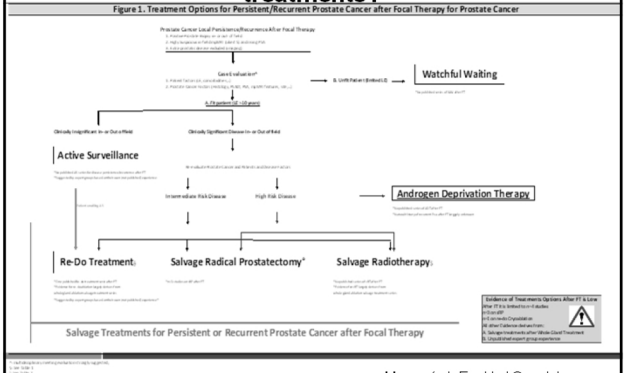
- **CONs**
- **mpMRI invisible lesions and diagnostic under-grading/staging**
- **Pca multifocal in 80%**

- **No intermediate/long term outcomes ?**

- **Salvage treatment after focal therapy jeopardize functional outcomes ?**

- **No RCTs with radical treatment ?**

FOCAL THERAPY – does it jeopardize salvage treatments?



Marra et al, Eur Urol Oncol, In press

FOCAL THERAPY – does it jeopardize salvage treatments?

- Until 2018 n=4 series (n=67 men)
- All retrospective = low evidence
- Oncological control acceptable although it seems lower compared to a primary treatment setting.
- Functional outcomes comparable to primary treatment with the exception of EF
- ……**overall, suggesting FT has little impact on subsequent salvage treatments.**

Marra et al, World J Urol, 2019

FOCAL THERAPY – does it jeopardize salvage treatments?

- Prospective - n=82 men sRARP after FT from two institutions
- 83% continent at 12 months and no major complications
- EF poor (14% at12 months)
- 36 months Pca free survival 36% (worse for in-field recurrences and pT3b)
- …….. **sRARP after FT safe with no increase in toxicity when compared to primary RALP**
- **in-field and pT3b additional need of multimodal approach**

Marconi et al, Eur Urol, 2019

FOCAL THERAPY

- **CONs**
- **mpMRI invisible lesions and diagnostic under-grading/staging**
- **Pca multifocal in 80%**
- **No intermediate/long term outcomes ?**
- **Salvage treatment after focal therapy jeopardize functional outcomes ?**
- **No RCTs with radical treatment ?**

FOCAL THERAPY – RCTs

- RCT in 47 centers – n=206 VTP - **207 AS**
- **All low risk GS=6**
- Median f-up 24 mo
- **disease progression 28% VTP vs 58%AS (p<0.001)**
- **negative prostate biopsy 49%VTP vs 14% (p<0.001)**
- **VTP and AS comparable high grade toxicities, AUR, erectile dysfunction (all being rare)**

However….

CURRENT STANDARD for Low risk PCa is AS

Azzouzi et al, Lancet Oncol, 2017

FOCAL THERAPY – RCTs

Do we really need RCTs?

1) Partial nephrectomy is standard in appropriate cases but the sole RCT did not prove any advantage

2) Systematic review 2013: already >2000 FT cases oublished
Valerio et al, Eur Urol, 2013

3) Pca trials: long term ouctomes. Need to wait 15-20 years
ProTect trial, Hamdy et al, NEJM

Stabile et al, BJUI, 2019

FOCAL THERAPY – RCTs

PART Trial completed and enrolled n=80 men
=
RCT of FT vs RP is feasible

Initially many recruiters found it difficult to maintain a position of equipoise and held preconceptions…

Individual and group feedback led to presentations to patients becoming clearer and enabled recruiters to reconsider their sense of equipoise.

Recruitment increased from 1.4 to 4.5 patients/month

Phase II trial in planning to provide level 1 evidence…

Hamdy et al, Health Tech Ass, 2018 and Elliott et al, BJUI, 2019

FOCAL THERAPY – are we ready for its prime time?

- 25-item questionnaire
- n=484 replies (majority being urologists and from EU)

- **44.8% FT would represent a step forward**
- **52% would suggest FT to a patient**
- **70.8% FT will become a standard option**

- **2 on 3 FT available (in their centre or region)**

Marra et al, Urol Oncol, 2018

FOCAL THERAPY – are we ready for its prime time?

- Could potentially reduce side effects when compared with established standard treatments

- Due to both the lack of clear results and difficulties in detecting all cancerous areas of the prostate should be considered an investigational modality only.

Van der Poel et al, Eur Urol, 2018

CONCLUSIONS – Focal Therapy

- Evidence based rationale

- Functional outcomes improved compared to radical treatment

- Promising medium term oncological outcomes

- Salvage surgery seems safe in expert hands (more data needed)

- Main limitations remain lack of long term results and RCTs with Radical treatment

- High interest of Urological community but it remains an experimental modality = should be performed in clinical trials

Treatment of the Primary Tumor in Newly Diagnosed Hormone-Naïve Metastatic Prostate Cancer

Steven Joniau, MD, PhD
Dept of Urology
University Hospitals Leuven
Belgium

Disclosures

Receipt of honoraria, research funding, consultation fees:

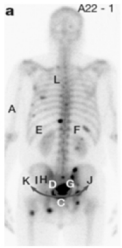
- Amgen
- Astellas
- AstraZeneca
- Bayer
- Ferring
- GSK
- Ipsen
- Janssen
- MDX Health
- Pfizer
- Roche
- Sanofi

The metastatic process

The evolutionary history of lethal metastatic prostate cancer

Gunes Gundem[1], Peter Van Loo[1,2,3], Barbara Kremeyer[1], Ludmil B. Alexandrov[4], Jose M. C. Tubio[1], Elli Papaemmanuil[5], Daniel S. Brewer[6,7], Heini M. L. Kallio[8], Gunilla Högnäs[9], Matti Annala[8], Kati Kivinummi[8], Victoria Goody[1], Calli Latimer[1], Sarah O'Meara[1], Kevin J. Dawson[1], William Isaacs[1], Michael R. Emmett-Buck[10], Matti Nykter[8], Christopher Foster[6], Zsofia Kote-Jarai[11], Douglas Easton[12], Hayley C. Whitaker[13], ICGC Prostate UK Group‡, David E. Neal[11,14]‡, Colin S. Cooper[6,15]‡, Rosalind A. Eeles[16,17]‡, Tapio Visakorpi[18], Peter J. Campbell[1], Ultan McDermott[19], David C. Wedge[1,20] & G. Steven Bova[21]*

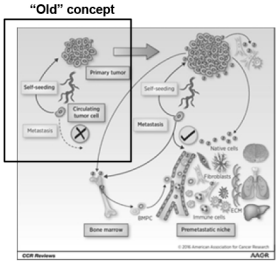
16 APRIL 2015 | VOL 520 | NATURE | 353



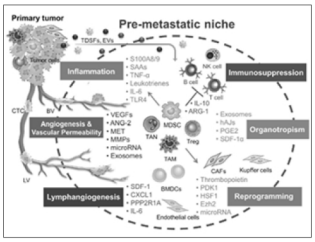
"Old" concept:
metastases originate from the primary tumor

The premetastatic niche

"Old" concept



Chin AR, et al. Clin Cancer Res 2016



Yang Liu, et al. Cancer Cell

The evolutionary history of lethal metastatic prostate cancer

Gunes Gundem[1], Peter Van Loo[1,2,3], Barbara Kremeyer[1], Ludmil B. Alexandrov[4], Jose M. C. Tubio[1], Elli Papaemmanuil[5], Daniel S. Brewer[6,7], Heini M. L. Kallio[8], Gunilla Högnäs[9], Matti Annala[8], Kati Kivinummi[8], Victoria Goody[1], Calli Latimer[1], Sarah O'Meara[1], Kevin J. Dawson[1], William Isaacs[1], Michael R. Emmett-Buck[10], Matti Nykter[8], Christopher Foster[6], Zsofia Kote-Jarai[11], Douglas Easton[12], Hayley C. Whitaker[13], ICGC Prostate UK Group‡, David E. Neal[11,14]‡, Colin S. Cooper[6,15]‡, Rosalind A. Eeles[16,17]‡, Tapio Visakorpi[18], Peter J. Campbell[1], Ultan McDermott[19], David C. Wedge[1,20] & G. Steven Bova[21]*

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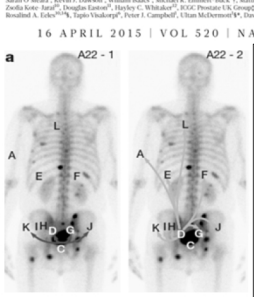

However:
metastases also metastasize!

The evolutionary history of lethal metastatic prostate cancer

Gunes Gundem[1], Peter Van Loo[1,2,3], Barbara Kremeyer[1], Ludmil B. Alexandrov[1], Jose M. C. Tubio[1], Elli Papaemmanuil[1], Daniel S. Brewer[4,5], Helmi M. L. Kallio[6], Gunilla Högnäs[6], Matti Annala[6], Kati Kivinummi[6], Victoria Goody[1], Calli Latimer[1], Sarah O'Meara[1], Kevin J. Dawson[1], William Isaacs[7], Michael R. Emmert-Buck[8], Matti Nykter[6], Christopher Foster[9], Zsofia Kote-Jarai[10], Douglas Easton[10], Hayley C. Whitaker[11], IICC Prostate UK Group[], David E. Neal[12,13], Colin S. Cooper[4,14], Rosalind A. Eeles[10,15], Tapio Visakorpi[6], Peter J. Campbell[1], Ultan McDermott[1]*, David C. Wedge[1]* & G. Steven Bova[16]*

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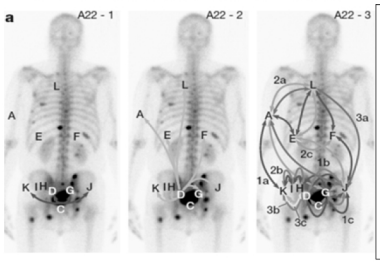
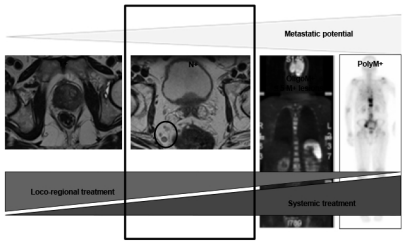


WORSE: metastases cross-talk with eachother and with primary!!!

Rationale for treatment of primary tumor and metastases in oligometastatic PCa

- "Break the chain"
  - Agressive local treatment halts the premetastatic niche and avoids (further) metastases
  - Efficiënt treatment of concomittant metastases may also stop (further) metastatic spread and cross-talk with other (micro-)metastases
- "Seek and destroy"
  - Early and accurate detection of oligometastases provides an opportunity for metastasis-directed treatment with surgery or SBRT

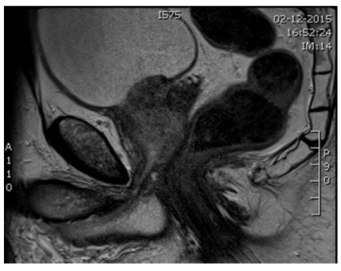
The Disease Spectrum of Prostate Cancer



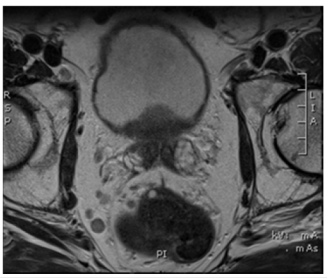
CASE 1

- **61-year old professor of Social Sciences**
- **11/2015: First PSA test 110 ng/mL**
- **DRE: stone-hard prostate**
- **TRUS biopsies: Gleason score 4+5=9 in 10/10 biopsies**

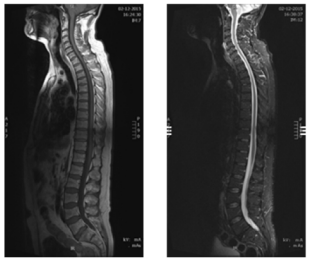
CASE 1



CASE 1



CASE 1



CASE of cT4 N1 M0 PCa

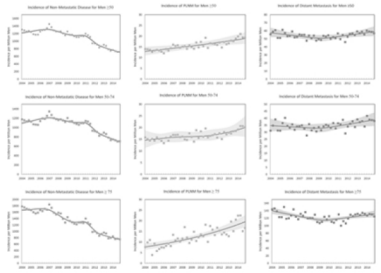
SUMMARIZING:

61-year old man with cT4 N1 M0 Gleason score 9 (4+5) PCa, iPSA 110 ng/mL

Patient was discussed at the local tumor board in the referring hospital and he was put on LHRH agonist with flare protection

Patient comes to our Department for second opinion and asks whether there is a role for local treatment

Incidence of pelvic lymph node metastatic PCa SEER database 2004-2014

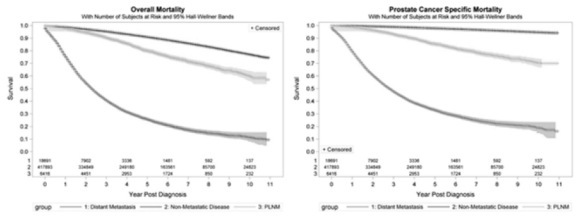


N=443,000

When stratified by initial therapy, the proportion of men with PLNM increased significantly in those who did and did not undergo prostatectomy, that is from 2.0% to 4.7% and from 0.7% to 1.4%, respectively, from 2004 to 2014 (each trend $p < 0.05$, supplementary table, http://urology.com/).

Bernstein AN, et al. J Urol 2018

Mortality of pelvic lymph node metastatic PCa SEER database 2004-2014



Bernstein AN, et al. J Urol 2018

Primary treatment of cN1 PCa NCDB 2006-2011

Table 2 Primary Treatment for Clinically Node-Positive Prostate Cancer Patients Within 1 Year of Diagnosis

Year	Prostatectomy	RT With ADT	RT Alone	ADT Alone	No Tx/Other[a]
2006	90 (8.3)	319 (29.2)	34 (3.1)	478 (43.8)	171 (15.7)
2007	91 (7.9)	328 (28.6)	40 (3.5)	492 (42.9)	195 (17.0)
2008	118 (8.8)	369 (27.5)	54 (4.0)	596 (44.5)	203 (15.2)
2009	149 (9.6)	413 (26.7)	59 (3.8)	726 (46.9)	201 (13.0)
2010	160 (9.8)	455 (27.9)	47 (2.9)	778 (47.7)	192 (11.8)
2011	114 (6.7)	488 (28.6)	51 (3.0)	822 (48.2)	231 (13.5)
Total	722 (8.5)	2372 (28.0)	285 (3.4)	3892 (46.0)	1193 (14.1)

Moon DH, et al. Clin Genitourin Cancer 2017

What do you propose?

1. Radical prostatectomy + super-extended LND
2. IMRT to the prostate & pelvic nodes with concomitant and adjuvant ADT
3. ADT monotherapy
4. ADT with 6 cycles of docetaxel
5. ADT with abiraterone + prednisone

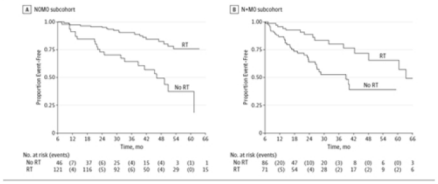
Original Investigation

Failure-Free Survival and Radiotherapy in Patients With Newly Diagnosed Nonmetastatic Prostate Cancer

Data From Patients in the Control Arm of the STAMPEDE Trial

Data from the control arm of STAMPEDE: ≥2 years of ADT
High-risk PCa: PSA >28 ng/mL, ~70% GS ≥8
Failure-free survival: time to BCR, CF or CRD

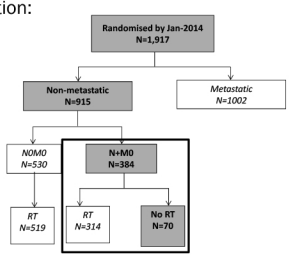
Figure 2. Failure-Free Survival for Reported Radical Radiotherapy Status, in N0M0 and N+M0 Subcohorts



James N, et al. JAMA Oncol 2015

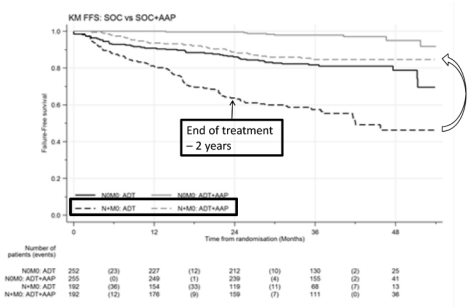
STAMPEDE: abiraterone in high-risk M0 PCa

- Prognosis of newly-diagnosed high-risk M0 disease
- Cohort selection:



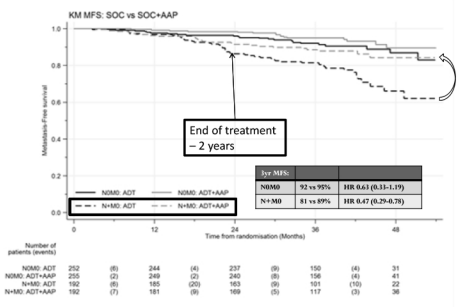
James ND, de Bono JS, Spears MR, Clarke NW, Mason MD, Dearnaley DP, et al. Proc ESMO 2017

Failure-free survival in M0 subgroup



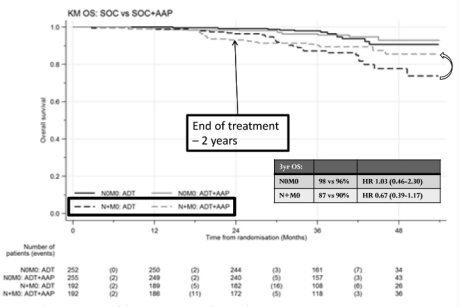
James ND, de Bono JS, Spears MR, Clarke NW, Mason MD, Dearnaley DP, et al. Proc ESMO 2017

Metastasis-free survival in M0 subgroup



James ND, de Bono JS, Spears MR, Clarke NW, Mason MD, Dearnaley DP, et al. Proc ESMO 2017

Overall survival in M0 subgroup

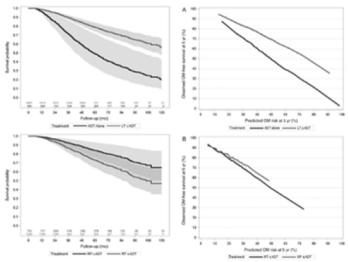


James ND, de Bono JS, Spears MR, Clarke NW, Mason MD, Dearnaley DP, et al. Proc ESMO 2017

Prostate Cancer

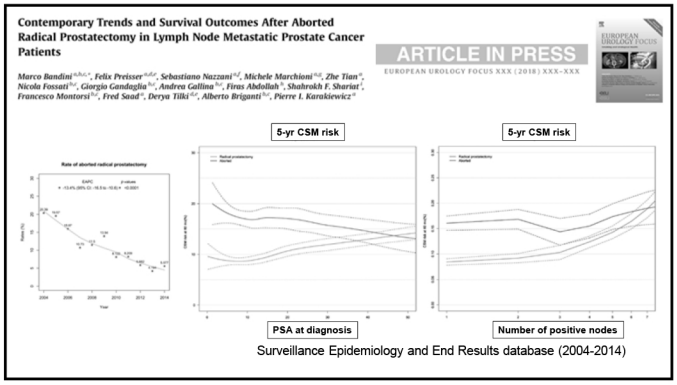
Efficacy of Local Treatment in Prostate Cancer Patients with Clinically Pelvic Lymph Node-positive Disease at Initial Diagnosis

Thomas Seisen[a,b,], Maître W. Vetterlein[a,b,*], Patrick Karabon[a], Tarun Jindal[a], Akshay Sood[a], Luigi Nocera[a], Paul L. Nguyen[c], Toni K. Choueiri[d], Quoc-Dien Trinh[e], Mani Menon[a], Firas Abdollah[a,c]*

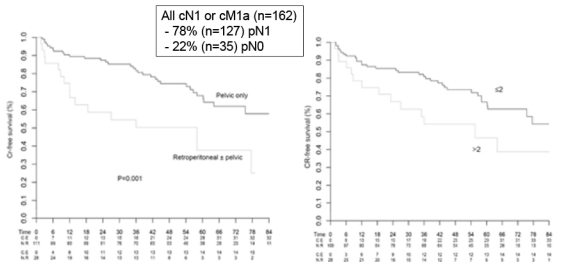


National Cancer Database (2003-2011)

Seisen T, et al. Eur Urol. 2017

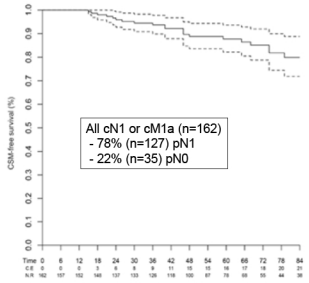


RP in cN1 and cM1a PCa
Joint analysis Milan, Mayo Clinic and Leuven



Gandaglia G, et al. Eur Urol, accepted

RP in cN1 and cM1a PCa
Joint analysis Milan, Mayo Clinic and Leuven



RP in cN1 and cM1a PCa
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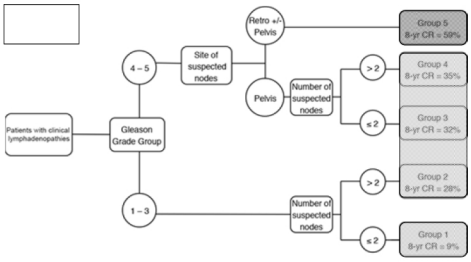


Gandaglia G, et al. Eur Urol, accepted

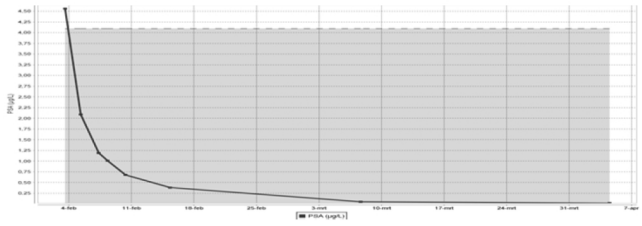
CASE of cT4 N1 M0 PCa

- **04-02-2016: Open RP + super-extended LND (ext iliac, obt fossa, int iliac, common iliac, presacral)**

CASE of cT4 N1 M0 PCa

- **Histopathology:**
  - **Massive invasion of the prostate by Gleason score 9 (5+4) PCa**
  - **Bilateral seminal vesicle invasion**
  - **Massive extracapsular extension and invasion in bladder neck**
  - **Multiple positive margins**
  - **Tumor volume: 46.6 mL; Tumor Vol/prostate Vol: 97%**
  - **sePLND: 49 lymph nodes removed, 14 positive nodes (1 micrometastasis, 13 macrometastases of which 11 have extracapsular extension)**
  - **pT4N1M1a**

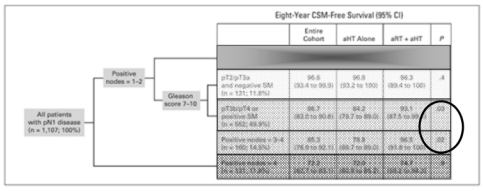
CASE of cT4 N1 M0 PCa



What do you propose?

1. IMRT to the prostate bed + pelvic/retroperitoneal nodes with concomitant and adjuvant ADT
2. Continue ADT
3. ADT with 6 cycles of docetaxel
4. ADT with abiraterone + prednisone
5. Stop ADT + observation

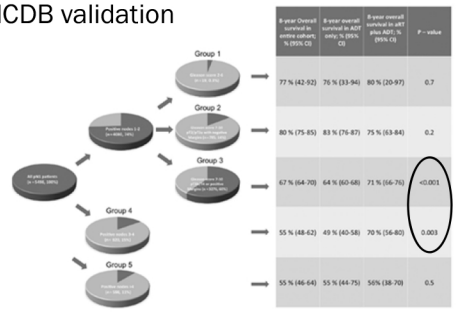
pN+ and adjuvant RT



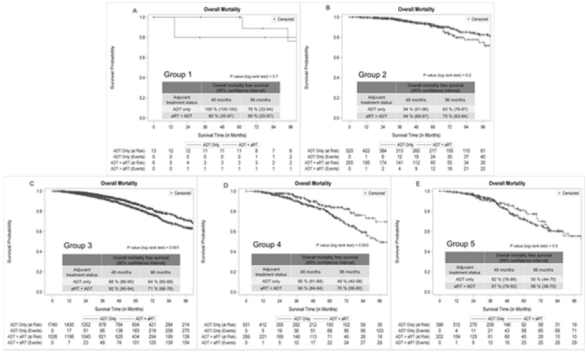
Abdollah et al, JCO 2014

Abdollah F, et al. J Clin Oncol 2014, 32(35):3939-47

pN+ and adjuvant RT, NCDB validation

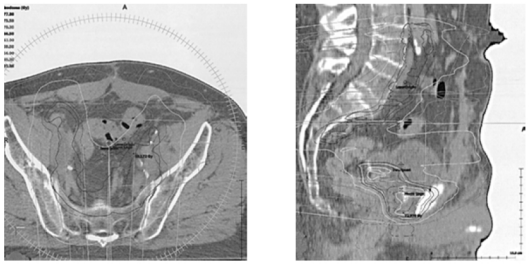


Abdollah F, et al. Eur Urol 2018

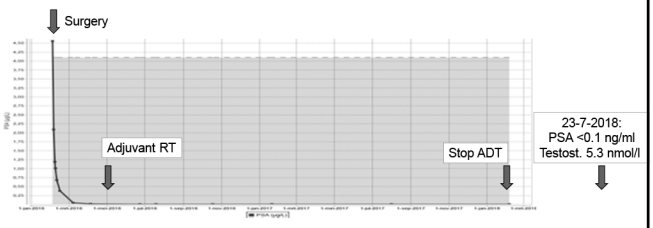


CASE of cT4 N1 M0 PCa

- **Continence almost fully recovered in the 4 months following RP, he uses 1 safety pad**
- **Erections are absent (he is still on ADT)**
- **There is no lymphedema**
- **Patient is discussed at the tumor board and it is decided to add IMRT to the prostate bed (70 Gy) and pelvis + para-aortic regions (56 Gy) in 35 fractions. LHRH is continued for 2 years.**
- **IMRT was given between 02/05/2016 and 22/06/2016**



CASE of cT4 N1 M0 PCa



cN+ and local treatment

"Due to the limited evidence, **local treatment of cN+ patients**, in association with a multimodal approach, **should be discussed** with the patients on an individual basis."

In patients with cN+ PCa offer pelvic external irradiation in combination with immediate long-term ADT.	2b	B
Offer RP in highly selected patients with locally advanced disease (cT3b-T4 N0 or any T N1) only as part of multi-modal therapy.	3	C

European Association of Urology

cN+ and local treatment

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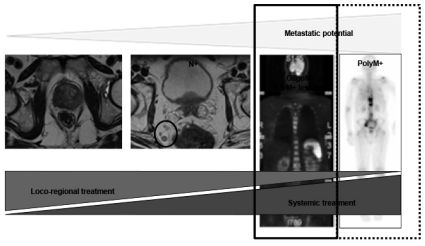
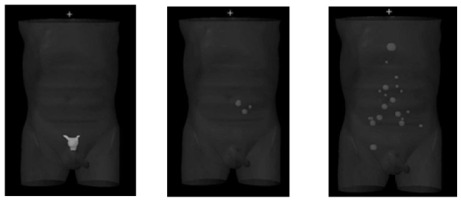
In patients with cN+ PCa offer pelvic external irrad… combination with immediate long-term ADT.	2b	B
Offer RP in highly selected patients with locally advanced disease (cT3b-T4 N0 or any T N1) only as part of multi-modal therapy.	3	C

European Association of Urology

The Disease Spectrum of Prostate Cancer

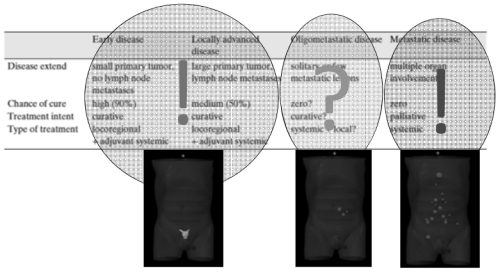


Localized Oligometastases Polymetastases

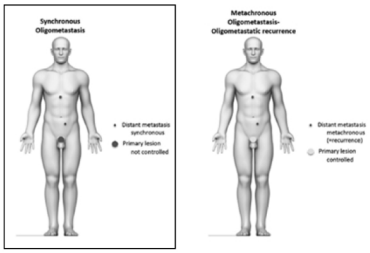


Hellman , J Clin Oncol, 1995

The traffic light principle:

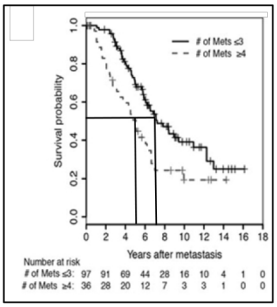


Primary oligometastatic Prostate Cancer



Decaestecker K, UH Ghent, PhD thesis 2015

Does the number of Mets matter in metastatic PCa?



All patients received **ADT** at time of metastasis

Patients with >3 Mets live 2 years less!

Schweizer et al. 2013, Annals of Oncology

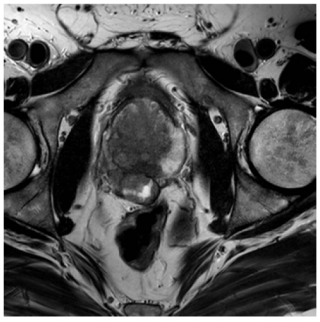
CHAARTED – STAMPEDE definitions of low-and high-volume metastatic PCa

- **LOW-volume**
  - ANY number of bone mets, confined to the vertebral column and pelvis
  - ANY number of extrapelvic lymph nodes
- **HIGH-volume**
  - ≥4 bone mets, with at least 1 outside the vertebral column and pelvis
  - ANY visceral mets

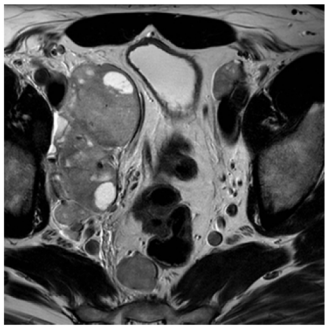
CASE 2

- 46-year-old Irish gentleman
- Paternal grandfather and maternal uncle had PCa
- PMH: knee arthroscopy, diverticular disease, psoriatric arthropathy
- 19-7-2017: presented at A&E with right leg weakness
- Neurologic problems were excluded
- Lab results showed PSA 748 ng/mL
- DRE: cT3-4
- mpMRI prostate was requested

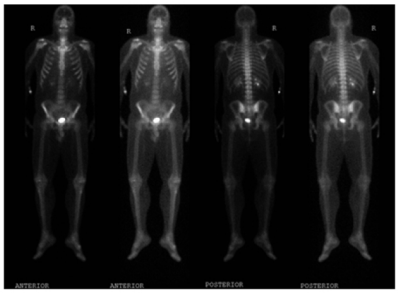
CASE 2



CASE 2



CASE 2

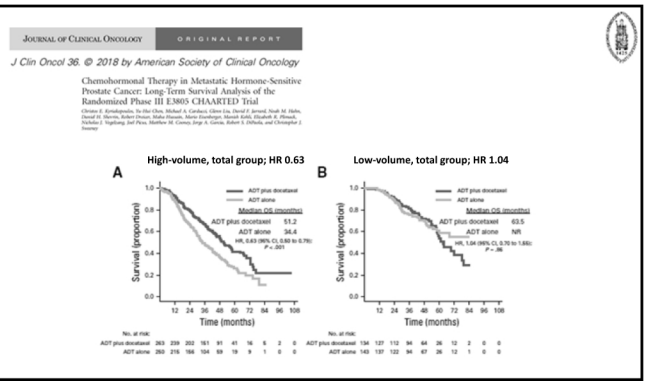


CASE 2

- MRI of the brain, lungs, liver and bone were unremarkable
- A biopsy of the large lymph node package was performed and showed PCa origin
- Prostate biopsies showed Gleason score 10 in 8/11 cores
- In summary, this 46-year old has a **cT4 N1 M1a, Gleason score 10 PCa, iPSA 748 ng/mL**

What do you propose?

1. Radical prostatectomy + pelvic and retroperitoneal LND
2. IMRT to the prostate & pelvic + retroperitoneal nodes with concomitant and adjuvant ADT
3. ADT monotherapy
4. ADT with 6 cycles of docetaxel
5. ADT with abiraterone/prednisone
6. IMRT to the prostate + ADT with abiraterone/prednisone

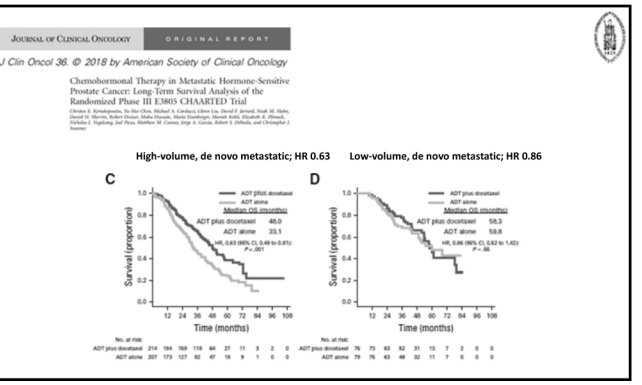

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

J Clin Oncol 36. © 2018 by American Society of Clinical Oncology

Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer: Long-Term Survival Analysis of the Randomized Phase III E3805 CHAARTED Trial

High-volume, total group; HR 0.63

Low-volume, total group; HR 1.04


JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

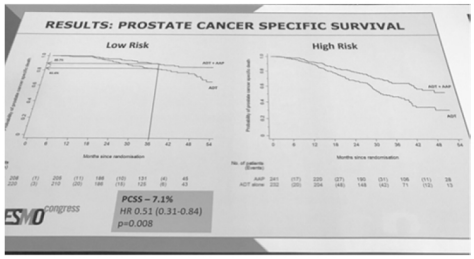
J Clin Oncol 36. © 2018 by American Society of Clinical Oncology

Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer: Long-Term Survival Analysis of the Randomized Phase III E3805 CHAARTED Trial

High-volume, de novo metastatic; HR 0.63

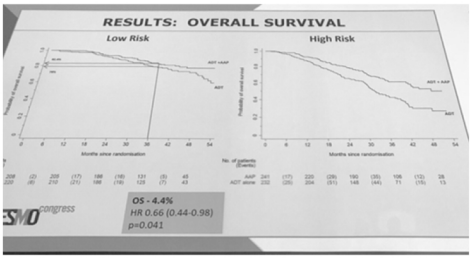
Low-volume, de novo metastatic; HR 0.86

STAMPEDE – Efficacy of abiraterone in low-volume



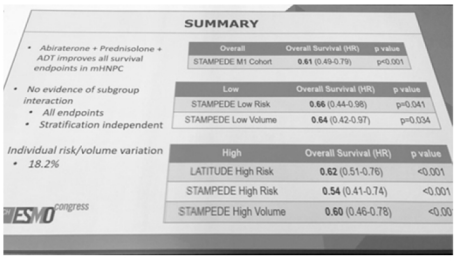
STAMPEDE – ESMO 2018

STAMPEDE – Efficacy of abiraterone in low-volume



STAMPEDE – ESMO 2018

STAMPEDE – Efficacy of abiraterone in low-volume

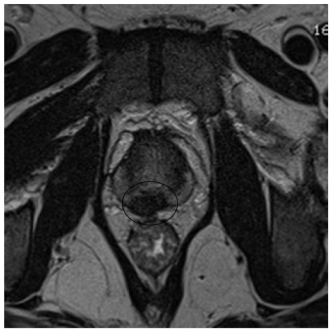


STAMPEDE – ESMO 2018

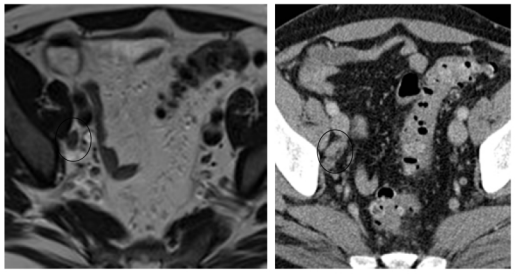
CASE 2

- **Patient was discussed at local tumor board and it was decided to start ADT and Docetaxel as in CHAARTED/Stampede-protocol after re-evaluation of the prostate biopsies to rule out small-cell or neuro-endocrine features.**
- **APO:**
  - **Prostate biopsies: partly acinar, partly highly suspicious for a neuroendocrine component;**
  - **pelvic lymph node biopsy: metastatic localization of the prostate tumour (the part with the neuroendocrine morphology).**
- **08-2017: start ADT, followed by 6 cycles docetaxel.**

CASE 2



CASE 2



CASE 2

- Status after 6 cycles docetaxel + ADT
- Imaging: small residual tumor in the prostate and reduction iliacal lymph node package, no other lymph nodes in pelvis or abdomen
- PSA: <0.01 (significance ?? => partly neuro-endocrine differentiation)

What do you propose?

1. Radical prostatectomy + pelvic and retroperitoneal LND
2. IMRT to the prostate & pelvic + retroperitoneal nodes with concomitant and adjuvant ADT
3. IMRT to the prostate only with ADT + abiraterone/prednisone
4. Continue ADT
5. ADT + abiraterone/prednisone

Why would controlling the primary be associated with extended survival?

Clinical basis for the contribution of the primary tumour to prostate cancer lethality:

- **Avoidance of the morbidity** related to uncontrolled progression of the primary (obstructive uropathy, infections, bleeding, and pain), which often decrease the patient's performance status and **limit the ability to apply additional systemic therapies**.

Aus G, et al. J Urol. 1995; 154: 466–469.
Patrikidou A, et al. Urol Oncol. 2015; 33: 202.e9–17.

Does robot-assisted radical prostatectomy benefit patients with prostate cancer and bone oligometastases?

Won Sik Jang, Myung Soo Kim, Won Sik Jeong, Ki Don Chang, Kang Su Cho, Won Sik Ham, Koon Ho Rha, Sung Joon Hong and Young Deuk Choi
Department of Urology, Urological Science Institute, Yonsei University College of Medicine, Seoul, Korea

Variable	ADT, *N* = 41 *n* (%)	RARP, *N* = 38 *n* (%)
TURP	6 (14.6)	0 (0.0)
Suprapubic cystostomy	2 (4.9)	0 (0.0)
PCN	2 (4.9)	0 (0.0)
Cystoscopic clot evacuation	1 (2.4)	0 (0.0)

ADT, androgen deprivation therapy; PCN, percutaneous nephrostomy; RARP, robot-assisted radical prostatectomy.

Jang WS, et al. BJUI 2018

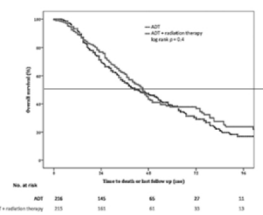
Why would controlling the primary be associated with extended survival?

Biological basis for the contribution of the primary tumour to prostate cancer lethality:

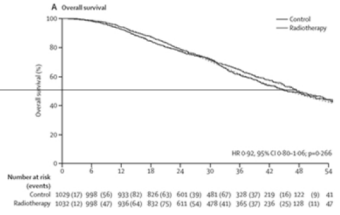
- Continuous **shedding of PCa cells** to distant sites
- **Tumor self-seeding** by circulating cancer cells
- Surgical removal of primary tumor **reverses tumor-induced immunosuppression**
- When treated systemically, **potentially lethal cancers persist in the primary tumor** and may contribute to progression
- **Cross-talk** between primary tumor and the microenvironment at the metastatic niche
- …

Kim MY, et al. Cell. 2009
Danna EA, et al. Cancer Res. 2004
Tselepi V, et al. J Clin Oncol. 2011
Carlini MJ, et al. Curr Pharm Biotechnol. 2011

HORRAD and STAMPEDE-RT: overall survival

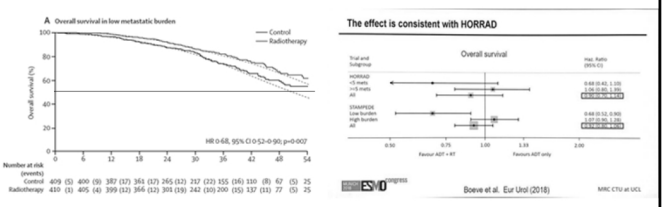


Boevè LMS, et al. Eur Urol. 2018; in press



Parker CC, et al. Lancet 2018

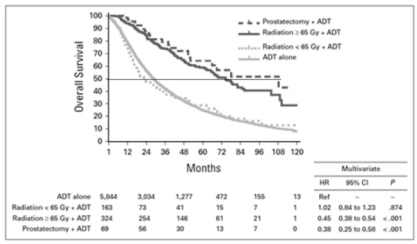
HORRAD and STAMPEDE-RT: oligometastatic



Parker CC, et al. Lancet 2018

Boevé LMS, et al. Eur Urol. 2018; in press

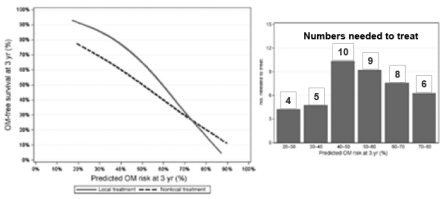
Some men with M+ PCa benefit from RP/RT - NCDB



						Multivariate		
						HR	95% CI	P
ADT alone	5,844	3,034	1,277	472	155	13	Ref	–	–
Radiation < 65 Gy + ADT	163	73	41	15	7	1	1.02	0.84 to 1.23	.874
Radiation ≥ 65 Gy + ADT	324	254	146	61	21	1	0.45	0.38 to 0.54	< .001
Prostatectomy + ADT	69	56	30	13	7	0	0.38	0.25 to 0.58	< .001

Rusthoven C, et al. J Clin Oncol. 2016; 34(24): 2835–42.

Some men with oligoM+ PCa benefit from RP/RT - NCDB



Löppenberg B, et al. Eur Urol. 2017; 72(1): 14–19.

Some men with M+ PCa benefit from RP/RT - SEER

Variables	Local treatment versus no local treatment	
	SHR (95% CI)	p value
Type of treatment		
No RT	Ref.	
Radiotherapy	0.48 (0.35–0.66)	<0.001
Radical prostatectomy	0.55 (0.04–0.46)	<0.001
Biopsy Gleason score		
≤7	Ref.	
≥8	1.84 (1.59–2.13)	<0.001
Unknown	1.72 (1.28–2.31)	<0.001
Clinical T stage		
T1/T2	Ref.	
T3	1.10 (0.87–1.40)	0.4
T4	1.85 (1.39–2.46)	<0.001
Clinical N stage		
N0/Nx	Ref.	
N1	1.18 (0.91–1.52)	0.20
AJCC M stage		
M1a	Ref.	
M1b	1.65 (1.31–2.08)	<0.001
M1c	1.98 (1.52–2.58)	<0.001
Age (yr)	1.00 (0.99–1.01)	0.4
Race		
Caucasian	Ref.	
African American	0.91 (0.76–1.09)	0.3
Other/unknown	0.77 (0.58–1.02)	0.07
Marital status		
Married	Ref.	
Divorced/widowed	1.25 (1.03–1.51)	0.024
Single	1.23 (0.97–1.57)	0.092
Unknown	0.75 (0.54–1.03)	0.074

CI = confidence interval; SHR = subhazard ratio; Ref. = reference; AJCC = American Joint Committee on Cancer.

- SEER database analysis of patients presenting with M1a-c PCa at diagnosis
- 13692 patients were identified, treated between 2004-2013
  - No surgery or radiation therapy (NSR), n=13218
  - Radical prostatectomy (RP), n=313
  - Radiotherapy, n=161
- **PROPENSITY SCORE MATCHING**
  - Biopsy Gleason score
  - cT stage
  - cN stage
  - cM substages

Leyh-Bannurah S-R, et al. Eur Urol 2017

Does Cytoreductive Prostatectomy Really Have an Impact on Prognosis in Prostate Cancer Patients with Low-volume Bone Metastasis? Results from a Prospective Case-Control Study

Thomas Steuber[a,b,], Kasper D. Berg[b,c], Martin A. Røder[b], Klaus Brasso[b], Peter Iversen[b], Hartwig Huland[d], Anne Tiebel[d], Thorsten Schlomm[e], Alexander Haese[e], Georg Salomon[e], Lars Budäus[d], Derya Tilki[d], Hans Heinzer[d], Markus Graefen[d], Philipp Mandel[d]*

[a]Martini-Klinik Prostate Cancer Center, University Hospital Hamburg-Eppendorf, Hamburg, Germany; [b]Copenhagen Prostate Cancer Center, Department of Urology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

- 2000-2015
- **83 mPCa patients:** ≤3 bone M+ lesions, PSA ≤150 ng/ml, ≤cT3, asymptomatic
- **RP (n=43):** Martini-Klinik Database (2008-2015)
  BST (n=40): Copenhagen Prostate Cancer Center (2000-2011)
- Median follow-up: 32.7 mo RP, 82.2 mo BST
- No additional metastasis-directed treatment
- CRPC-free survival, OS, MVA (CR-free survival)

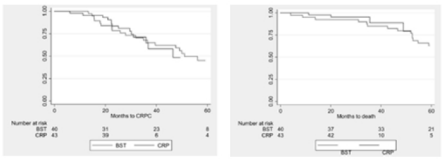
Steuber T, et al. Eur Urol Focus 2017

Does Cytoreductive Prostatectomy Really Have an Impact on Prognosis in Prostate Cancer Patients with Low-volume Bone Metastasis? Results from a Prospective Case-Control Study

Thomas Steuber[a,b,], Kasper D. Berg[b,c], Martin A. Røder[b], Klaus Brasso[b], Peter Iversen[b], Hartwig Huland[d], Anne Tiebel[d], Thorsten Schlomm[e], Alexander Haese[e], Georg Salomon[e], Lars Budäus[d], Derya Tilki[d], Hans Heinzer[d], Markus Graefen[d], Philipp Mandel[d]*

[a]Martini-Klinik Prostate Cancer Center, University Hospital Hamburg-Eppendorf, Hamburg, Germany; [b]Copenhagen Prostate Cancer Center, Department of Urology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

CRPC-free survival **Overall survival**



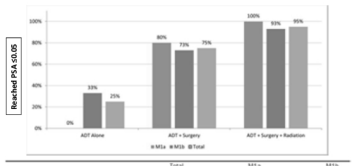
Patients benefit from a **significant reduction in locoregional complications** (7.0% vs 35%; p < 0.01)

Steuber T, et al. Eur Urol Focus 2017

A Pilot Study of a Multimodal Treatment Paradigm to Accelerate Drug Evaluations in Early-stage Metastatic Prostate Cancer

UROLOGY 102: 164–172, 2017

Matthew J. O'Shaughnessy, Sean M. McBride, Hebert Alberto Vargas, Karim A. Touijer, Michael J. Morris, Daniel C. Danila, Vincent P. Laudone, Bernard H. Bochner, Joel Sheinfeld, Erica S. Doyan, Lawrence P. Bellomo, Daniel D. Sjoberg, Glenn Heller, Michael J. Zelefsky, James A. Eastham, Peter T. Scardino, and Howard I. Scher



	Total N = 20	M1a N = 5	M1b N = 15
Time of follow-up (mo) median (range)	40 (17-89)	34 (18-40)	47 (17-89)
Time off ADT (mo) median (range)	9 (0-54)	6 (0-15)	9 (0-54)
PSA ≤.05 ng/mL at 12 months			
Castrate	10 (50%)	3 (60%)	7 (47%)
Non-castrate*	3 (15%)	0 (0%)	3 (13%)
PSA ≤.05 ng/mL at 20 months			
Castrate	6 (30%)	2 (50%)†	4 (27%)†
Non-castrate*	4 (20%)	0 (0%)‡	4 (27%)‡

CASE 2

- After extensive counseling, the patient opted for 'consolidating' radical surgery.
- On 14 March 2018, an open RRP + PLND + RPLND was performed
- Preoperative PSA was 0.20 ng/mL

CASE 2

- **Histopathology:**
  - Presence of Gleason score 9(4+5) PCa
  - Extracapsular extension over 9 mm, posterior
  - Bilateral seminal vesicle invasion
  - Perineural and lymphovascular invasion
  - Tumour volume: 3.1 mL (7.8%)
  - Super-extended PLND+RPLND (internal iliac, obturator, external iliac, presacral, common iliac, para-aortic, para-caval, interaortocaval):

    26 positive nodes out of 61 nodes resected

pT3a+b N1 M1a R0 PN+ LV+

CASE 2

- 1 safety pad per day
- Patient received RT to fossa, pelvis and para-aortic
- ADT will be continued for 2 years
- PSA-evolution:

Date	PSA µg/L
20-09-2018	<0.01
21-04-2018	<0.01
23-03-2018	0.04
19-03-2018	0.05
15-03-2018	0.12

Ongoing prospective trials

Study (ClinicalTrials.gov ID)	Phase	Number	Design	Primary outcome measure	Estimated completion
TRoMbone: Testing Radical prostatectomy in men with oligometastatic PCa that has spread to the bone (1-3 metastases) (ISRCTN15704862)	II	50	Randomised, open-label, parallel assignment	Quality of Life (EQ5D5L) Time to castrate resistance	Completed April 2018
BST or BST plus definitive treatment (RT or surgery) of the primary tumour in mPCa (NCT01751438) - MD Anderson Cancer Center	II	180	Randomised, open-label, parallel-assignment	PFS	March 2019
ADT or ADT plus definitive treatment (RT or surgery) in mPCa (NCT02742675) - Fudan University, Shanghai	II	200	Randomised, open-label, parallel assignment	PFS	March 2019
LoMP: Local treatment with RP for newly-diagnosed mPCa (NCT02138721)	II	80	Non-randomised, open-label, parallel assignment	CRPC-PFS; Time to first disease-related event	May 2019
g-RAMPP: Impact of RP as primary treatment in patients with PCa with limited bone metastases (NCT02454543)	III	452	Randomised, open-label, parallel assignment	Cancer-specific survival	April 2020
Standard Systemic Therapy With or Without Definitive Treatment (RT or Surgery) in Treating Participants With Metastatic PCa (NCT03678025) – SWOG	III	1273	Randomised, open-label, parallel assignment	Overall survival	April 2023
LoMP II: Cytoreductive Prostatectomy Versus Cytoreductive Prostate Irradiation as a Local Treatment Option for Metastatic Prostate Cancer: a Multicentric Feasibility Trial (NCT03655886)	II	86	Randomised, open-label, parallel assignment	Feasibility of randomization between both treatment arms	August 2020

Conclusions

- Local treatment, associated with ADT and/or RT is accepted by international guidelines in:
  - **High-risk PCa**
  - **Locally advanced PCa**
  - **Very high-risk PCa**
- Many of those patients have micrometastatic disease, as witnessed by high mortality rates when not treated with a curative intent
- Data is emerging on the role of local treatment in **cN+ disease**, and guidelines accept local treatment in selected cases

Conclusions

- **Primary Oligometastatic PCa** is an infrequent disease entity
- ADT alone or in combination with docetaxel/abiraterone is considered standard treatment by international guidelines
- When only treated systemically, many patients face morbidity from local disease progression and most face cancer-related death
- Very recent data from RCT's show prostate RT significantly improves survival outcomes
- The addition of metastasis-directed treatment might further improve outcomes

New treatment options in metastatic disease

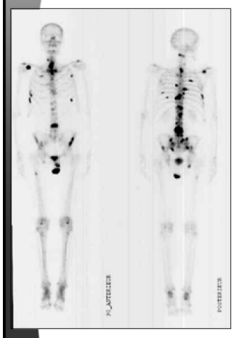
Prof. dr. Jeroen van Moorselaar
Department of Urology
Amsterdam University Medical Centers, loc. VUmc
Amsterdam, NL

Conflict of Interest Disclosure

I have the following potential conflicts of interest to report:

consultant or advisor for:
Astellas, AstraZeneca, Bayer, Janssen, Sanofi-Genzyme

Prostate Cancer is Hormone-Dependent



Despite regressions of great magnitude, it is obvious that there are many failures of endocrine therapy to control the disease but; on the whole, the life span had been extended by the novel treatments and there had been a decrease of man-pain hours.

Charles B. Huggins
Nobel Lecture, December 13, 1966

http://nobelprize.org/nobel_prizes/medicine/laureates/1966/huggins-lecture.html

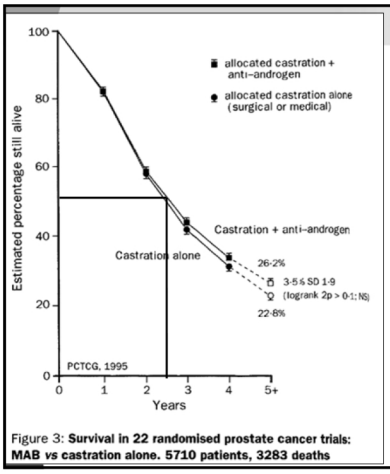
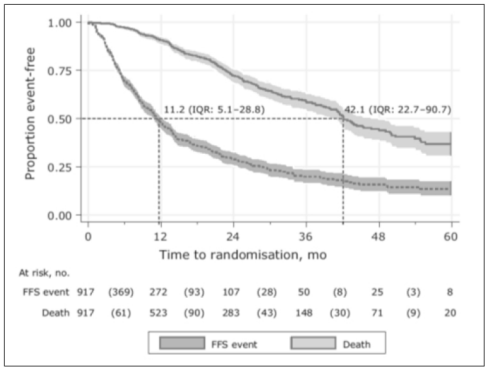


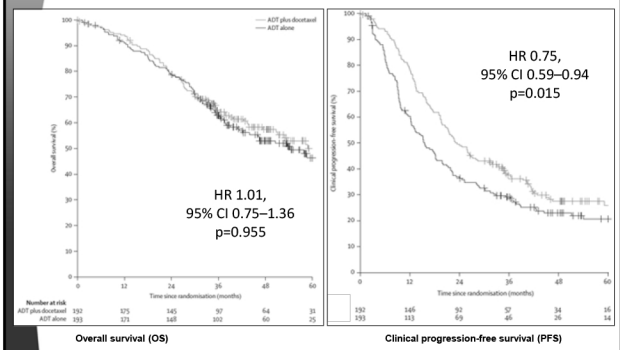
Figure 3: **Survival in 22 randomised prostate cancer trials: MAB *vs* castration alone. 5710 patients, 3283 deaths**

Prostate Cancer Trialists
Lancet 346: 265, 1995



James et al, Eur Urol 67: 1028, 2015

GETUG-15



Overall survival (OS) | Clinical progression-free survival (PFS)

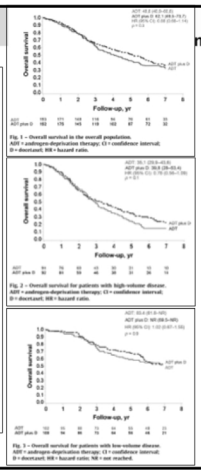
Gravis et al. Lancet Oncol 14:149, 2013

GETUG-15

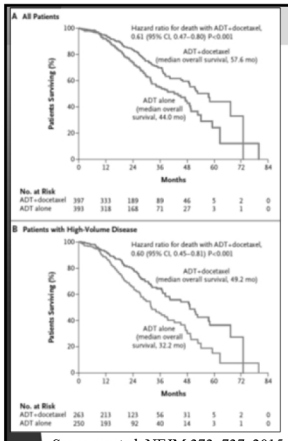
Table 1 – Characteristics of the patients (n = 385)

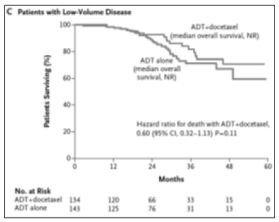
	ADT (n = 193)	ADT plus D (n = 192)
Age, yr, median (IQR)	64.0 (58.0–70.0)	63.0 (57.0–68.2)
ECOG performance status, n (%)		
0	176 (96)	181 (99)
1–2	7 (4)	2 (1)
Gleason score, n (%)		
≤7	78 (41)	84 (45)
≥8	113 (59)	103 (55)
Metastases after treatment for local disease, n (%)	46 (24)	62 (33)
Metastases at diagnosis, n (%)	144 (76)	128 (67)
PSA, ng/ml, median (IQR)	25.8 (5.0–126)	26.7 (5.0–106)
Alkaline phosphatase, n (%)		
Normal	113 (61)	106 (57)
Elevated	71 (39)	79 (43)
Bone metastases, n (%)	156 (81)	155 (81)
Visceral metastases, n (%)	23 (12)	28 (15)
Four or more bone metastases with one or more beyond pelvis or spine, n (%)	95 (49)	82 (43)
Low-volume disease (%)	102 (53)	100 (52)
High-volume disease (%)	91 (47)	92 (48)

ADT = androgen deprivation therapy; ECOG = Eastern Cooperative Oncology Group; IQR = interquartile range; PSA = prostate-specific antigen.



Gravis et al. Eur Urol 70:256, 2016

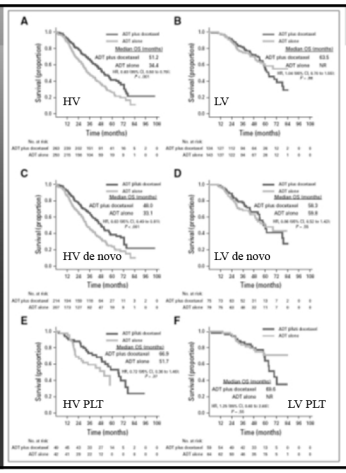




CHAARTED =
ChemoHormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer

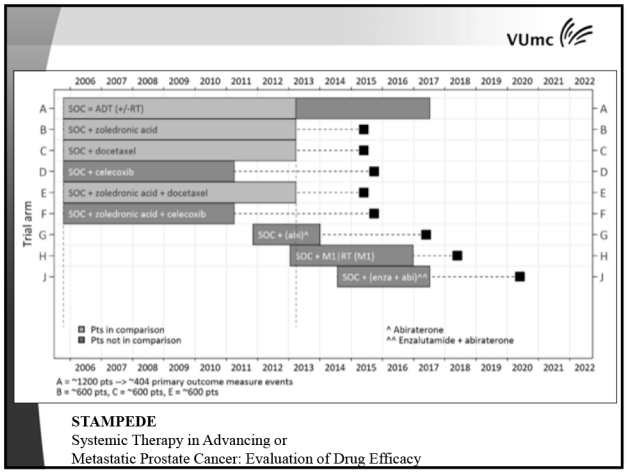
Sweeney et al. NEJM 373: 737, 2015

CHAARTED



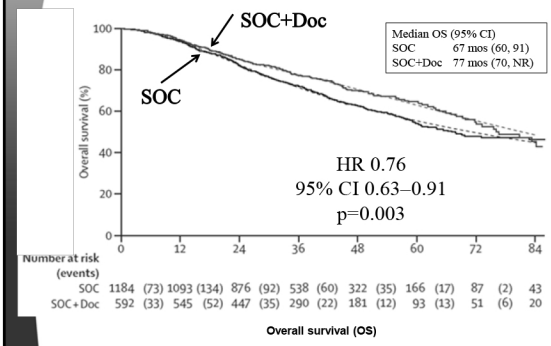
Follow-up 53.7 months

Kyriakopoulos et al.
J Clin Oncol 36: 1080, 2018



STAMPEDE
Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy

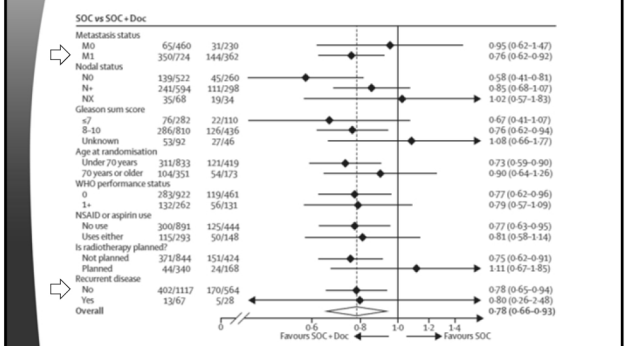
STAMPEDE



James ND et al. Lancet 2015; 50140-6736(15)01037-5

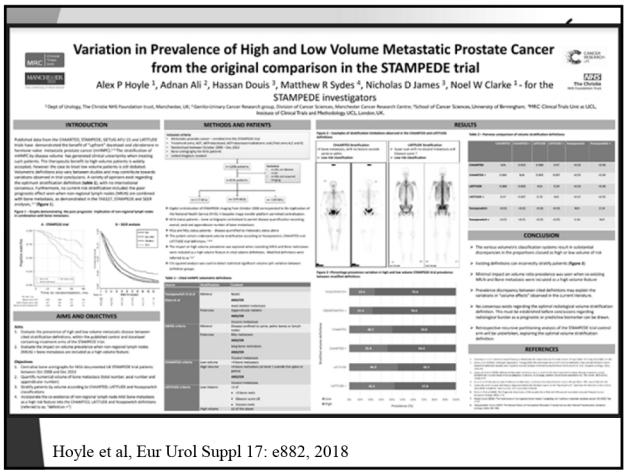
James et al, Lancet 387: 1163, 2016

STAMPEDE



James ND et al. Lancet 2015; 50140-6736(15)01037-5

James et al, Lancet 387: 1163, 2016



Variation in Prevalence of High and Low Volume Metastatic Prostate Cancer from the original comparison in the STAMPEDE trial

Alex P Hoyle [1], Adnan Ali [2], Hassan Douis [3], Matthew R Sydes [4], Nicholas D James [3], Noel W Clarke [1] - for the STAMPEDE investigators

[1]Dept of Urology, The Christie NHS Foundation trust, Manchester, UK; [2]Genito-Urinary Cancer Research group, Division of Cancer Sciences, Manchester Cancer Research Centre; [3]School of Cancer Sciences, University of Birmingham; [4]MRC Clinical Trials Unit at UCL, Institute of Clinical Trials and Methodology, UCL, London, UK.

INTRODUCTION

METHODS AND PATIENTS

RESULTS

CONCLUSION

AIMS AND OBJECTIVES

REFERENCES

Hoyle et al, Eur Urol Suppl 17: e882, 2018

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Table 1 – Cited mHNPC volumetric definitions

Source	Stratification	Content
Yossepowitch O et al Glass et al	Minimal	Nodal **AND/OR** Axial skeletal metastasis
	Extensive	Appendicular skeletal **AND/OR** Visceral metastasis
SWOG criteria	Minimal	Disease confined to spine, pelvic bones or lymph nodes
	Extensive	Ribs metastasis **AND/OR** long bone metastasis **AND/OR** Visceral metastasis
CHAARTED criteria	Low volume	<4 bone metastasis
	High Volume	≥4 bone metastasis (at least 1 outside the spine or pelvis) **AND/OR** Visceral metastasis
LATITUDE criteria	Low Volume	<2 of • >3 bone mets • Gleason score ≥8 • Visceral mets
	High volume	≥2 of the above

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Figure 2 – Examples of stratification limitations observed in the CHAARTED and LATITUDE definitions

CHAARTED Stratification
>4 bone metastasis, with no lesions outside spine or pelvis
➢ Low risk classification

LATITUDE Stratification
➢ Super scan with no visceral metastasis and Gleason score 7
➢ Low risk classification

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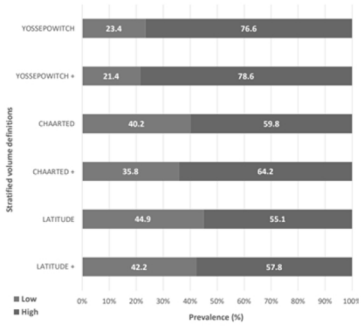
Figure 3 –Percentage prevalence variation in high and low volume STAMPEDE trial prevalence between stratified definitions



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M1 ADT + docetaxel – overall survival (OS)

Results based on 2993 men / 1254 deaths

	Control	Treatment	Hazard ratio (95% CI)
CHAARTED[7]	136/393	101/397	0·61 (0·47–0·80)
GETUG-15[9,10]	NA/193	NA/192	0·90 (0·69–1·81)
STAMPEDE[8] (SOC +/– Doc)	350/724	144/362	0·76 (0·62–0·93)
STAMPEDE[8] (SOC + ZA +/– Doc)	170/366	158/365	0·85 (0·65–1·10)
Overall			**0·77 (0·68–0·87)**

Heterogeneity: χ^2=4·80; df=3; p=0·187; I^2=37·5%

0·5 1 2

Favours SOC + docetaxel Favours SOC

Vale et al, Lancet Oncol 17:243, 2016

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Study design of LATITUDE

Newly diagnosed patients with high-risk mCNPC: high risk defined as at least 2 of 3 criteria:
- Gleason ≥ 8
- ≥ 3 lesions on bone scan
- Measurable visceral lesion

Stratification factors
- Visceral disease (yes/no)
- ECOG PS (0, 1 vs 2)

Exclusion Criteria
- Low risk disease, prior docetaxel or localized treatment (e.g. surgery or XRT)

RANDOMIZED 1:1

ADT + Abiraterone acetate 1000 mg QD + Prednisone 5 mg QD (n = 597)

ADT + placebos (n = 602)

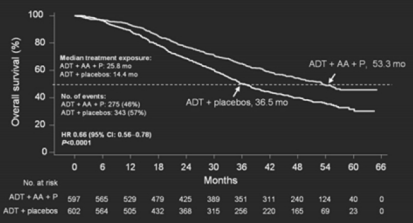
Efficacy end points
Co-primary:
- OS
- rPFS

Secondary: time to
- pain progression
- PSA progression
- next symptomatic skeletal event
- chemotherapy
- subsequent PC therapy

- **Conducted at 235 sites in 34 countries in Europe, Asia-Pacific, Latin America, and Canada**
- **Results of rPFS (coprimary endpoint) published previously [1]**

Presented By Karim Fizazi at 2019 Genitourinary Cancers Symposium

Final Analysis: Overall Survival



- **Median OS for patients receiving ADT + AA+P reached 4.5 years, 16.8 months longer than ADT+ placebos**

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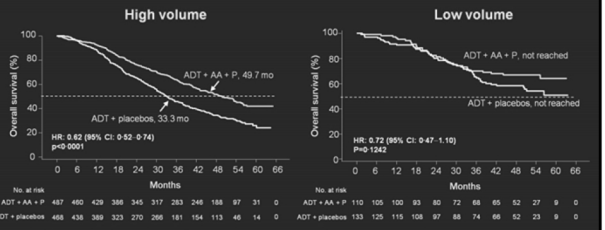
LATITUDE: Overall Survival in High and Low Volume (CHAARTED definition*)



CHAARTED Definition of High and Low Volume: *Presence of visceral metastases and/or ≥4 bone metastases, with at least one outside the vertebral column or pelvis

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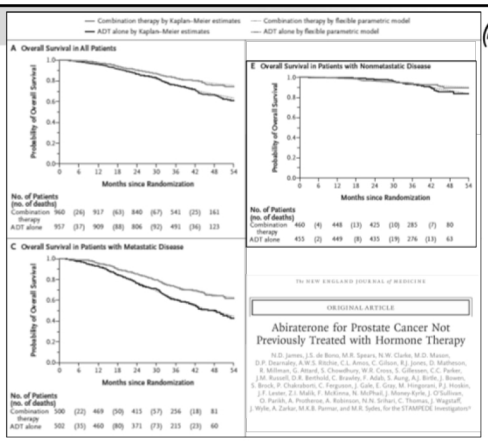
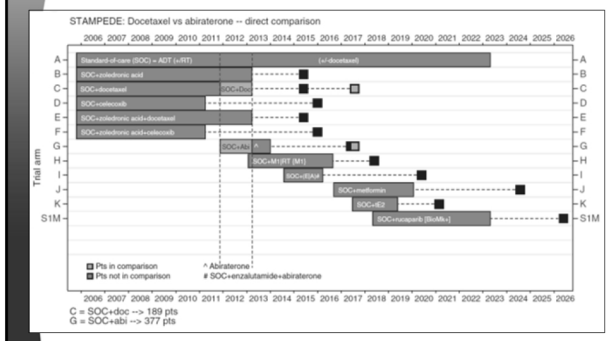
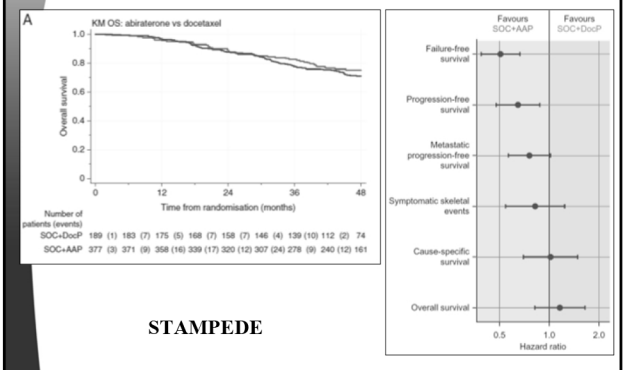


James et al. NEJM 377: 338, 2017



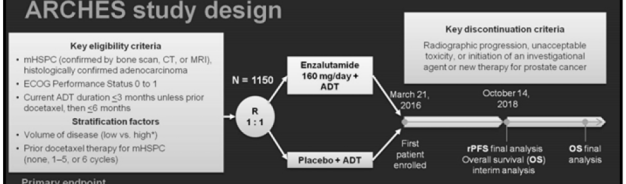
Sydes et al. Ann Oncol 29: 1235, 2018



STAMPEDE

Sydes et al. Ann Oncol 29: 1235, 2018

ARCHES study design



Primary endpoint

- rPFS: time from randomization to first objective evidence of radiographic progression assessed centrally, or death from any cause within 24 weeks of treatment discontinuation, whichever occurs first
  - Radiographic disease progression was defined by RECIST 1.1 criteria for soft tissue disease or by appearance of ≥2 new lesions on bone scan compared to baseline (at week 13) or vs. best response on treatment (week 25 or later). New bone scan lesions observed at week 13 required confirmation of ≥2 additional new bone lesions on subsequent scans

*Defined as metastases involving the viscera or, in the absence of visceral lesions, ≥4 bone lesions, ≥1 of which must be in a bony structure beyond the vertebral column and pelvic bone

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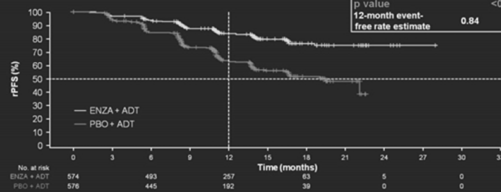
Primary endpoint: rPFS

	ENZA + ADT (n = 574)	PBO + ADT (n = 576)
Median, month (95% CI)	NR (NR, NR)	19.45 (16.59, NR)
HR (95% CI)	0.39 (0.30, 0.50)	
p value	<0.0001	
12-month event-free rate estimate	0.84	0.64



- At data cut-off, there were 262 events of radiographic progression (enzalutamide + ADT, 77; placebo + ADT, 185) and 25 deaths without radiographic progression (enzalutamide + ADT, 12; placebo + ADT, 13)
- Median follow-up time is 14.4 months; median duration of therapy was 12.8 (range 0.2–26.6) months for enzalutamide + ADT and 11.6 (range 0.2–24.6) months for placebo + ADT
- As of October 14, 2018 (cut-off date), 769 patients were still on treatment, 437 (76%) for enzalutamide + ADT and 332 (58%) for placebo + ADT

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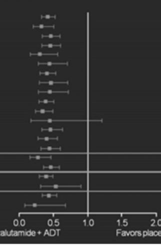
Subgroup analysis of rPFS

Subgroup	Enzalutamide + ADT / placebo + ADT N (E)	Hazard ratio (95% CI)
All patients	574 (89) / 576 (198)	0.39 (0.30, 0.50)
Age <65 years	149 (21) / 152 (57)	0.30 (0.18, 0.49)
Age ≥65 years	426 (68) / 424 (141)	0.43 (0.32, 0.58)
Geographic region – Europe	341 (55) / 344 (121)	0.43 (0.31, 0.59)
Geographic region – North America	86 (12) / 77 (28)	0.27 (0.14, 0.54)
Geographic region – rest of the world	147 (22) / 155 (49)	0.41 (0.25, 0.68)
ECOG status 0 at baseline	448 (65) / 443 (143)	0.38 (0.28, 0.51)
ECOG status 1 at baseline	125 (24) / 133 (55)	0.43 (0.27, 0.70)
Gleason score at initial diagnosis <8	171 (21) / 187 (47)	0.42 (0.25, 0.70)
Gleason score at initial diagnosis ≥8	386 (63) / 373 (148)	0.36 (0.27, 0.48)
Disease localization at baseline – bone only	268 (33) / 245 (81)	0.31 (0.21, 0.47)
Disease localization at baseline – soft tissue only	51 (5) / 45 (12)	0.42 (0.15, 1.20)
Disease localization at baseline – bone and soft tissue	217 (50) / 241 (102)	0.44 (0.31, 0.61)
Baseline PSA value at or below overall median	293 (40) / 305 (95)	0.37 (0.26, 0.54)
Baseline PSA value above overall median	279 (49) / 269 (102)	0.41 (0.29, 0.58)
Low volume of disease	220 (13) / 203 (46)	0.24 (0.13, 0.45)
High volume of disease	354 (76) / 373 (152)	0.44 (0.33, 0.57)
No prior docetaxel therapy	471 (68) / 474 (164)	0.36 (0.27, 0.48)
Prior docetaxel therapy	103 (21) / 102 (34)	0.53 (0.31, 0.92)
Previous use of ADT or orchiectomy	535 (86) / 515 (177)	0.41 (0.31, 0.52)
No previous use of ADT or orchiectomy	39 (3) / 61 (21)	0.20 (0.06, 0.66)



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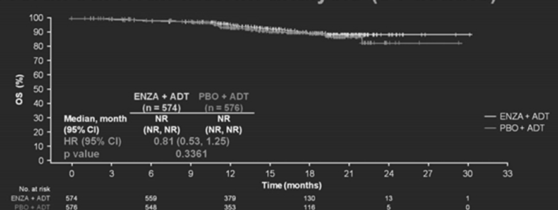
Overall survival: interim analysis (84 deaths)



- At the time of interim analysis, OS data are not mature, with 25% of 342 events required for final analysis (enzalutamide plus ADT, 39; placebo plus ADT, 45) and 19% reduction in risk of death that is not statistically significant
- Final OS analysis will be conducted with ~342 deaths at 4% significance level

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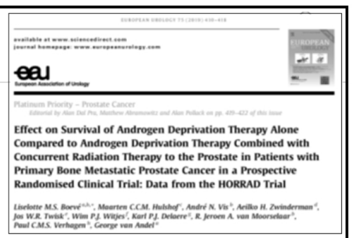
Context: adding abiraterone or enzalutamide to ADT

	ARCHES (N=1150)	LATITUDE (N=1199)	STAMPEDE (N=1917)	CHAARTED (N=790)
Agent	Enzalutamide (vs placebo)	Abiraterone/pred (vs placebos)	Abiraterone/pred	Docetaxel
Primary endpoint: HR (CI)	rPFS: 0.39 (0.30-0.50)	OS: 0.66 (0.56-0.78) rPFS: 0.47 (0.39-0.55)	OS: 0.63 (0.52-0.76)	OS: 0.72 (0.59-0.89)
Duration	Median NR vs 19.5mo	Median OS: 53.3 vs 36.5mo Median rPFS: 33.0 vs 14.8mo	3yr 83% vs 76%	Median 57.6 vs 47.2mo
Prior ADT (median)	Up to 6mo (70% ≤3mo)	Up to 3mo	Up to 3mo	Up to 120d (35d)
Anti-androgen with ADT	Study design	62%	94%	42% >30d
Prior docetaxel	18% (180/205: 6 cycles)	Exclusion	Exclusion	Exclusion
De novo M1	67%	100%	49%	73%
Visceral metastases	48% (incl nodes)	Liver 5%, lung 12%	~5%	15%
Undetectable PSA (≤0.2) Harshman LC et al. JCO 36: 376-382, 2018	68.1% vs 17.6% (best response)	47.6% vs 7.5% @6mo	Not reported	32% vs 19.6% @6mo

Presented By Ian Davis at 2019 Genitourinary Cancers Symposium



EUROPEAN UROLOGY 75 (2019) 410–418

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

European Association of Urology

Platinum Priority – Prostate Cancer
Editorial by Alan Dal Pra, Matthew Abramowitz and Alan Pollack on pp. 419–422 of this issue

Effect on Survival of Androgen Deprivation Therapy Alone Compared to Androgen Deprivation Therapy Combined with Concurrent Radiation Therapy to the Prostate in Patients with Primary Bone Metastatic Prostate Cancer in a Prospective Randomised Clinical Trial: Data from the HORRAD Trial

Liselotte M.S. Boevé[a,b,], Maarten C.C.M. Hulshof[c], André N. Vis[b], Aeilko H. Zwinderman[d], Jos W.R. Twisk[e], Wim P.J. Witjes[f], Karl P.J. Delaere[g], R. Jeroen A. van Moorselaar[b], Paul C.M.S. Verhagen[h], George van Andel[a]*

Inclusion

Primary bone metastatic prostate cancer

- Histologically proven adenocarcinoma of the prostate
- Osseous metastases on a bone scan
- Informed consent

Exclusion

- Earlier treatment for prostate cancer
- PSA < 20 ng/ml
- Age > 80 yrs

METHODS

Randomization 1:1

1. Androgen deprivation therapy + EBRT (radiotherapy group)
2. Androgen deprivation therapy (control group)

Radiotherapy

70 Gy in 35 fractions of 2 Gy, during 7 wk (82%)
57.76 Gy in 19 fractions of 3.04 Gy, 3 times a week for 6 wk (18%)

QoL

Cancer-specific questionnaire (EORTC QLQC30)
Prostate cancer-specific questionnaire (EORTC PR25)
Baseline and after 3, 6, 12 and 24 months

Boeve et al, Eur Urol 75: 410, 2019

BASELINE CHARACTERISTICS

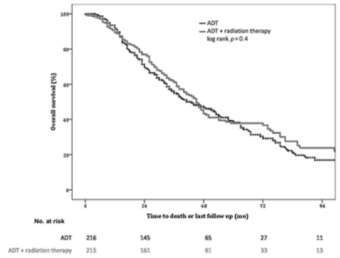
	ADT + radiotherapy (N=216)	ADT alone (N=216)
Age – year	67 (62-71)	66.5 (61-71)
PSA concentration at start of ADT (ng/ml)		
Median (range)	125 (8-14000)	149.4 (3.8-6991)
Q1	48	50.4
Q3	433	483
Missing data	3 (1%)	5(2%)
Gleason sum score		
6	7(3%)	7(3%)
7	66(31%)	64 (30%)
8	48(22%)	65(30%)
9	85(39%)	72(33%)
10	9(4%)	7(3%)
Missing data	1 (1%)	1(1%)
T stage		
T1	7 (3%)	5 (3%)
T2	33 (15%)	20 (9%)
T3	125 (58%)	128 (59%)
T4	51 (24%)	59 (27%)
Missing data	0	4 (2%)
Osseous metastases		
<5 lesions	89 (41%)	71 (33%)
5-10	53 (25%)	65 (30%)
>15	74 (34%)	80 (37%)
WHO Performance status		
0	187 (87%)	176 (82%)
1	22 (10%)	31 (14%)
2	4 (2%)	6 (3%)
3	3 (1%)	3 (1%)

Boeve et al, Eur Urol 75: 410, 2019

RESULTS

Median follow-up
- 47 mo

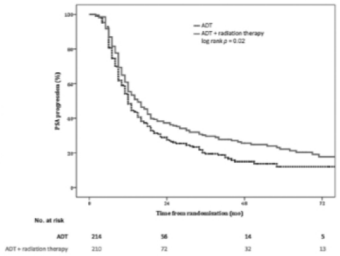
Median overall survival
- Radiotherapy group:
  - 45 mo (95%CI 40.4-49.6)
- Control group:
  - 43 mo (95%CI 32.6-53.4)



Boeve et al, Eur Urol 75: 410, 2019

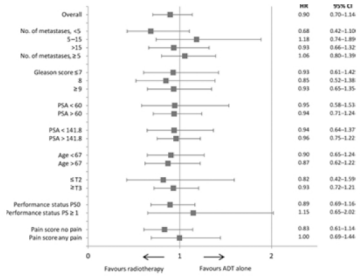
RESULTS

Median time to PSA progression
- Radiotherapy group:
  - 15 mo (95%CI 11.8-18.2)
- Control group:
  - 12 mo (95%CI 10.6-13.4)



Boeve et al, Eur Urol 75: 410, 2019

RESULTS

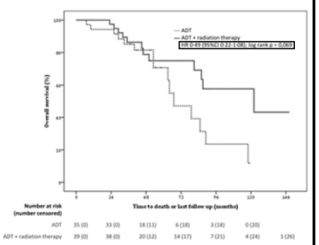


Boeve et al, Eur Urol 75: 410, 2019

RESULTS

Explorative subgroup analysis
- PSA < median of 142 ng/ml
- Gleason score ≤ 8
- < 5 osseous metastases

- Radiotherapy group n=39
- Control group n=35

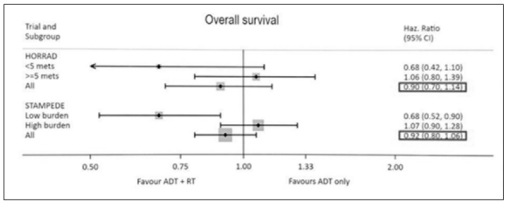


Boeve et al, Eur Urol 75: 410, 2019

DISCUSSION

- Findings consistent with report from STAMPEDE trial (Parker et al, Lancet 392: 2353, 2018)

- Meta analysis



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PEACE-1 trial, ClinicalTrials.gov NCT01957436

androgen deprivation therapy + docetaxel

androgen deprivation therapy + docetaxel + abiraterone acetate + prednisone

Arm A + radiotherapy

Arm B + radiotherapy

Recruiting

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ARASENS trial, ClinicalTrials.gov NCT02799602

Experimental: BAY1841788 /darolutamide (ODM-201) + standard ADT + Docetaxel

Placebo Comparator: Placebo + standard ADT + Docetaxel

Recruiting

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ENZAMET trial, ClinicalTrials.gov NCT02446405

Experimental: Enzalutamide plus ADT

Placebo Comparator: Placebo plus ADT

TITAN trial, ClinicalTrials.gov NCT02489318

Experimental: Apalutamide plus ADT

Placebo Comparator: Placebo plus ADT

Active, not recruiting

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Janssen Announces ERLEADA® (apalutamide) Phase 3 TITAN Study Unblinded as Dual Primary Endpoints Achieved in Clinical Program Evaluating Treatment of Patients with Metastatic Castration-Sensitive Prostate Cancer

Phase 3 Study Unblinded Following Recommendation of Independent Data Monitoring Committee

Spring House, PA, January 30, 2019 – The Janssen Pharmaceutical Companies of Johnson & Johnson announced today the unblinding of the Phase 3 TITAN study evaluating ERLEADA® (apalutamide) plus androgen deprivation therapy (ADT) in the treatment of patients with metastatic castration-sensitive prostate cancer (mCSPC). The decision resulted from an Independent Data Monitoring Committee (IDMC) recommendation coinciding with a pre-planned analysis that showed the dual primary endpoints were both achieved, significantly improving radiographic progression-free survival (rPFS) and overall survival (OS). Based on these results, the IDMC recommended that patients in the placebo plus ADT group be given the opportunity to cross over to treatment with ERLEADA plus ADT. Patients will continue to be followed for OS and long-term safety as part of the TITAN study.

"The TITAN study was designed to evaluate the efficacy and safety of ERLEADA in combination with androgen deprivation therapy in patients with newly-diagnosed metastatic castration-sensitive prostate cancer, regardless of the extent of their disease," said Margaret Yu, M.D., Vice President, Oncology Clinical Development, Janssen Research & Development, LLC. "We look to continue to build upon our understanding of ERLEADA for patients with metastatic prostate cancer as there remains a significant unmet need for additional treatment options."

30 Jan 2019

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6.4.9 ***Guidelines for the first-line treatment of metastatic disease***

Recommendations	Strength rating
In M1 symptomatic patients, offer immediate systemic treatment to palliate symptoms and reduce the risk for potentially serious sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction, extra-skeletal metastasis).	Strong
Offer luteinizing hormone-releasing hormone (LHRH) antagonists, especially to patients with an impending spinal cord compression or bladder outlet obstruction.	Weak
In M1 asymptomatic patients, offer immediate systemic treatment to improve survival, defer progression to a symptomatic stage and prevent serious disease progression-related complications.	Strong
In M1 asymptomatic patients, discuss deferred castration with a well-informed patient since it lowers the treatment side-effects, provided the patient is closely monitored.	Weak
In M1 patients treated with a LHRH agonist, offer short-term administration of anti-androgens to reduce the risk of the 'flare-up' phenomenon.	Weak
Do not offer anti-androgen monotherapy for M1 disease.	Strong
Offer castration combined with chemotherapy (docetaxel) to all patients whose first presentation is M1 disease and who are fit enough for docetaxel.	Strong
Offer castration combined with abiraterone acetate plus prednisone to all patients whose first presentation is M1 disease and who are fit enough for the regimen.	Strong
Offer castration alone, with or without an anti-androgen, to patients unfit for, or unwilling to consider, castration combined with docetaxel or abiraterone acetate plus prednisone.	Strong

EAU ESUR ESTRO SIOG
Guidelines Prostate Cancer 2018

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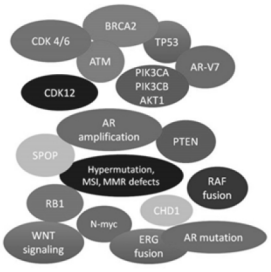
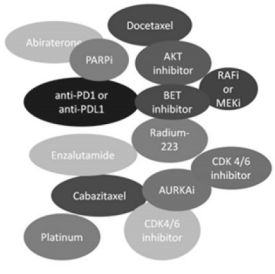
Molecular Alterations in CRPC



Approved or Emerging Therapies



Overall increased genomic testing has led to more biomarker driven trials, and sometimes off label use of drugs

Presented By Himisha Beltran at 2019 Genitourinary Cancers Symposium

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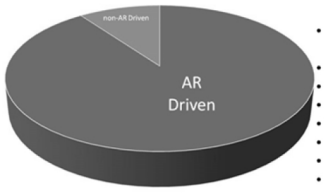
AR signaling is still the major driver of CRPC



- Intratumoral production of androgens
- AR overexpression
- AR amplification
- AR point mutations
- AR splice variants
- AR structural alterations
- AR pathway crosstalk, bypass
- AR co-factors

Continuous evolution of somatic AR alterations with subsequent therapies

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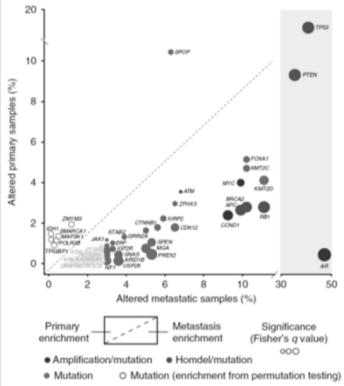

The most common tumor suppressors lost in CRPC:
RB1 **20%** vs. 3% primary
TP53 **45%** vs 15% primary
PTEN **40%** vs 20% primary

Clinical utility as prognostic biomarkers?

Early detection of resistant disease?

Armenia et al,
Nat Genet 2018 epub

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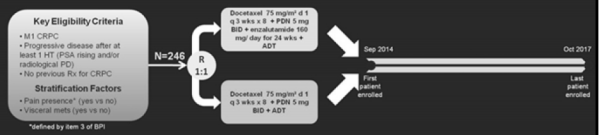
CHEIRON Study Design



Primary endpoint

- Rate of pts w/out progression (according to PCWG2) at 6 mos after docetaxel first administration (end of treatment)

Statistical Design

- Target of 232 pts provides 80% power to detect a target difference in PD-free rate of 15% (50% vs 65%) with an α-error of 0.10

Secondary endpoints

- ORR
- bRR
- PFS
- rPFS
- OS
- Safety
- Pain (BPI)
- QoL (FACT-P)

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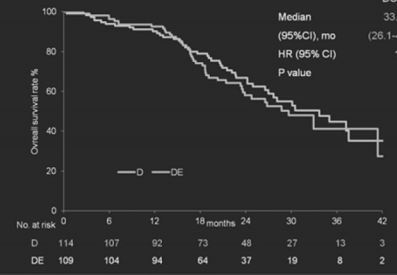
Overall survival



	DOC	DOC+ENZ
Median	33.7	29.6
(95%CI), mo	(26.1-41.2)	(21.3-37.9)
HR (95% CI)	1.13 (0.75-1.71)	
P value	0.5	

No. at risk	0	6	12	18	24	30	36	42
D	114	107	92	73	48	27	13	3
DE	109	104	94	64	37	19	8	2

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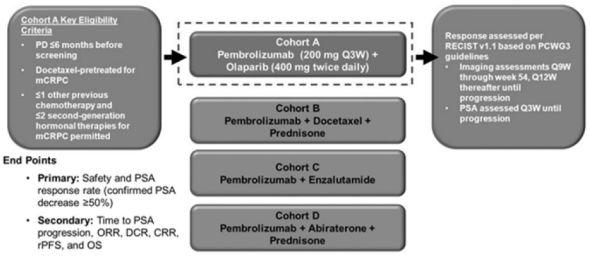
KEYNOTE-365 Study Design (NCT02861573)



End Points

- **Primary:** Safety and PSA response rate (confirmed PSA decrease ≥50%)
- **Secondary:** Time to PSA progression, ORR, DCR, CRR, rPFS, and OS

Database cutoff: July 27, 2018.

Presented By Evan Yu at 2019 Genitourinary Cancers Symposium

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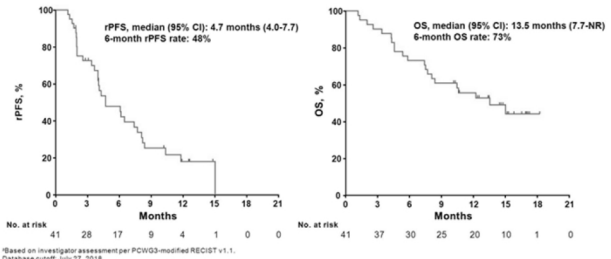
Kaplan-Meier Estimates of rPFS[a] and OS



[a]Based on investigator assessment per PCWG3-modified RECIST v1.1.
Database cutoff: July 27, 2018.

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- Pembrolizumab plus olaparib is generally well tolerated and has promising activity in a molecularly unselected population of mCRPC patients previously treated with chemotherapy and second-generation hormonal therapies
  - Safety/tolerability profile of the combination is consistent with profiles of each agent
    - Most common treatment-related AE, anemia (37%)
    - All immune-mediated AEs grade 1 or 2; most common, hypothyroidism (5%)
  - Confirmed PSA response rate: Total population, 12%; RECIST-measurable disease, 14%
  - Tumor burden reduction from baseline: RECIST-measurable disease, 39%
  - In the total population
    - Median rPFS, 4.7 months; median OS, 13.5 months
- Results support further evaluation of pembrolizumab and olaparib in this patient population
  - Enrollment to cohort A of KEYNOTE-365 to increase to 100 patients
  - Randomized phase 3 study of olaparib with pembrolizumab in patients with molecularly unselected mCRPC who were enzalutamide or abiraterone pretreated and progressed on chemotherapy currently open to enrollment (KEYLYNK-010, NCT03834519)

Presented By Evan Yu at 2019 Genitourinary Cancers Symposium

Initial Results From a Phase 2 Study of Nivolumab Plus Ipilimumab for the Treatment of Metastatic Castration-Resistant Prostate Cancer (CheckMate 650)

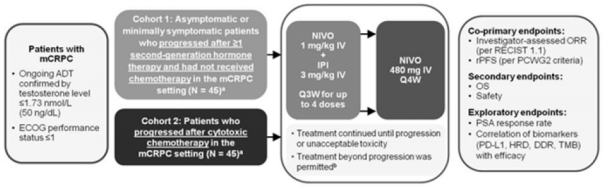
Padmanee Sharma,[1] Russell Pachynski,[2] Vivek Narayan,[3] Aude Fléchon,[4] Gwenaelle Gravis,[5] Matthew D. Galsky,[6] Hakim Mahammedi,[7] Akash Patnaik,[8] Sumit K. Subudhi,[1] Marika Ciprotti,[9] Burcin Simsek,[10] Abdel Saci,[10] Sarah Hu,[10] G. Celine Han,[10] Karim Fizazi[11]

[1]MD Anderson Cancer Center, University of Texas, Houston, TX, USA; [2]Washington University School of Medicine, St. Louis, MO, USA; [3]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA; [4]Centre Léon Bérard, Lyon, France; [5]Institut Paoli-Calmettes, Marseille, France; [6]Icahn School of Medicine at Mount Sinai, New York, NY, USA; [7]Centre Jean Perrin, Clermont-Ferrand, France; [8]The University of Chicago Medicine, Chicago, IL, USA; [9]Bristol-Myers Squibb, Uxbridge, UK; [10]Bristol-Myers Squibb, Princeton, NJ, USA; [11]Gustave Roussy, University of Paris Sud, Villejuif, France

Presented By Padmanee Sharma at 2019 Genitourinary Cancers Symposium

Study Design

Open-label, multicenter, phase 2 study (NCT02985957)



- Patients who had received ≥1 combination dose and who had toxicity that did not meet discontinuation criteria were permitted to begin NIVO maintenance before completion of all 4 combination doses

[a]In both cohorts, ≥30 patients were required to have measurable disease. [b]If the patient sustained clinical benefit while tolerating treatment, had stable performance status, and if continued treatment would not delay imminent interventions to prevent serious complications of progressive disease.
ADT, androgen deprivation therapy; DDR, DNA damage repair; HRD, homologous recombination deficiency; PCWG2, Prostate Cancer Working Group 2; rPFS, radiographic PFS; TMB, tumor mutational burden.

Presented By Padmanee Sharma at 2019 Genitourinary Cancers Symposium

Association of PD-L1 Expression With Response

Objective response, n (%)	Cohort 1		Cohort 2	
PD-L1[a]	PD-L1 <1% (n = 21)	PD-L1 ≥1% (n = 6)	PD-L1 <1% (n = 12)	PD-L1 ≥1% (n = 5)
Complete or partial response	4 (19.0)	2 (33.3)	0 (0)	2 (40.0)
Stable disease	8 (38.1)	2 (33.3)	6 (50.0)	0 (0)
Progressive disease/undetermined	9 (42.9)	2 (33.3)	6 (50.0)	3 (60.0)

- In both cohorts, numerically higher objective response rates were observed in patients with PD-L1 expression ≥1%

PSA response, n (%)	Cohort 1		Cohort 2	
	PD-L1 <1% (n = 22)	PD-L1 ≥1% (n = 6)	PD-L1 <1% (n = 17)	PD-L1 ≥1% (n = 6)
Confirmed PSA response rate (PSA decline ≥50% from baseline)	2 (9.1)	3 (50.0)	1 (5.9)	0 (0)
Patients with PSA <0.2 ng/mL	1 (4.5)	3 (50.0)	0 (0)	0 (0)

- In cohort 1, numerically higher PSA response rates were observed in patients with PD-L1 expression ≥1%; PD-L1 status did not appear to influence PSA response in cohort 2

[a]Tumor PD-L1 expression was assessed in pretreatment biopsy specimens at a central laboratory using a validated, automated immunohistochemical assay (Dako, an Agilent Technologies, Inc. company, Santa Clara, CA).

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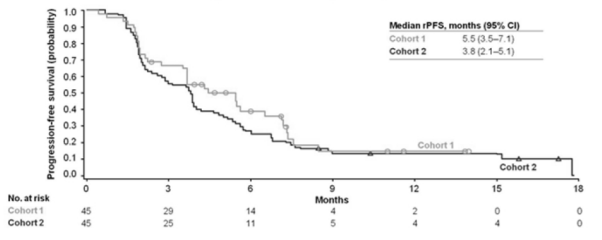
Radiographic PFS (per Investigator)



- Median (95% CI) time to PSA progression was 4.4 (3.5–6.5) months in cohort 1 and 3.9 (3.0–5.2) months in cohort 2

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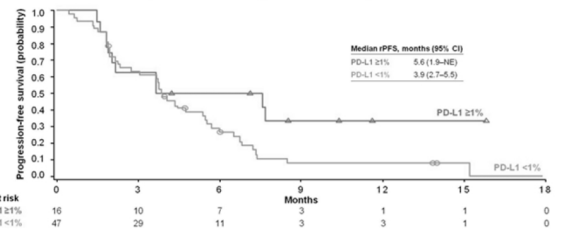
rPFS by PD-L1: Cohort 1 (Chemo-naïve) and Cohort 2 (Chemo-experienced) Combined



- Patients with PD-L1 ≥1% had numerically longer median rPFS versus patients with PD-L1 <1%

NE, not estimable.

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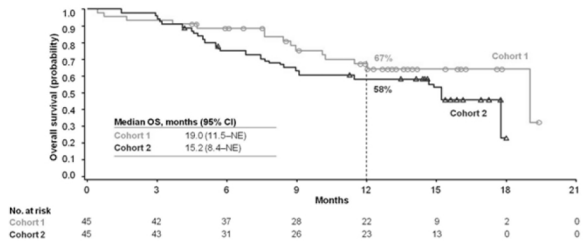
CheckMate 650

Overall Survival



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- In a malignancy where immune checkpoint monotherapy has shown limited activity, NIVO+IPI demonstrated antitumor activity in patients with mCRPC
  - Benefit was observed regardless of prior exposure to chemotherapy, but appeared to be more pronounced in patients not receiving prior chemotherapy for mCRPC
  - Deep and durable objective responses, as well as PSA <0.2 ng/mL, were observed in a subgroup of patients
- Preliminary data suggest that biomarkers may have a role in identifying patients with mCRPC likely to respond to immunotherapy
  - Patients with PD-L1 ≥1% and/or HRD+ or DDR+ tumors achieved numerically higher objective response rates, although there was a small number of patients in the analysis
- Despite TMB being relatively low in prostate cancer versus other tumor types (melanoma, NSCLC), a significant association was observed between higher TMB and improved outcomes in this population
- The safety profile of NIVO+IPI was generally consistent with prior studies of the NIVO1+IPI3 dosing schedule; however, dose/schedule optimization will be important for patients with mCRPC given the number of patients not completing all 4 combination doses and discontinuing study treatment due to toxicity
- Further study of NIVO+IPI in patients with mCRPC is warranted

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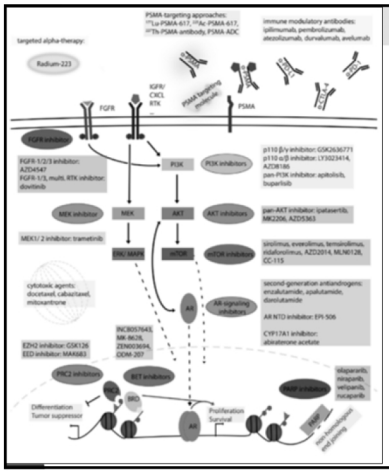

Nevedomskaya et al, Int J Mol Sci 19: 1359, 2018

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