





Urological Cancer,

Combining local and systemic therapy,

Our side of the fence

Prof. Dr. Henk van der Poel Juni 30, 2022

Disclosure

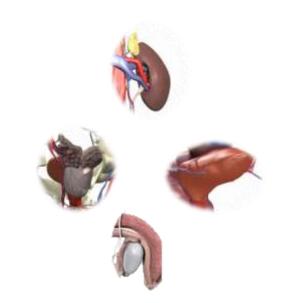
• Astellas, Ipsen, Intuitive, Storz



ECOP 5

Content, fields in urology

- 1. History
- 2. Management/innovations
- = prostate cancer
- = bladder cancer
- = kidney cancer
- = penile cancer
- = testis cancer
- 3. European Association of Urology

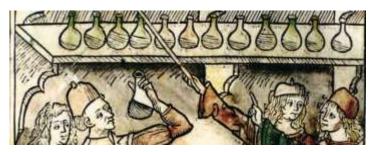


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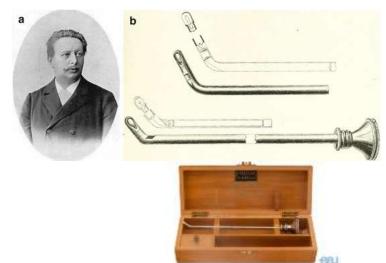
History





Cystoscopy: Maximillian Nitze, 1879

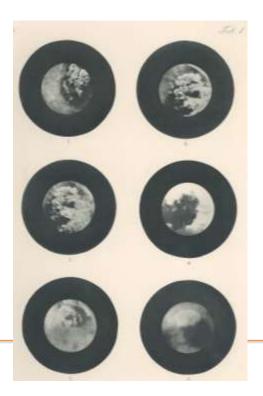




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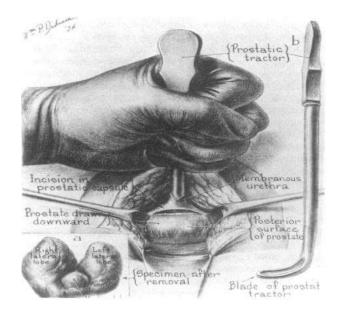
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Hugh Hampton Young 1870-1945

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Eugene Bricker 1908-2000





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Cure might not be possible in those whom it is needed...

... but cure may not be needed in those whom it is possible...

(Whitmore 1988)

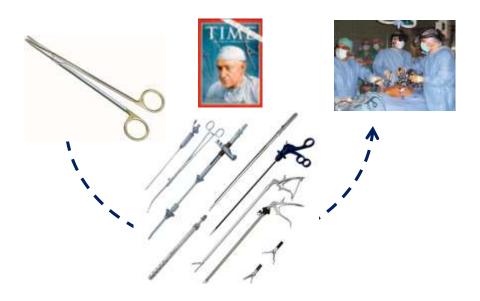


Whitmore WF Jr, Warner JA, Thompson IM Jr. Expectant management of localized prostatic cancer. Cancer 1991;67:1091–6.

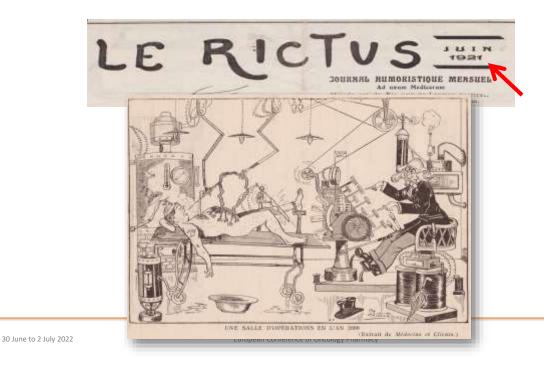
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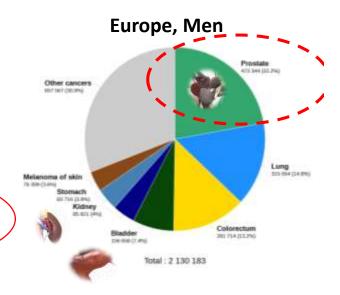
Cancer incidence 2020

World wide:

- 19.2million
- · Men: 10million
- Women: 9.2million

Europe:

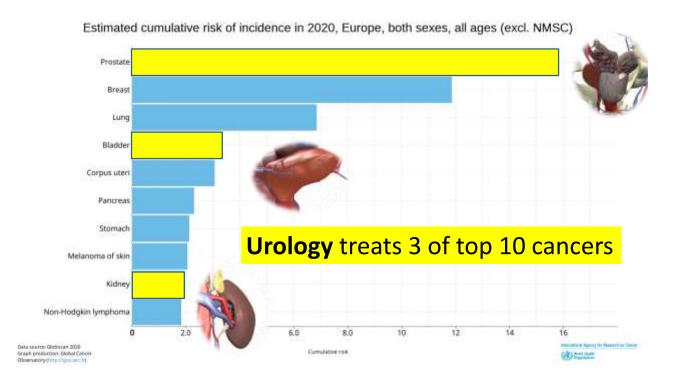
- 3.9million (20%)
- 0.8million (22%) urological cancers



Globocan 2020

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Number of urologists

US: 13.044 (2019) EU: 10.000 (est.)

2 new oncological patients weekly

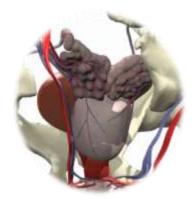


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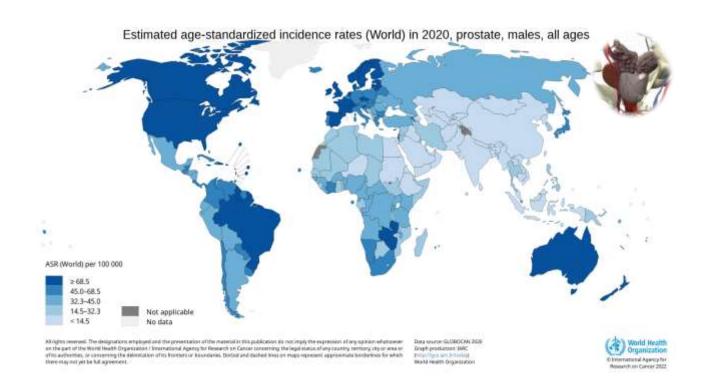
Prostate

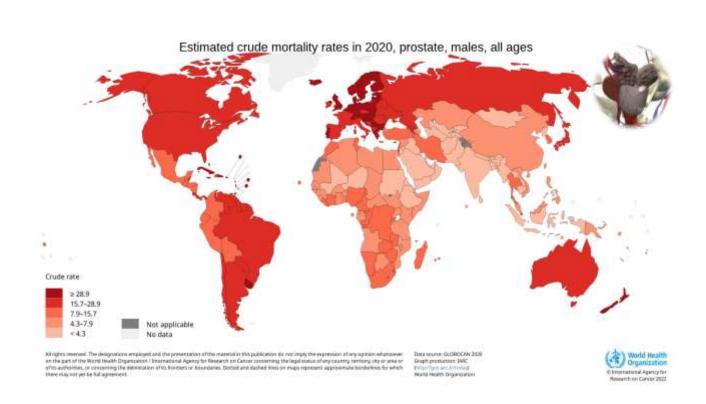


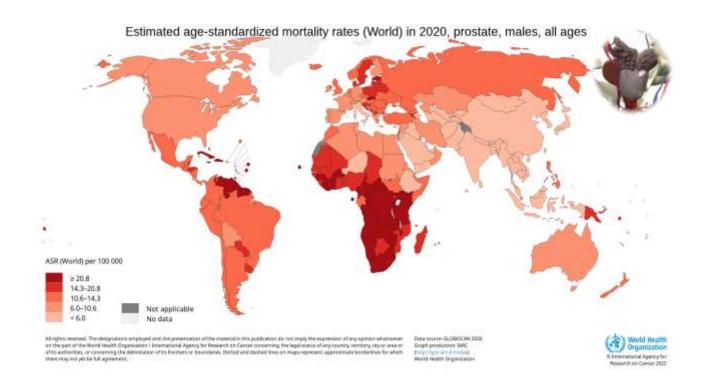
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Risk calculators





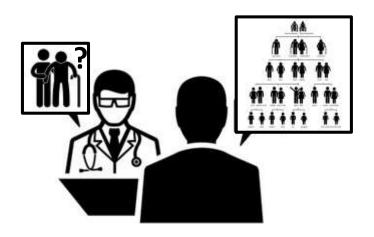
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http://www.prostatecancer-riskcalculator.com/seven-prostate-cancer-riskcalculators



Family history



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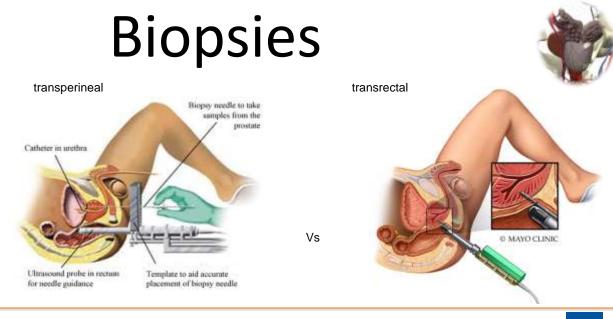
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5.1.3 Guidelines for screening and early detection

Recommendations	LE	Strength rating
Do not subject men to prostate-specific antigen (PSA) testing without counselling them on the potential risks and benefits.	3	Strong Weak
Offer an individualised risk-adapted strategy for early detection to a well-informed man with a good performance status (PS) and a life-expectancy of at least 10 to 15 years.		
Offer early PSA testing in well-informed men at elevated risk of having PCa: men > 50 years of age; men > 45 years of age and a family history of PCa; men of African descent > 45 years of age; Men carrying BRCA2 mutations > 40 years of age.	2b	Strong
Offer a risk-adapted strategy (based on initial PSA level), with follow-up intervals of 2 years for those initially at risk: men with a PSA level of > 1 ng/mL at 40 years of age; men with a PSA level of > 2 ng/mL at 60 years of age; Postpone follow-up to 8 years in those not at risk.	3	Weak
Stop early diagnosis of <u>PCa</u> based on life expectancy and PS; men who have a life-expectancy of < 15 years are unlikely to benefit.	3	Strong

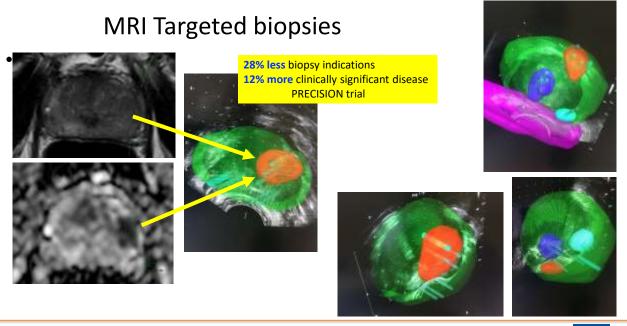
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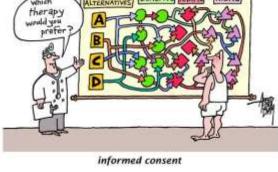




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Surgery





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Treatment localized prostate cancer



- 1. Low risk: active surveillance (30% 5y progression)
- 2. Surgery vs radiotherapy: no difference in 10y outcome (lower risk: PRoTect, SPCG-15 ongoing)
- 3. Radiotherapy ADT 6m-3y (LHRHa) dependent on risk group
- 4. Adjuvant systemic therapy after surgery limited value
- Management of recurrence: delayed salvage RT (RADICALS, GETUG17, RAVES)



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Landscape of metastasized disease



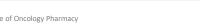
- 1. More extensive and early systemic therapy (ADT + docetaxel, abiraterone, enzalutamide, darolutamide, apalutamide)
- 2. Low vs high **volume** (CHAARTED, LATITUDE)
- 3. Localized treatment in metastasized disease (Stampede H: 3% survival benefit)



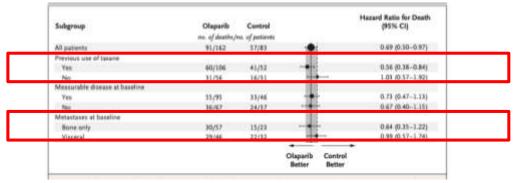
(m)CRPC, novelties

- 1. 177Lu-PSMA-617 radiopharmaceutical: 5.3m PFS benefit (VISION, TheraP)
- 2. Olaparib (PARPI): 3.8m delay in progression (PROFOUND, BRCA1,2, ATM)





PROfound OS: Prior taxanes and non-visceral mets



Cohort A: BRCA1/2_{mut}, ATM

*Hussain NEJM 2020

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I. Routine
II. Investigational
III. Other cancers
IV. Preclinical
V. Co-targeting
X. No-evidence

Gene	Alteration	Prevalence	ESCAT	References
BRCA1/ 2	Somatic mutations/ deletions	9%	IA.	De Bono J, et al. N Engl J Med. 2020 ¹¹
	MSI-H	1%	IC	Cortes-Ciriano I, et al. Nat Commun. 2017 Abida W, et al. I Clin Oncol 2018 ³ Marous I, et al. Clin Conce Res. 2019 ³
PTEN	Deletions/ mutations	40%	HA"	Abida W, et al. Proc Not/ Acad Sci. 2019 De Bono J, et al. Clin Concer Res. 2019 NCT03072238
ATM	Mutations/ deletions	5%	HA	De Bono J, et al. N Engl J Med. 2020 ⁴¹
PALB2	Mutations	1%	108	Mateo J, et al. N Engl J Med. 2015 De Bono J, et al. N Engl J Med. 2020
РІКЗСА	Hotspot mutations	3%	IIIA	Crumbaker M, et al. Concers. 2017 ¹¹¹
AKTI	Mutations	1%	IIIA	Crumbaker M, et al. Concers. 2017

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When to test during disease progression?

NCCN:

	localized	mHRPC	mCRPC
HRR**	consider	do	do
MSI/MMR		consider	do

^{**} BRCA1/2, ATM, PALB2, FANCA, RAD51D, CHEK2, CDK12

EAU: all men with <u>metastasized</u> disease HRR gene and MMR defects

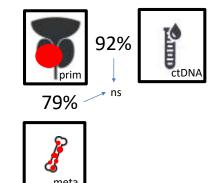
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Concordance of tests is high

- N=51
- Primary tumor vs ctDNA vs metastases



Differences mainly explained by sampling

Schweizer JAMA Oncol 2021

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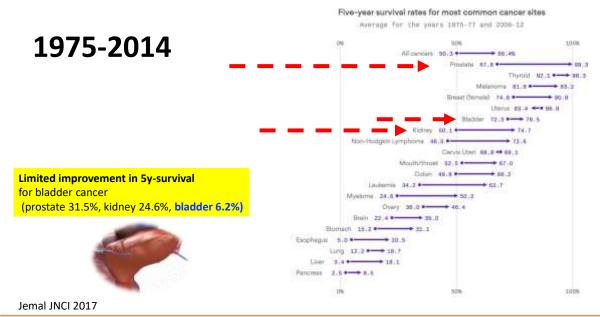
Bladder cancer



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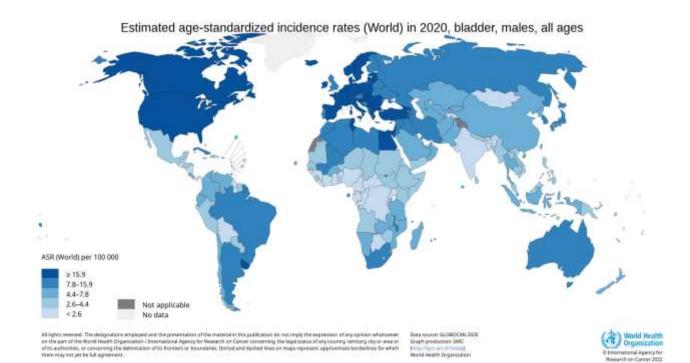
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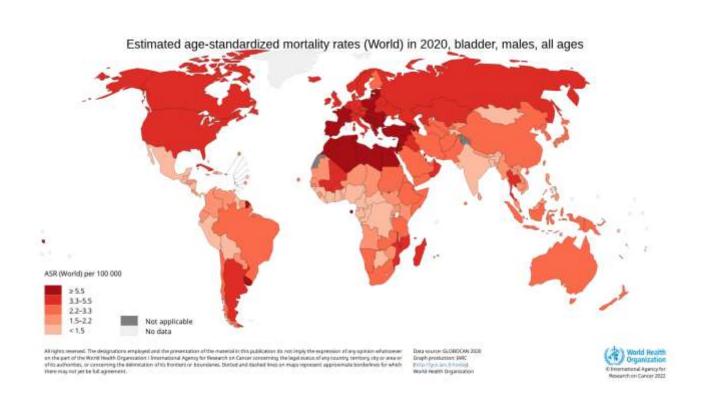




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Hematuria and risk factors



- Screening theoretically feasible in a high-risk population, there is currently insufficient evidence to recommend it. (Larre Eur Urol 2013)
- 2. Urine molecular markers insufficient
- **3.** Risk adapted screening cystoscopy, ultrasound, CT-U:
 - a. Smoking (50% of cases, 5x risk)
 - **b. Occupational** hazard (10% of cases)
 - c. Limited: family/genetic, diet
 - d. Increased risk: cyclophosphamide, pioglitazone, schistosomiasis

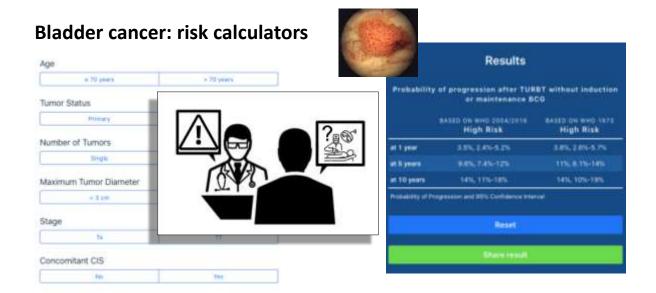




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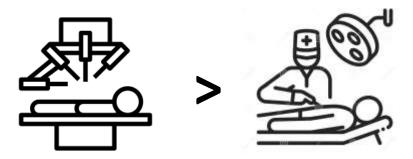
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Surgery

RCT robot vs open: 8 vs 10 days admission (> 50% reduction in DVT/infections, similar 18m survival)



Catto JAMA 2022

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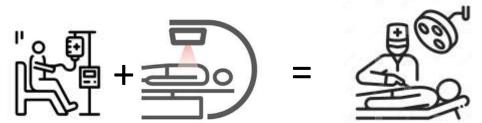
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High-risk non-metastasized bladder cancer



Chemoradiotherapy in selected cases (n=1002, propensity matched) cisplatin, 5FU/TMC, carbogen/nicotinamide or gemcitabine

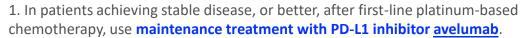


Zhong AMJCO 2019, Giacalon Eur Urol 2017, de Ruiter Eur Urol 2022

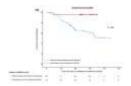


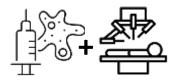
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Systemic therapy bladder cancer: <u>Immunotherapy</u>



- 2. <u>Unfit for chemo</u>: checkpoint inhibitors **pembrolizumab or atezolizumab** in case of high PD-1
- 3. Second line: pembrolizumab
- 4. Later line: FGFR3i, vinflunine, pacli/docetaxel, enfortumab
- 5. Immunotherapy (ipi/nivo) + Surgery: pCR = 46% (22% for chemo)



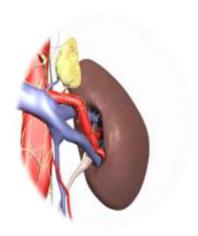


Einerhand IJC 2022

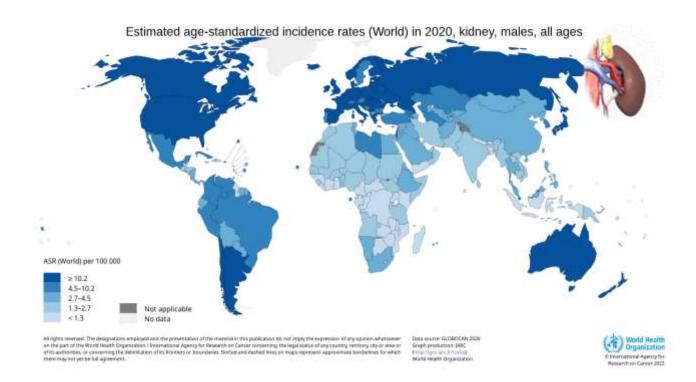
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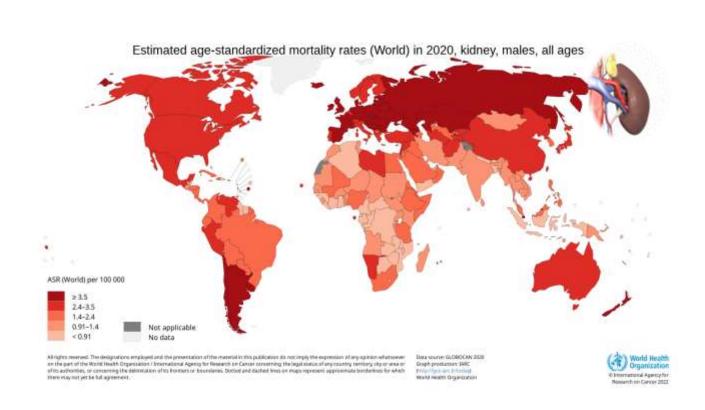


Kidney









Renal cancer

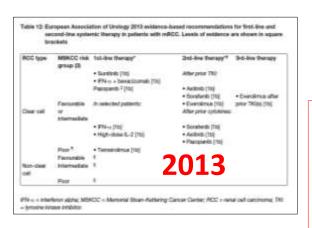
- 1. Incidentaloma 60%, 87% for smaller (<4cm) tumors.
- 2. Small renal masses management: ablation or (robot)partial nephrectomy
- 3. Adjuvant TKI: no benefit, Adjuvant PD-1i: pembrolizumab HR 0.54 for OS! (Keynote 564)
- 4. Non-clear cell RCC (pembrolizumab, cabozantinib, savolitinib)
- 5. Role of surgery in metastasized disease limited to responders

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Metastasized renal cancer: Immuno →TKI → Checkpoint-i







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Penis



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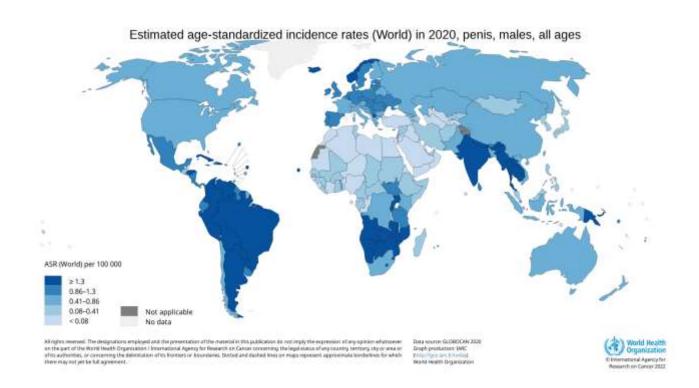
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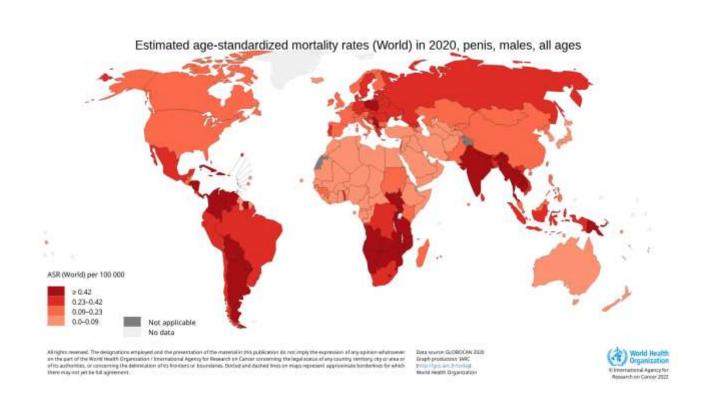




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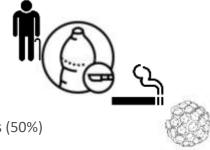






Etiology

- Age (peak > 70y)
- Phimosis (>50%)
- Smoking (>50%)
- High risk Human Papilloma Virus (50%)
- Protective: circumcision



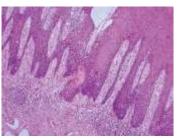


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Topical treatment PelN:

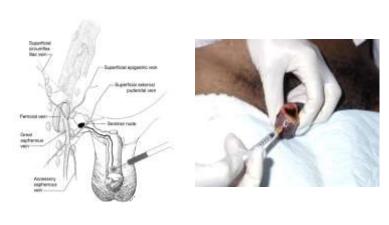
5-fluorouracil (57% CR) Imiquimod (85% needed additional surgical tx)

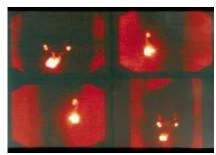


T1-T2 peniscarcnoom



Dynamic sentinel node biopsy



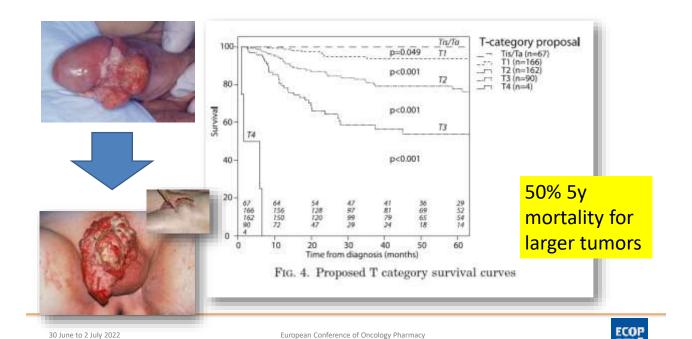




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Neoadjuvant (TIP):
paclitaxel, ifosfamide, and cisplatin
50% objective response

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HPV, penile cancer, vaccination

- 1. 50% of penile cancers attributable to HPV
- 2. 90% cervical cancer reduction on vaccination (12-13y)

55% of WHO member states
>12 years of age
One third included boys



Bruni Prev Med 2021

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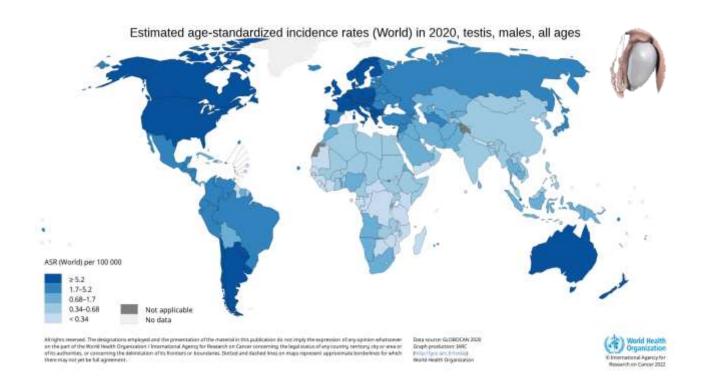
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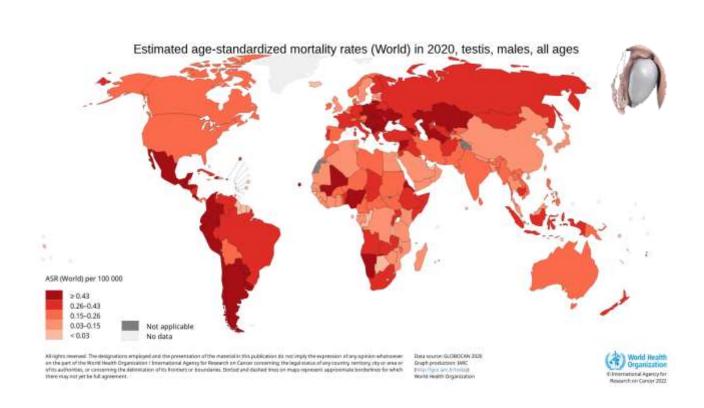


Testis





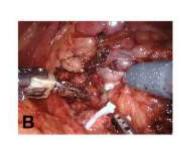




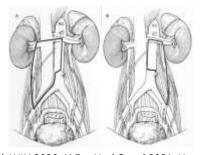
Management

- 1. Chemotherapy has not changed over decades
- 2. Challenges: secondary retroperitoneal surgery
- 3. Salvage treatment: conventional vs HD chemo

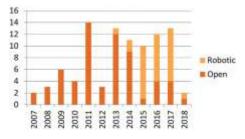
(cisplatin/ifosfamide/paclitaxel) (carbo/etoposide)











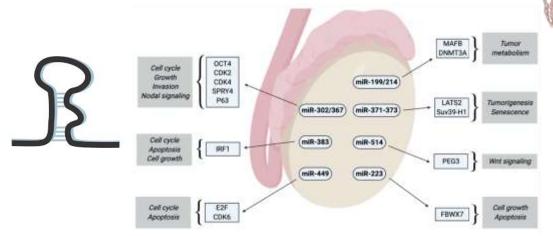
Blok WJU 2020, Li Eur Urol Oncol 2021, Honecker Ann Oncol 2018

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Risk factors: miRNA markers



Regouc Cancers 2020

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Siemens Can J Urol 2020

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Intraop complications 100 Transfusion Prolonged stay costs

Annual prostatectomy



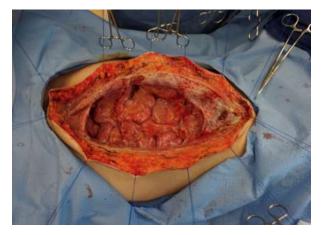
>100 yearly seems Reasonable quality

N=140.671, RARP 2472 hospitals 2009-2011

Gershman et al., J Urol Vol. 198, 1-8, July 2017



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Medtronics: HUGO



Growth in robotic surgery market



https://www.meddeviceonline.com/doc/the-market-outlook-for-robotic-assisted-surgery-in-0001

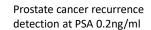
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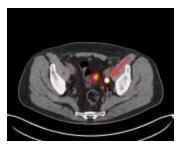
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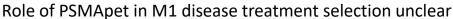


Prostate specific membrane antigen (PSMA) PET imaging











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- 1. From niche profession to multidisciplinary care (chair)
- 2. Minimal invasive surgery
- 3. Increase in systemic therapy options
- 4. Strong European Organization
- Care and research networks
- Technology / genetics driven



- Jul. 111
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Conclusions Urological Cancer

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