VESTFOLD HOSPITAL

Crash-kurs i Cancer vesica

(Epidemiologi, Etiologi, Patologi og Kirurgisk behandling)

Erik Skaaheim Haug

Urolog, Sykehuset i Vestfold

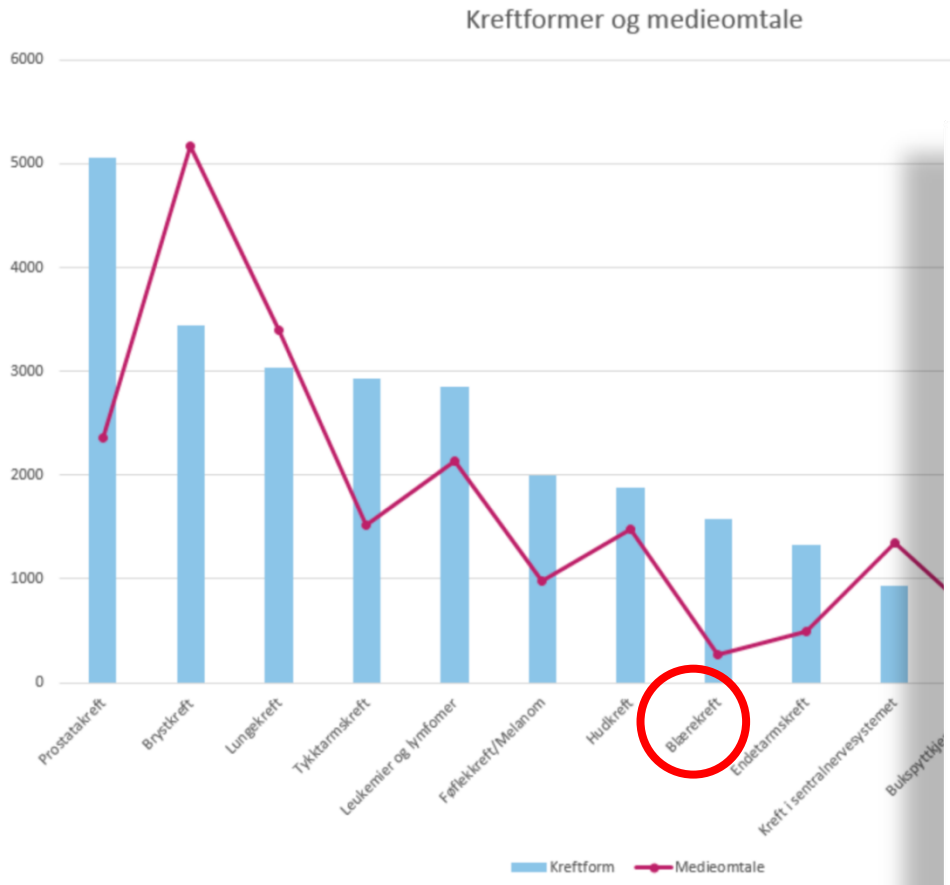
&

Norsk Blærekreftgruppe (NUCG)

Erik Skaaheim Haug

- Overlege dr. med. urologisk seksjon, Sykehuset i Vestfold HF
- Forsker i deltid, Institutt for Kreftgenetikk og informatikk, OUS
- Rådgiver i deltid, Kreftregisteret
- Forskning på prostata og blærekreft
- Leder Norsk urologisk cancer gruppe
- Leder Norsk Blære- og urotelialcancergruppe (NUCG)
- Leder Hdir's handlingsprogram-gruppe for blærekreft
- Medlem Nordisk urothelialcancergruppe
- Leder referansegruppen for Nasjonalt kvalitetsregister for prostatakreft
- Deltatt i advisory board og med foredrag for Photocure innen blærekreft
- **Ingen interessekonflikter/ no disclosures**

Kreftforekomst og medieoppslag
Er det en sammenheng?



Brystkreft får mest oppmerksomhet

Brystkreft er kreftformen som oftest omtales i norske medier, viser en ny kartlegging fra Kreftregisteret.

16 Tirsdag 9. mai 2017 Aftenposten

VITEN HELSE

Blærekreft får langt mindre oppmerksomhet enn mange andre kreftformer. Hvorfor er det sånn? Og hvilke konsekvenser får det for pasientene?

Hvorfor holder alle kjeft om blærekreft?

Kreftformer og medieomtale

Erik Skaaheim Haug overlege, Sykehuset i Vestfold og leder av Norsk Blærekreftgruppe

Bettina Kulle Andreassen forsker, Kreftregisteret

Blærekreft får lite medieomtale og forskes mindre på enn andre krefttyper.

Kreftform/ søkeord | Antall nye kreftfeller (2015) | Atekst (Medieovervåker) | Pubmed (Forskningsdatabase) | Google

Prostatakreft 5.061 17.682 181.420 138.000
Brystkreft 3.439 38.816 351.125 344.000
Lungekreft 3.035 25.517 356.650 161.000
Tykktarmskreft 2.935 11.373 187.774 56.900
Leukemier og lymfomer 2.845 16.024 407.269 767.000
Føflekkreft/Melanom 2.001 7.344 127.150 89.000
Hudkreft 1.884 11.057 229.080 116.000
Blærekreft 1.578 2.052 92.976 24.700
Endetarmskreft 1.333 3.739 53.052 26.200
Kreft i sentralnervesystemet 937 10.137 261.479 69.500
Bukspyttkjertelkreft 825 4.406 104.553 34.900
Livmorhalskreft 370 11.142 109.144 107.000
Testikkelkreft 293 7.185 39.884 38100

Klde: Atekst/Kreftregisteret

Slik har Kreftregisteret søkt

Søk i Atekst er gjort 03.05.2017. Tabellen viser ulike kreftformer, sortert etter antall nye kreftfeller i 2015. Livmorhalskreft og testikkelkreft er ikke blant de største kreftformene, men er med fordi dette er kreftformer som det har vært mye oppmerksomhet rundt.

Søkeordene har vært navn på kreftform, samt noen kjente begreper som ofte brukes for de ulike sykdommene, som «hjernesvulst», «blodkreft» og «kreft i tykktarmen».

I Pubmed er engelske søkeord brukt.

Søket har nok ikke greid å fange opp alle omtaler, men viser noe om forholdet mellom omtalene av ulike kreftformer.

Atekst har digitalisert artikler tilbake til 1945, men de aller fleste treffene kommer etter år 2000. I Pubmed finnes det forskningsartikler datert helt tilbake til begynnelsen av 1900-tallet.

Mulig å forebygge

En annen konsekvens av stillheten rundt denne kreftformen er at folk flest ikke er klar over at den i stor grad er mulig å forebygge.

Selv om sammenhengen med røyking er mest kjent for lungekreft, er dette den klart største risikofaktoren også for blærekreft. Fagfolk mener at nærmere halvparten av blærekreftfellene kunne vært unngått om ingen hadde røykt. Vi i Kreftregisteret forsker også på forekomst og overlevelsestrender over tid. Det ser ut som om forekomsten fortsatt øker til tross for at denne kreftformen kan forebygges.

Forsker mindre

Og apropos forskning. Er det kanskje slik at vi forskere og fagfolk selv passer på at vi ikke diskriminerer blærekreft, men vier denne kreftformen like mye oppmerksomhet som andre, mer «populære» kreftformer?

Nei.

Ifølge den medisinske forskningsdatabasen Pubmed, forsker vi langt mindre på blærekreft enn på andre kreftformer.

Her finner vi at leukemier og lymfomer er blant de virkelig mye studerte kreftformene med 407.000 treff i basen. Også her scorer brystkreft høyt, med 350.000 omtaler. Lungekreft og hudkreft har henholdsvis 357.000 og 229.000 treff.

Blærekreft: 93.000 treff.

Viktig å forske mer

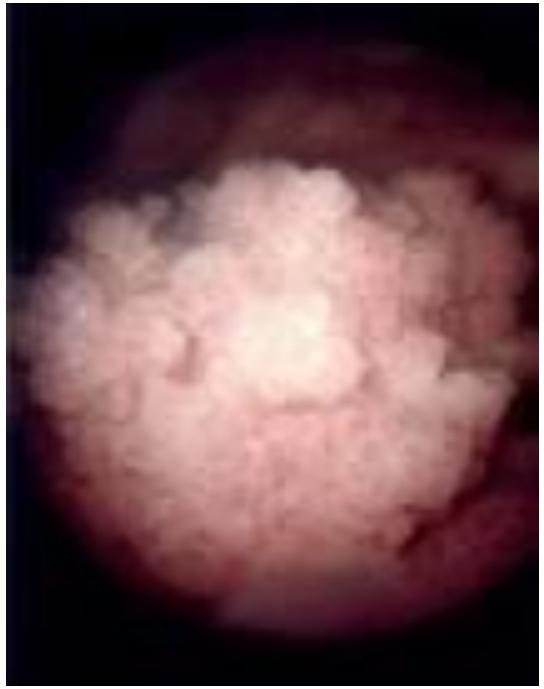
Snakker vi ikke om blærekreft fordi det er så lite forskning på det, eller forskes det mindre på sykdommen siden det ikke er så mye fokus på den?

Vi mener i alle fall at det er viktig å forske mer på denne kreftformen, og legge mer kunnskap til det vi allerede vet. I dag vet vi blant annet at dette er en kreftsykdom med meget stor variasjon, fra mange, relativt lite farlige svulster, til en svært aggressiv sykdom med høy dødelighet.

VESTFOLD HOSPITAL

Blærekreft

- Vår mest ressurskrevende kreftform
  - Den hyppigst residiverende
  - 50% av NMIBC får rekurrens
- Lett økende insidens
- 70 år i snitt ved diagnose
- Ofte raskt voksende
- Kjente risikofaktorer
  - Røyking, aromatiske aminer
  - Hereditet, Lynch syndrom
  - Tidligere kreftbehandling
- 3,5% av alle krefttilfeller
  - 4. hyppigste blant menn – nr 8 totalt



Typisk Henvisning:

- Eldre mann
- Røker eller tidligere røkende
- Industriarbeider, brannmann?
- Makroskopisk hematuri
- Vedvarende positiv Urin-stix evt m/ vannlatingsbesvær
- Vannlatingsmerter
- UL- / CT-funn

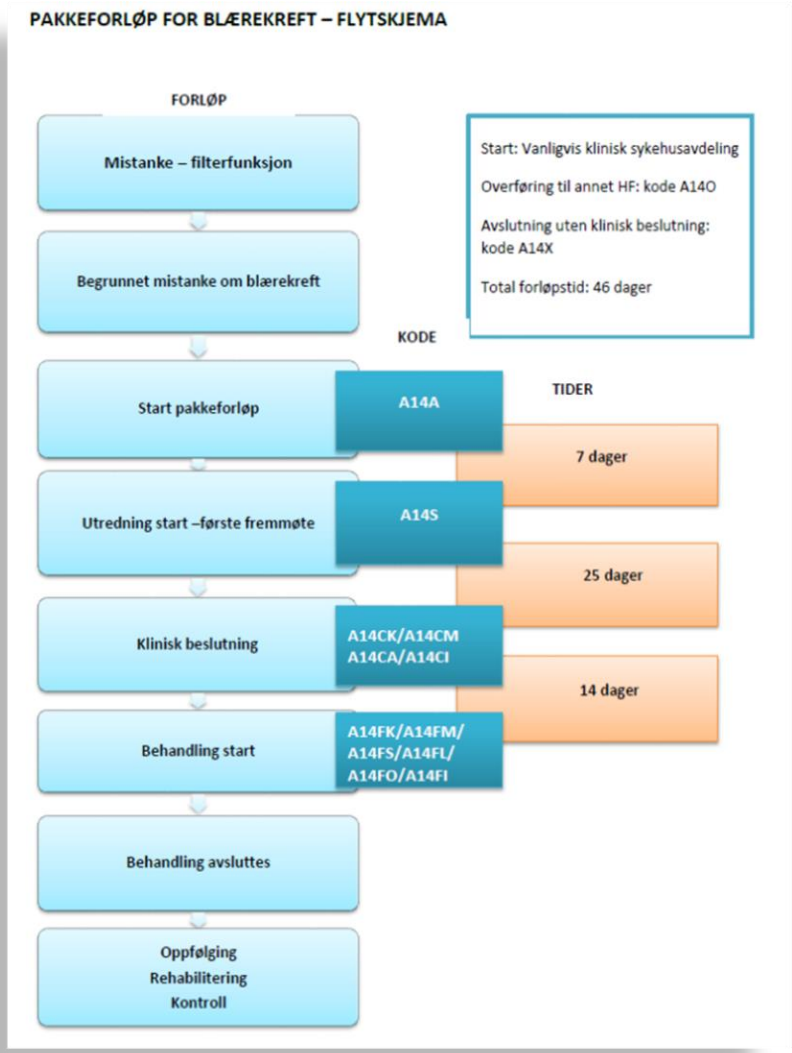
Epidemiologi – Blærekreft

Insidens- Prevalens

- 1852 nye tilfeller i Norge i 2020
  - 1578 nye tilfeller i Norge i 2015
- 442 Kvinner 1442 Menn (ratio 3,7)
- Median alder diagnose 73 år
- Ca. 50-60 nye tilfeller i Vestfold
- 13.382 mennesker levde med blærekreft i Norge i 2015
- 5 års relativ overlevelse alle former;
  - Kvinner 68,2 %
  - Menn 76,1 %

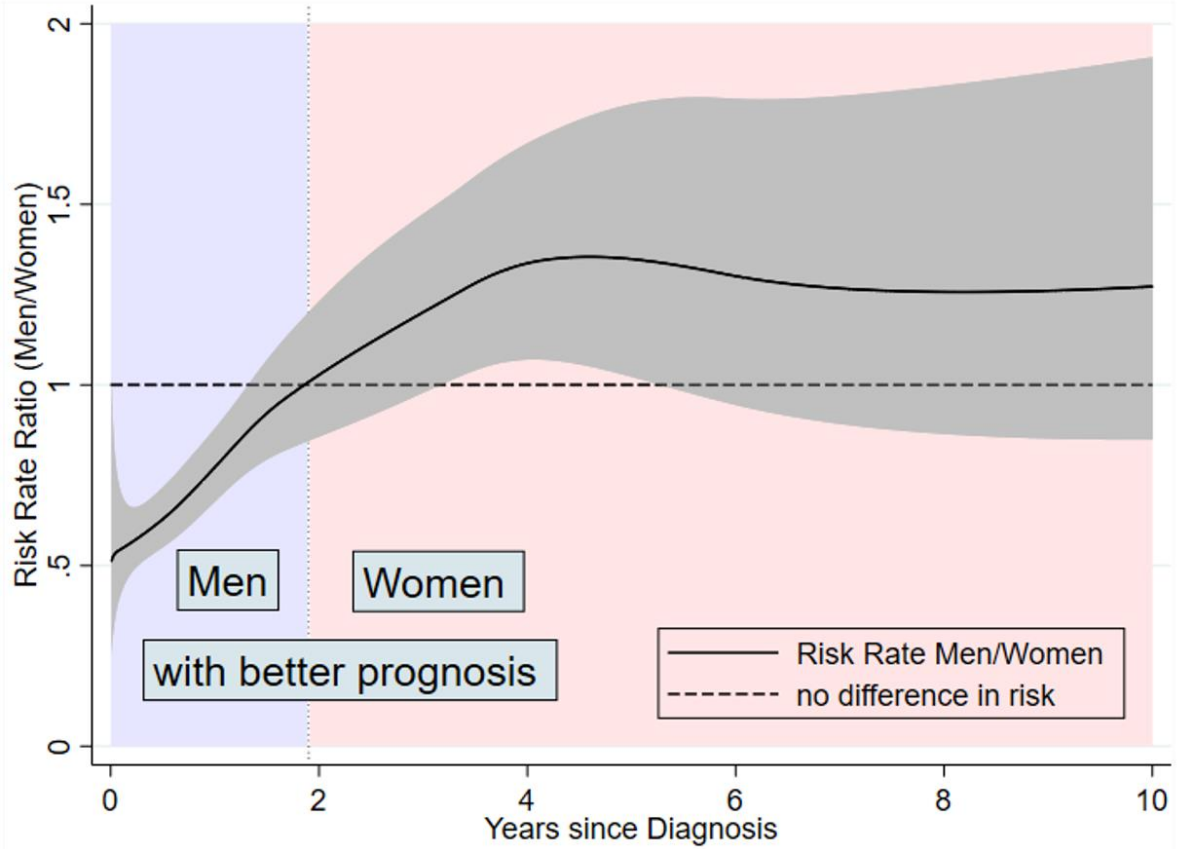
Forekomst av kreft i blære og urinveier i Norge i 2018

	Nyrebekken (C65)	Urinleder (C66)	Blære (C67)	Uspes. urinveier (C68)
Antall (%) pasienter i 2018	108 (6 %)	53 (3 %)	1516 (87 %)	71 (4 %)



VESTFOLD HOSPITAL

Har kvinner reelt høyere dødelighet av blærekreft?



Andreassen B, et al. Eur J Cancer. 2018

«Den høye forekomsten av (hemorragiske) cystitter kan gi dødelige forsinket diagnose hos kvinner»

VESTFOLD HOSPITAL

Inndeling av blærekreft
-(minst) 2 ulike sykdommer?

Det vesentlige:

T-Stadium: Tumors utbredelse i blæras vegglag

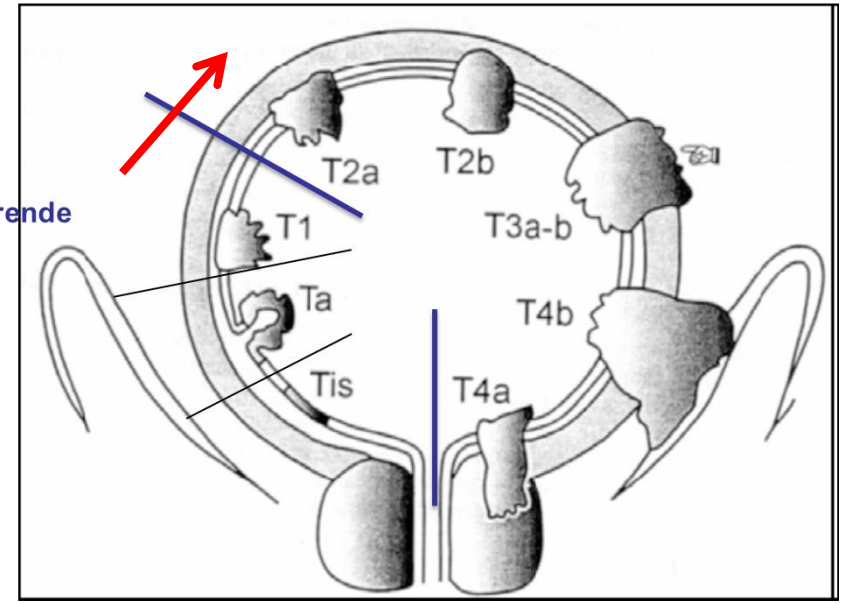
Histologisk Grad:

- WHO 1973;WHO 1-2-3
- WHO/ISUP – 1998/2004:
  - PUNLMP
  - **Lavgradig**
  - **Høygradig**
- **Cis (Tis)**

Muskelinfiltrerende

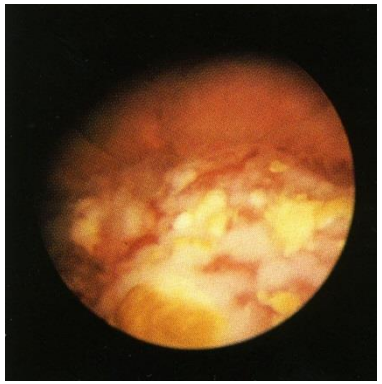
Ikke-muskelinfiltrerende

75-85%

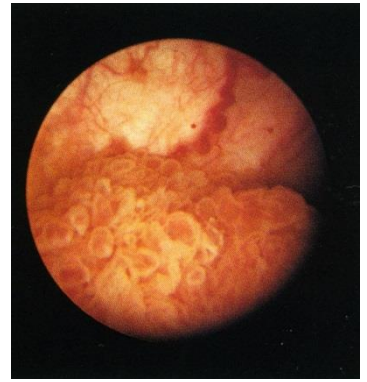


Progresjon; 10-15%

cTa



cT3-4

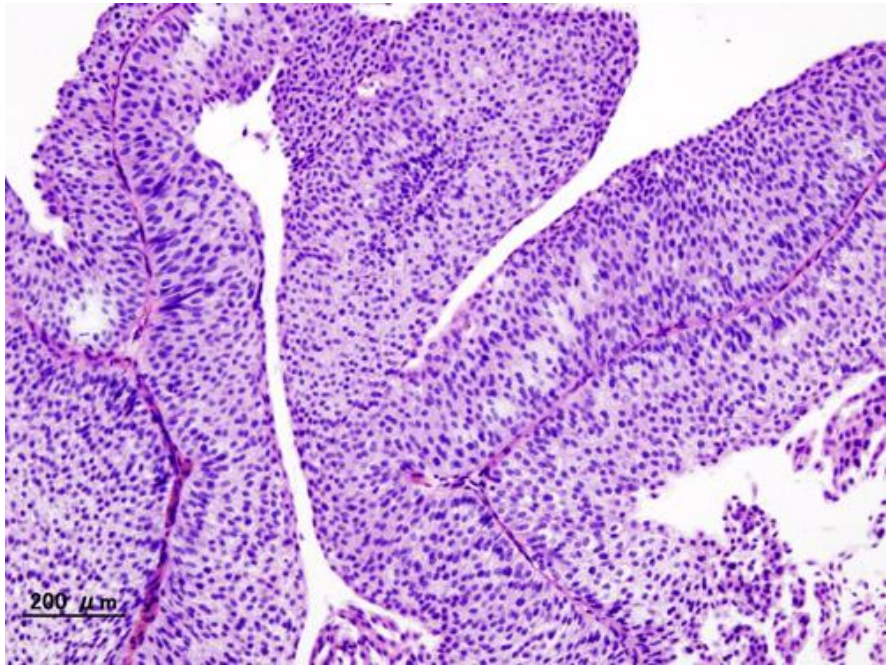


cT?

Blærekreft ≈ Urothelialt carcinom (UTC)

- 6% - Nyrebekken
- 3% - Ureter
- **90%- Blære**
- 1% - Uretra

- Mens 5 % av Blærekreft er ikke UTC
  - Platepitelcancere
  - Adenocarcinom
  - Småcellet



Variant histology

- Variant Bladder cancer histology;
  - =Any kind of **non**-urothelial transitional carcinoma
  - **Pure** Variant: No component of UTC
  - **Mixed** : any percentage of UTC + component of any other histology (**= Differentiation**)
- All Variant histology are **High Grade**
- More **advanced stage**
  - Worse prognosis stage by stage?
    - Probably not for most types
- Prevalence: 5-40 %
- Correct diagnosis depend on
  - TURB- sampling
  - Pathology expertise
- Percentage of variant should be reported

Table 1 World Health Organization classification of tumors of the urothelial tract

Glandular neoplasms
Adenocarcinoma, NOS
Enteric
Mucinous
Mixed
Villous adenoma

Table 1 | Classification of urothelial tract tumours

Tumour type	ICD-O	Behaviour*
Urothelial tumours		
Infiltrating urothelial carcinoma	8120	3
Nested, including large nested microcystic	NR	NR
Micropapillary	8131	3
Lymphoepithelioma-like	8082	3
Plasmocytoid / signet ring cell / diffuse	NR	NR
Sarcomatoid	8122	3
Giant cell	8031	3
Poorly differentiated	8020	3
Lipid-rich	NR	NR
Clear cell	NR	NR
Non-invasive urothelial neoplasms		
Urothelial carcinoma *in situ*	8120	2
Non-invasive papillary urothelial carcinoma, low-grade	8130	2
Non-invasive papillary urothelial carcinoma, high-grade	8130	2
Papillary urothelial neoplasm of low malignant potential	8130	1
Urothelial papilloma	8120	0
Inverted papilloma	8121	0
Urothelial proliferation of uncertain malignant potential	NR	NR
Urothelial dysplasia	NR	NR
Squamous cell neoplasm		
Pure squamous cell carcinoma	8070	3
Verrucous carcinoma	8051	3
Squamous cell papilloma	8052	0
Glandular neoplasms		
Adenocarcinoma, NOS	8140	3
Enteric	8144	3
Mucinous	8480	3
Mixed	8140	3
Villous adenoma	8261	0
Urachal carcinoma	8010	3
Tumours of Müllerian-type		
Clear cell carcinoma	8310	3
Endometroid carcinoma	8380	3
Neuroendocrine tumours		
Small cell neuroendocrine carcinoma	8041	3
Large cell neuroendocrine carcinoma	8013	3
Well-differentiated neuroendocrine tumour	8240	3
Paraganglioma	8693	1
Melanocytic tumours		
Malignant melanoma	8720	3
Naevus	8720	0
Melanosis	NR	NR

Table 1 (cont). | Classification of urothelial tract tumours

Tumour type	ICD-O	Behaviour*
Mesenchymal tumours		
Rhabdomyosarcoma	8900	3
Leiomyosarcoma	8890	3
Angiosarcoma	9120	3
Inflammatory myofibroblastic tumour	8825	1
Perivascular epithelioid cell tumour	NR	NR
Benign	8714	0
Malignant	8714	3
Solitary fibrous tumour	8815	1
Leiomyoma	8890	0
Haemangioma	9120	0
Granular cell tumour	9580	0
Neurofibroma	9540	0
Urothelial tract haematopoietic and lymphoid tumours		
Miscellaneous tumours		
Carcinoma of Skene, Cowper and Littre glands	8140	3
Metastatic tumours and tumours extending from other organs	NR	NR
Epithelial tumours of the upper urinary tract	NR	NR
Tumours arising in a bladder diverticulum	NR	NR
Urothelial tumours of the urethra	NR	NR

*Behaviour is coded 0 for benign tumours; 1 for unspecified, borderline, or uncertain features; 2 for carcinoma *in situ* and grade III intraepithelial neoplasia; and 3 for malignant tumours. ICD-O, International Classification of Diseases for Oncology; NR, not reported. Adapted from WHO Classification of Tumours of the Urinary System and Male Genital Organs. Moch *et al.* (2016) with permission from Elsevier[1].

tion of
Organs.

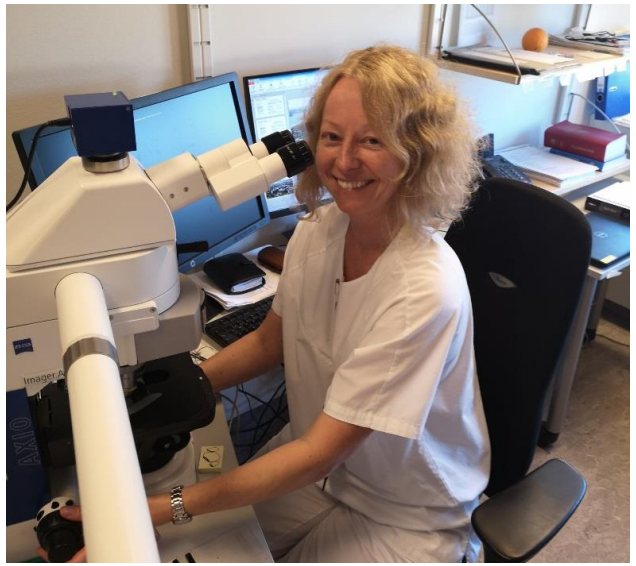
och H, Humphrey PA, Ulbright TM,
on Classification of Tumours of the
gans. IARC, Lyon, 2016

VESTFOLD HOSPITAL

The Vestfold Experience

- 241 cystectomy-specimens, 2000-2016 containing tumor
- Re-examined by a uropathologist
- **Pure** Histology
  - 93,8 % UTC
  - 4,1 % Squamous cell carcinoma
  - 0,4 % Adenocarcinoma
  - 1,7 % Small cell/ Neuroendocrin carcinoma

- 35,5 % of UTC had **Mixed** histology
  - 19,5 % Squamous differentiation
  - 2,9 % Glandular differentiation
  - 6,6 % Micropapillary differentiation
  - 2,1 % Lymfoepiteliomalike/Plasmacytoid/signet ringcell
  - 1,2 % Nested differentiation
  - 1,2 % Sarkomatoid differentiation
  - 1,2 % Mixed/ several patterns
  - 0,8 % Undifferentiated



Pathologist Birgitte Carlsen

VESTFOLD HOSPITAL

Development of Variant histology

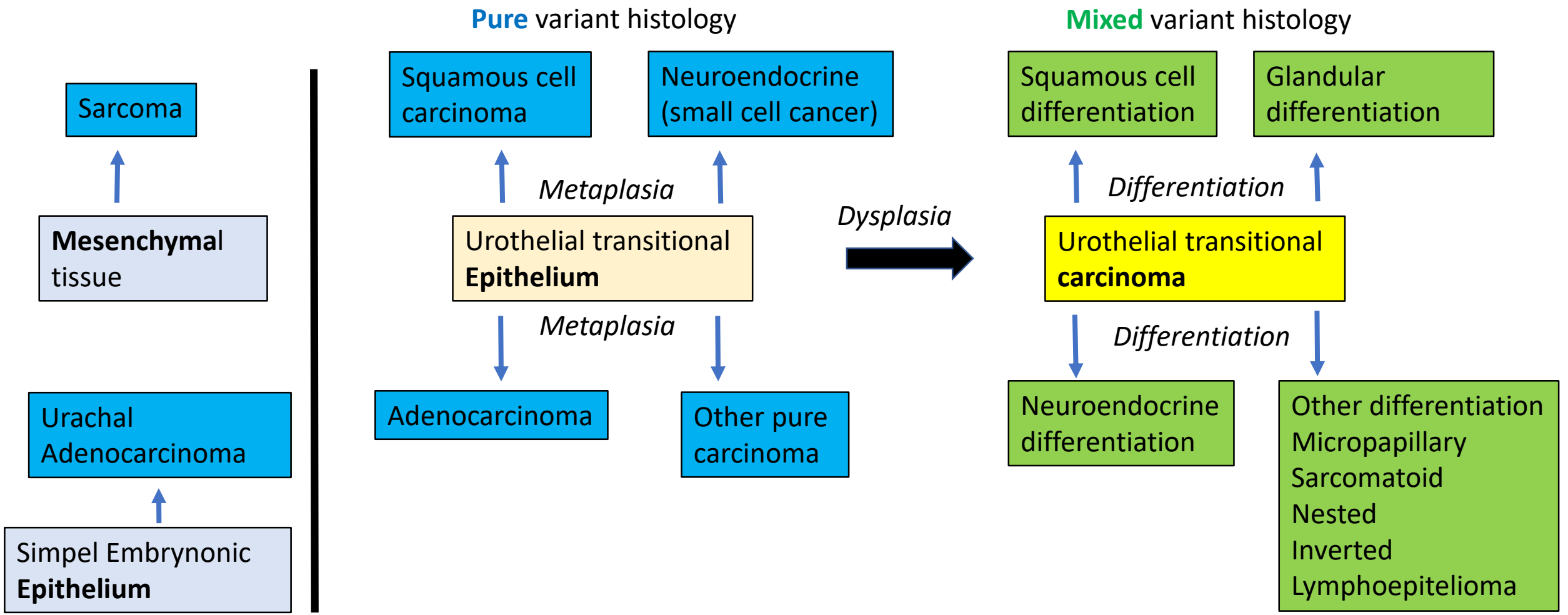


Figure: ES Haug 2019

VESTFOLD HOSPITAL

Variant histology – Urothelial type

- Micropapillary
  - 0,6-2,0 % of all Bca
  - Extremely aggressiv behaviour
  - Amount seems associated with Disease Specific Survival.
- Sarcomatoid (=carcinosarcoma?)
  - 0,3-0,6 %
  - May consist of different sarcomas
  - Previous radiation, cyclophosphamid are risk factors
- Rare;
  - Nested
  - Plasmacytoid/ signet ring
  - Lymphoepitelioma-like

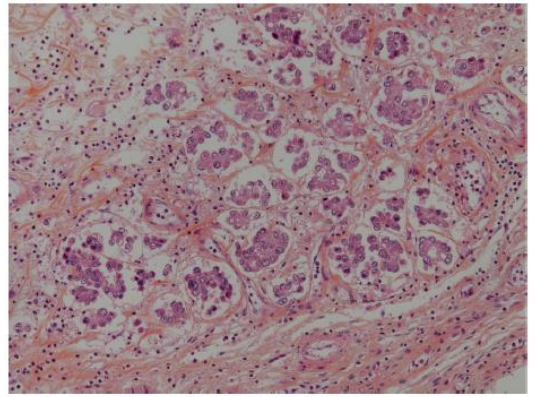


Figure 4 | **Micropapillary variant.** The empty spaces around the tumour cells can be mistaken for lymphovascular invasion. Immunohistochemistry can be helpful in the differential diagnosis (haematoxylin, eosin, and saffron stain, magnification x 200).

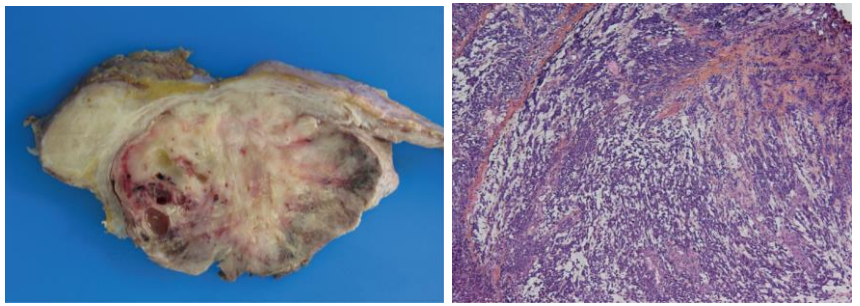


Figure 5 | **Gross aspects of a sarcomatoid carcinoma in the bladder. a** | Huge mass with haemorrhage and necrotic areas, largely invading the bladder wall. **b** | Corresponding histology. Fusiform cells with poorly differentiated fascicles, destroying the underlying bladder wall (haematoxylin, eosin, and saffron stain, magnification ×50).

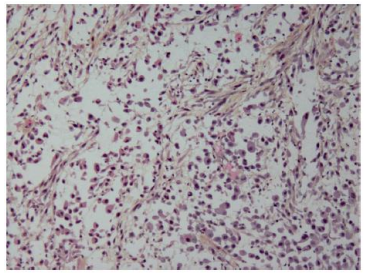


Figure 6 | **The plasmacytoid aspects with independent floating cells.** Tumour cells look similar to plasma cells, they invade the bladder wall in a diffuse manner (haematoxylin, eosin, and saffron stain, magnification ×100).

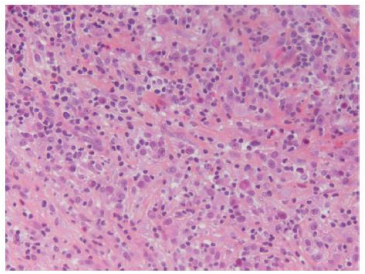


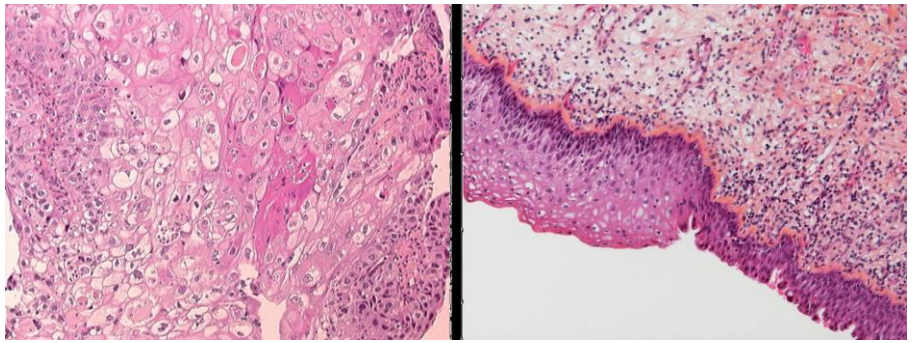
Figure 7 | **The lymphoepithelioma like variant.** Tumour cells and lymphocytes can be difficult to distinguish in this variant (haematoxylin, eosin, and saffron stain, magnification ×200).

Pictures from Moschinin M et al; Nat Rev Urol. 2017

VESTFOLD HOSPITAL

Variant histology – Non-urothelial type

- Squamous (SCC)
  - 5 % of all Bca
  - 30 % in the middle east due to *Schistosoma hematobium*
  - Preceeded by Metaplasia
  - Related to chronic inflammation,
  - Often bulky, necrotic with keratinization,
  - Discrimination from SCC-differentiation may be irrelevant?



Carcinoma *Metaplasia*

- Glandular/Adenocarcinoma
  - Present in upto 18 % of invasiv tumors
  - Mucous-producing
  - Enteric, Mucinous, Villous, Mixed, (**Urachal)**

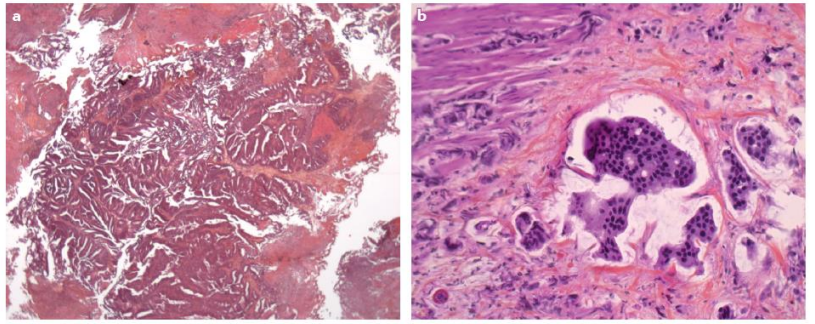
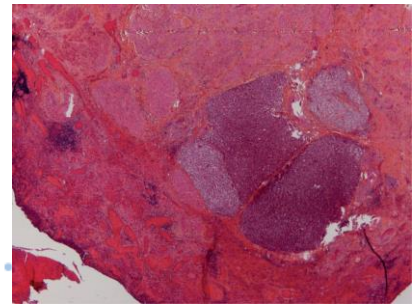
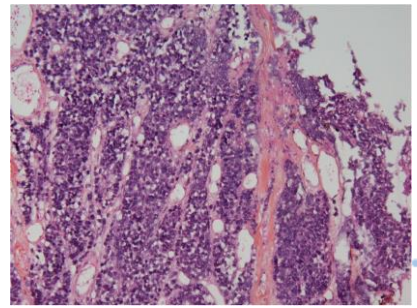


Figure 2 | **Glandular variant. a** | Resection specimen of an enteric adenocarcinoma (haematoxylin, eosin, and saffron stain (HES), magnification ×25). **b** | The mucinous type (HES, magnification ×200).

- Neuroendocrine
  - <1%
  - Similar to Small Cell Lung Cancer
  - Small cell = most common neuroendocrine
  - Large cell, paraganglioma
  - May have adrenergic symptoms





Paraganglioma

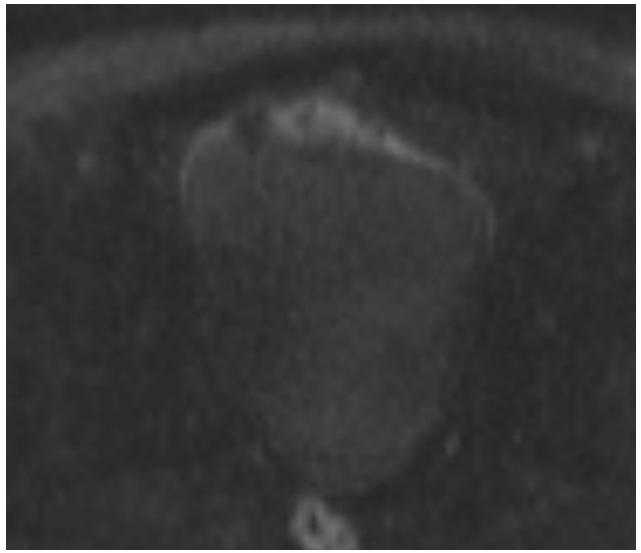
VESTFOLD HOSPITAL

Urachal carcinoma

- 10 % of adenocarcinoma of the bladder
- Sheldon/ MDA-criteria for diagnosis
- Sheldon classification (Stage)
  - *I. Confined to urachal mucosa*
  - *II. Confined to urachus*
  - *III. Local extension into*
    - *A. Bladder*
    - *B. Abdominal wall*
    - *C. Peritoneum*
    - *Local Viscera*
  - *IV. Metastasis to*
    - *A. regional LN*
    - *B. Distant sites*
- Treatment:
  - Partial = radical cystectomy(?)
  - LND + Umbilectomy
  - FLOX-chemo?

Table 1 Criteria for the diagnosis of urachal adenocarcinoma

(A) Mandatory criteria
Location of the tumor in the bladder dome and/or anterior wall
Epicenter of the carcinoma in the bladder wall
Absence of widespread cystitis cystica and/or cystitis glandularis beyond the dome or the anterior wall
Absence of a known primary elsewhere
(B) Optional criteria
Presence of urachal remnants in association with the tumor



Diffusion weigthed MRI og urachal adenocarcinoma

Development of Bladder Cancer

EUROPEAN UROLOGY 75 (2019) 18–22

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

European Association of Urology

Platinum Priority – Brief Correspondence
Editorial by Jon L. Griffin on pp. 23–24 of this issue

Intratumoral Heterogeneity of Bladder Cancer by Molecular Subtypes and Histologic Variants

Joshua I. Warrick[a,b,], Gottfrid Sjödahl[c], Matthew Kaag[b], Jay D. Raman[b], Suzanne Merrill[b], Lauren Shuman[a], Guoli Chen[a], Vonn Walter[d], David J. DeGraff[a,b]*

[a] Department of Pathology—Penn State College of Medicine, Hershey, PA, USA; [b] Department of Surgery, Division of Urology—Penn State College of Medicine, Hershey, PA, USA; [c] Division of Urological Research, Department of Translational Medicine, Lund University, Skåne University Hospital, Malmö, Sweden; [d] Department of Public Health Sciences, Penn State College of Medicine, Hershey, PA, USA

Article info

Article history:
Accepted September 1, 2018

Associate Editor:
James Catto

Statistical Editor:
Andrew Vickers

Keywords:
Molecular subtype
Histologic variant
Intratumoral heterogeneity

Abstract

Molecular subtyping may inform on prognosis and treatment response in bladder cancer. However, intratumoral molecular heterogeneity is not well studied in this disease and could complicate efforts to use molecular subtyping to guide patient management. To investigate intratumoral heterogeneity in bladder cancer, we examined molecular subtypes in a consecutive, retrospective cystectomy series of histologic variant bladder cancers and conventional urothelial carcinomas co-occurring with them. Molecular subtypes were assigned as per the approach reported by Lund University, an approach that incorporates cell cycle alterations and markers of differentiation, to give the urothelial-like, genomically unstable, basal-squamous, mesenchymal-like, and neuroendocrine-like subtypes. The majority (93%) of tumors were classified as urothelial like, genomically unstable, or basal squamous. Among patients with more than one tumor histology, 39% demonstrated molecular heterogeneity among the different tumor histologies. This was greatest for the basal-squamous subtype, 78% of which co-occurred with either urothelial-like or genomically unstable carcinoma (among cases with multiple histologies). In contrast, there was no co-occurrence of urothelial-like and genomically unstable carcinoma in the same patient. The findings indicate that bladder cancer is often molecularly heterogeneous, particularly in the basal-squamous subtype. This raises the concern for sampling error in laboratory tests that guide therapy based on molecular subtyping.

Patient summary: In this report, we investigated molecular diversity among different areas from the same tumor in patients with bladder cancer. We found that different areas from the same tumor are often molecularly different. We conclude that this biological diversity must be taken into account when interpreting clinical molecular tests performed on bladder cancer samples.

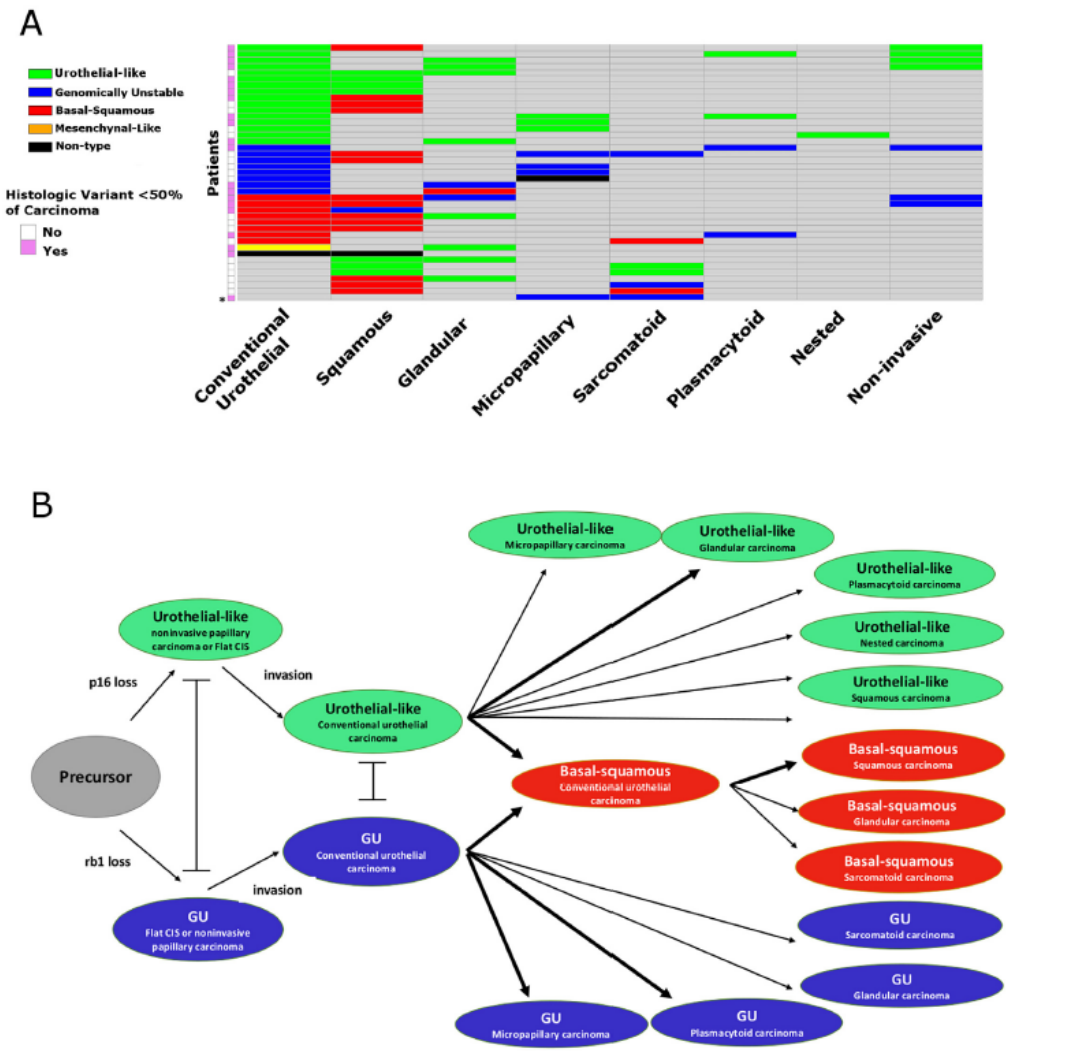


Fig. 2 – Molecular and histomorphologic heterogeneity in bladder cancer. (A) Histologic and molecular heterogeneity presented for each patient with multiple histologies; each row is an individual patient, and each column represents a different histology. Also indicated is whether histologic variant accounted for <50% of tumor burden, an observation relevant to inclusion in clinical trials. Noninvasive = either flat urothelial carcinoma in situ or noninvasive papillary urothelial carcinoma. *This cancer contained >50% conventional urothelial carcinoma, but immunohistochemistry failed for this histology and it was thus not subtyped. (B) Theoretical framework for evolution of bladder cancer. In this model, bladder cancer begins as early, noninvasive neoplasia. This precursor then loses expression of a major cell cycle regulator, either p16 or RB1. The tumor then invades as conventional urothelial carcinoma, either urothelial like or genomically unstable, either of which may evolve to basal-squamous carcinoma. Histologic variants evolve from these, through additional genomic alterations. Greater arrow thickness indicates increased probability that a case will follow the given evolutionary step. CIS = carcinoma in situ; GU = genomically unstable.

VESTFOLD HOSPITAL

Basis for response to chemotherapy

Current Oncology Reports (2019) 21: 23
https://doi.org/10.1007/s11912-019-0772-8

GENITOURINARY CANCERS (DP PETRYLAK AND JW KIM, SECTION EDITORS)

Clinical and Genomic Considerations for Variant Histology in Bladder Cancer

Justin T. Matulay[1] · Vikram M. Narayan[1] · Ashish M. Kamat[1]

Published online: 26 February 2019

Abstract

Purpose of Review Urothelial carcinoma demonstrates remarkable plasticity in its ability to differentiate into divergent histologic subtypes in both a pure and mixed form. This review presents the most current data pertaining to bladder cancer with variant histology.

Recent Findings Recognition of bladder cancer variants has increased profoundly in the past two decades with their inclusion in the pathologic guidelines and increased awareness among pathologists and urologists. Most of the available literature consists of small single-institutional studies, but there is compelling evidence to support deviation from the normal urothelial carcinoma management pathways for certain subtypes. While traditionally diagnosed by microscopic appearance, next-generation sequencing and molecular profiling have enabled identification of genomic markers associated with specific variants that exist in tumors lacking classic histologic hallmarks. This genomic information holds promise for predicting response to specific treatments or even in the development of novel targeted therapies.

Summary Combining increased awareness of variant histology, its impact on clinical outcomes, and genomic data will result in a more nuanced treatment approach to reduce morbidity and optimize oncologic outcomes for our patients.

Keywords Bladder cancer · Variant histology · Molecular profiling

Introduction

Bladder cancer, the world's 10th most common malignancy, is often referred to synonymously with urothelial carcinoma (UC) since this is the histology in roughly 90% of cases [1, 2]. The urothelium of the bladder exhibits a remarkable ability for divergent differentiation resulting in several histologic variants of urothelial cell origin [3]. Classification is made based on microscopic cytoarchitectural appearance, and much of the nomenclature is borrowed from neoplasms of other organ sites with similar morphology [3, 4••]. It is important to define what exactly is meant by the term "variant histology" since it impacts the spectrum of disease and, for our purposes, any non-pure UC bladder cancer is considered a variant (Table 1).

Under the heading of variant histology, there are pure divergent histologies where a single morphologic subtype is present throughout without a distinct urothelial component, e.g., squamous cell carcinoma (SCC) of the bladder [4••]. If the divergent morphology occurs with at least some degree of typical UC, then the tumor is classified as urothelial carcinoma "with divergent differentiation." This distinction is important due to differences in prognosis and management (addressed later). It is worth mentioning that variant histology is not limited to the bladder but has been described throughout the urothelial-lined surfaces of the urinary tract including 9 to 24% of nephroureterectomy specimens; however, the body of literature is very limited for extravesical sites [5–7].

Impact of Variant Histology

The incidence of variant histology appears to be increasing over time; however, this is due in large part to increased recognition of histologic subtypes and improved reporting. On blinded

This article is part of the Topical Collection on *Genitourinary Cancers*

✉ Ashish M. Kamat
akamat@mdanderson.org

Justin T. Matulay
jtmatulay@mdanderson.org

Vikram M. Narayan
vmnarayan@mdanderson.org

[1] Department of Urology, Division of Surgery, University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd., Unit 1373, Houston, TX 77030, USA

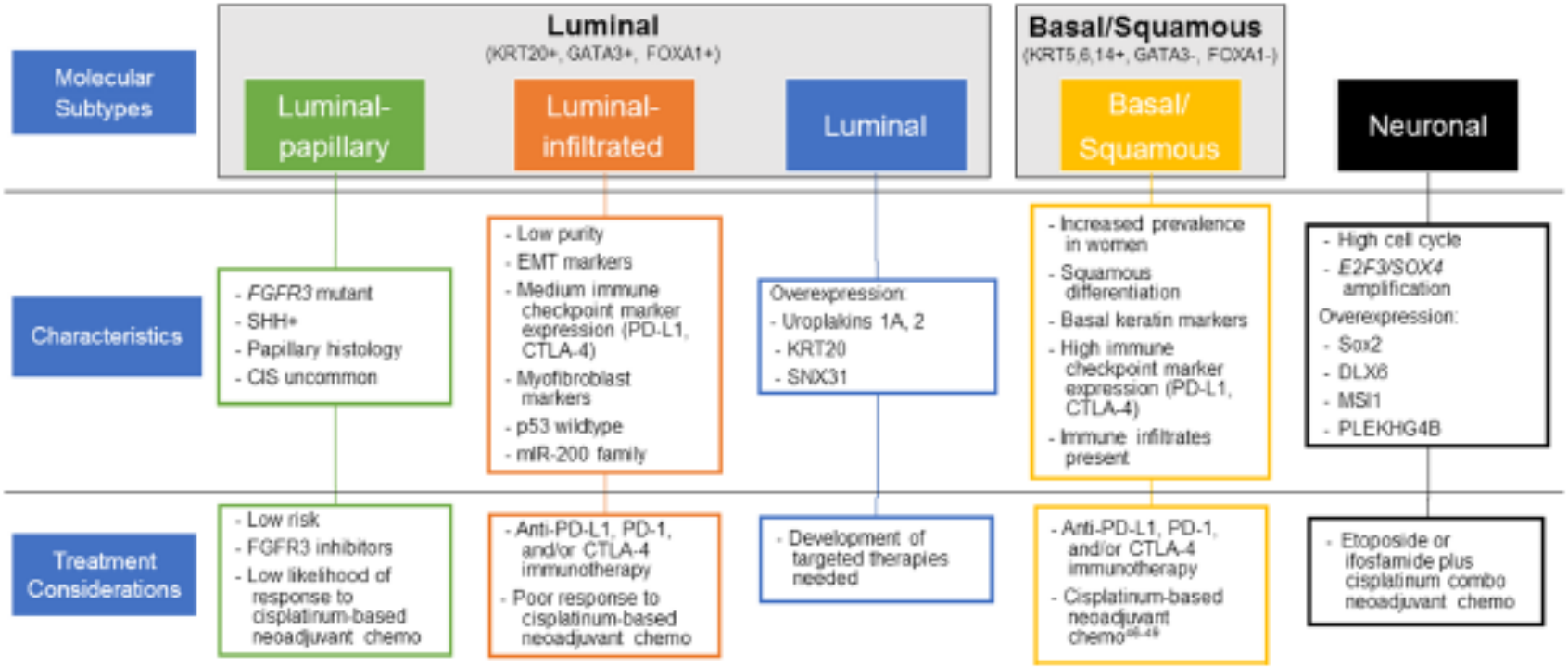


Fig. 1 Molecular subtypes of muscle invasive bladder cancer. Characteristics and specific treatment considerations are listed for each category. Reprinted from *Cell*, Volume 171, Issue 3, Robertson AG, Kim J, Al-Ahmadie H, et al., *Comprehensive Molecular Characterization of Muscle-Invasive Bladder Cancer*, pages 540–556 e525, ©2017, with permission from Elsevier

VESTFOLD HOSPITAL

Effect of Neo-adjuvant Chemo in Mixed Variant

Scosurev E, et al. BJU Int 2010; 108: 693-700

Do mixed histological features affect survival benefit from neoadjuvant platinum-based combination chemotherapy in patients with locally advanced bladder cancer? A secondary analysis of Southwest Oncology Group-Directed Intergroup Study (S8710)

BJUI

Emil Scosyrev[1], Benjamin W. Ely[2], Edward M. Messing[1], V.O. Speights[3], H. Barton Grossman[4], David P. Wood[5], Ralph W. de Vere White[6], Nicholas J. Vogelzang[7], Donald L. Trump[8], Ronald B. Natale[9], Catherine M. Tangen[2], E. David Crawford[10] and Ian M. Thompson[11]

[1]University of Rochester, Rochester, NY, [2]Southwest Oncology Group Statistical Center, Seattle, WA, [3]Scott and White Clinic, Temple, TX, [4]M.D. Anderson Cancer Center, Houston, TX, [5]University of Michigan, Ann Arbor, MI, [6]University of California at Davis, Sacramento, CA, [7]Comprehensive Cancer Centers of Nevada, Las Vegas, NV (Southwest Oncology Group and previously, Cancer and Leukemia Group B), [8]Roswell Park Cancer Institute, Buffalo, NY (Eastern Cooperative Oncology Group), [9]Cedars-Sinai Comprehensive Cancer Center, Los Angeles, CA, and [10]University of Colorado, Aurora, CO, and [11]University of Texas Health Science Center, San Antonio, TX, USA

Accepted for publication 1 September 2010

Study Type – Therapy (RCT)
Level of Evidence 1b

What's known on the subject? and What does the study add?

In a meta-analysis of randomized trials, neoadjuvant platinum-based combination chemotherapy administered before definitive local treatment improved survival of patients with muscle-invasive bladder cancer compared with definitive local treatment alone. However, it was not known whether chemotherapy was equally effective for pure urothelial carcinoma versus urothelial carcinoma with mixed histological features, such as squamous or glandular differentiation.

To address this question we performed a secondary analysis of the Southwest Oncology Group-directed intergroup randomized trial S8710 of neoadjuvant methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) followed by cystectomy versus cystectomy alone for treatment of locally advanced urothelial cancer of the bladder. Our findings suggest that presence of squamous or glandular differentiation does not confer resistance to combination chemotherapy with MVAC and in fact may be an indication for the use of neoadjuvant chemotherapy before radical cystectomy.

OBJECTIVE

- To determine whether the effect of neoadjuvant chemotherapy with methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) on the survival of patients with locally advanced urothelial carcinoma (UC) of the bladder treated with radical cystectomy varies with the presence of non-urothelial components in the tumour.

PATIENTS AND METHODS

- This is a secondary analysis of the Southwest Oncology Group-directed intergroup randomized trial S8710 of neoadjuvant MVAC followed by cystectomy versus cystectomy alone for treatment of locally advanced UC of the bladder.
- For the purpose of these analyses, tumours were classified based on the presence of non-urothelial components as either pure UC ($n = 236$) or mixed tumours ($n = 59$). Non-urothelial components included squamous and glandular differentiation.
- Cox regression models were used to estimate the effect of neoadjuvant MVAC on all-cause mortality for patients with pure UC and for patients with mixed tumours, with adjustment for age and clinical stage.

RESULTS

- There was evidence of a survival benefit from chemotherapy in patients with mixed tumours (hazard ratio 0.46; 95% CI 0.25–0.87; $P = 0.02$). Patients with pure UC had improved survival on the chemotherapy arm but the survival benefit was not statistically significant (hazard ratio 0.90; 95% CI 0.67–1.21; $P = 0.48$).
- There was marginal evidence that the survival benefit of chemotherapy in patients with mixed tumours was greater than it was for patients with pure UC (interaction $P = 0.09$).

CONCLUSION

- Presence of squamous or glandular differentiation in locally advanced UC of the bladder does not confer resistance to MVAC and in fact may be an indication for the use of neoadjuvant chemotherapy before radical cystectomy.

KEYWORDS

urothelial carcinoma, mixed histological features, neoadjuvant chemotherapy

TABLE 5 Estimated five-year survival probabilities

		Pure UC		Mixed Tumors	
Stage	Treatment	5-yr survival*	95% CI	5-yr survival*	95% CI
cT2	Cystectomy-only	0.61	(0.52, 0.72)	0.54	(0.39, 0.74)
cT2	MVAC + cystectomy	0.64	(0.55, 0.74)	0.73	(0.62, 0.86)
cT3-T4a	Cystectomy-only	0.42	(0.34, 0.53)	0.34	(0.21, 0.55)
cT3-T4a	MVAC + cystectomy	0.46	(0.37, 0.56)	0.58	(0.45, 0.75)

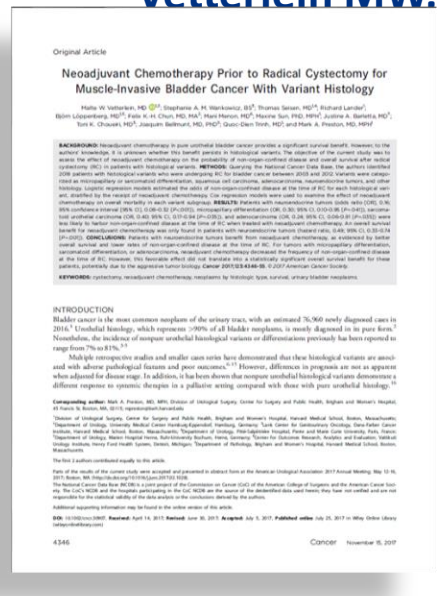
**Adjusted for age by conditional standardization (conditioned on the average age of all patients in the study); cT2 = clinical stage T2, cT3-T4a = clinical stage T3-T4a. UC, urothelial carcinoma; MVAC, methotrexate, vinblastine, doxorubicin and cisplatin.*

- Subgroup analysis from SWOG-S8710
- Randomized:
  - RC: 121 UTC + 27 Mixed
  - NAC + RC: 115 UTC + 32 Mixed
- **Benefit of NAC in mixed variant, e.g. squamous and glandular differentiation**

VESTFOLD HOSPITAL

Effect of NeoAdjuvans in Pure Variant

- Vetterlein MW. et al. Cancer 2017; Nov: 4346-4355



Original Article

Neoadjuvant Chemotherapy Prior to Radical Cystectomy for Muscle-Invasive Bladder Cancer With Variant Histology

Malte W. Vetterlein, MD[1,2]; Stephanie A. M. Wankowicz, BS[3]; Thomas Seisen, MD[1,4]; Richard Lander[3]; Björn Löppenberg, MD[1,2]; Fadie K. H. Chun, MD, PhD[1]; Hani Menon, MD[3]; Maxine Sun, PhD, MPH[3]; Justine A. Barletta, MD[3]; Toni K. Choueiri, MD[3]; Joaquim Bellmunt, MD, PhD[3]; Quoc-Dien Trinh, MD[3]; and Mark A. Preston, MD, MPH[3]

BACKGROUND: Neoadjuvant chemotherapy in pure urothelial bladder cancer provides a significant survival benefit. However, to the authors' knowledge, it is unknown whether this benefit persists in histological variants. The objective of the current study was to assess the effect of neoadjuvant chemotherapy on the probability of non-organ-confined disease and overall survival after radical cystectomy (RC) in patients with histological variants. **METHODS:** Querying the National Cancer Data Base, the authors identified 2018 patients with histological variants who were undergoing RC for bladder cancer between 2003 and 2012. Variants were categorized as micropapillary or sarcomatoid differentiation, squamous cell carcinoma, adenocarcinoma, neuroendocrine tumors, and other histology. Logistic regression models estimated the odds of non-organ-confined disease at the time of RC for each histological variant, stratified by the receipt of neoadjuvant chemotherapy. Cox regression models were used to examine the effect of neoadjuvant chemotherapy on overall mortality in each variant subgroup. **RESULTS:** Patients with neuroendocrine tumors (odds ratio [OR], 0.16; 95% confidence interval [95% CI], 0.08-0.32; $P<.001$), micropapillary differentiation (OR, 0.30; 95% CI, 0.10-0.93; $P=.04$), sarcomatoid urothelial carcinoma (OR, 0.40; 95% CI, 0.17-0.94; $P=.036$), and adenocarcinoma (OR, 0.24; 95% CI, 0.08-0.81; $P=.020$) were less likely to harbor non-organ-confined disease at the time of RC when treated with neoadjuvant chemotherapy. An overall survival benefit for neoadjuvant chemotherapy was only found in patients with neuroendocrine tumors (hazard ratio, 0.48; 95% CI, 0.30-0.74; $P<.001$). **CONCLUSIONS:** Patients with neuroendocrine tumors benefit from neoadjuvant chemotherapy, as evidenced by better overall survival and lower rates of non-organ-confined disease at the time of RC. For tumors with micropapillary differentiation, sarcomatoid differentiation, or adenocarcinoma, neoadjuvant chemotherapy decreased the frequency of non-organ-confined disease at the time of RC. However, this favorable effect did not translate into a statistically significant overall survival benefit for these patients, potentially due to the aggressive tumor biology. *Cancer* 2017;123:4346-55. © 2017 American Cancer Society.

KEYWORDS: cystectomy, neoadjuvant chemotherapy, neoplasms by histologic type, survival, urinary bladder neoplasms

INTRODUCTION

Bladder cancer is the most common neoplasm of the urinary tract, with an estimated 76,960 newly diagnosed cases in 2016.[1] Urothelial histology, which represents >90% of all bladder neoplasms, is mostly diagnosed in its pure form.[2] Nonetheless, the incidence of nonpure urothelial histological variants or differentiation previously has been reported to range from 7% to 81%.[3-5]

Multiple retrospective studies and smaller cases series have demonstrated that these histological variants are associated with adverse pathological features and poor outcomes.[6-13] However, differences in prognosis are not as apparent when adjusted for disease stage. In addition, it has been shown that nonpure urothelial histological variants demonstrate a different response to systemic therapies in a palliative setting compared with those with pure urothelial histology.[14]

Corresponding author: Mark A. Preston, MD, MPH, Division of Urological Surgery, Center for Surgery and Public Health, Brigham and Women's Hospital, 45 Francis St, Boston, MA, 02115, mpreston@partners.org

[1] Division of Urological Surgery, Center for Surgery and Public Health, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; [2] Department of Urology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [3] Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts; [4] Department of Urology, Pitié-Salpêtrière Hospital, Pierre and Marie Curie University, Paris, France; [5] Department of Urology, Marien Hospital Herne, Ruhr-University Bochum, Herne, Germany; [6] Center for Outcomes Research, Analytic and Evaluation, Yakkult Urology Institute, Henry Ford Health System, Detroit, Michigan; [7] Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts

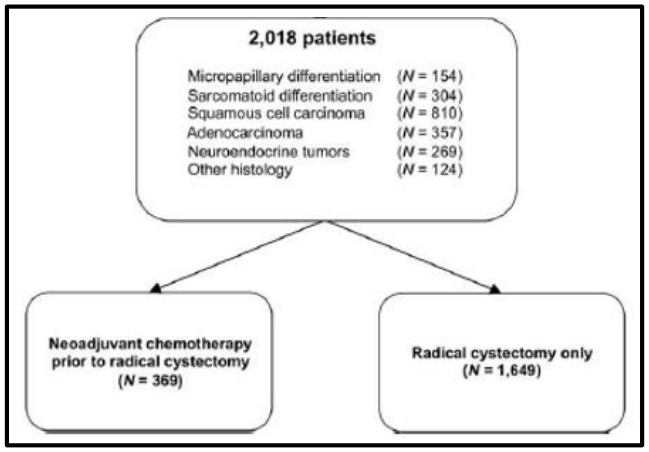
The first 2 authors contributed equally to this article.

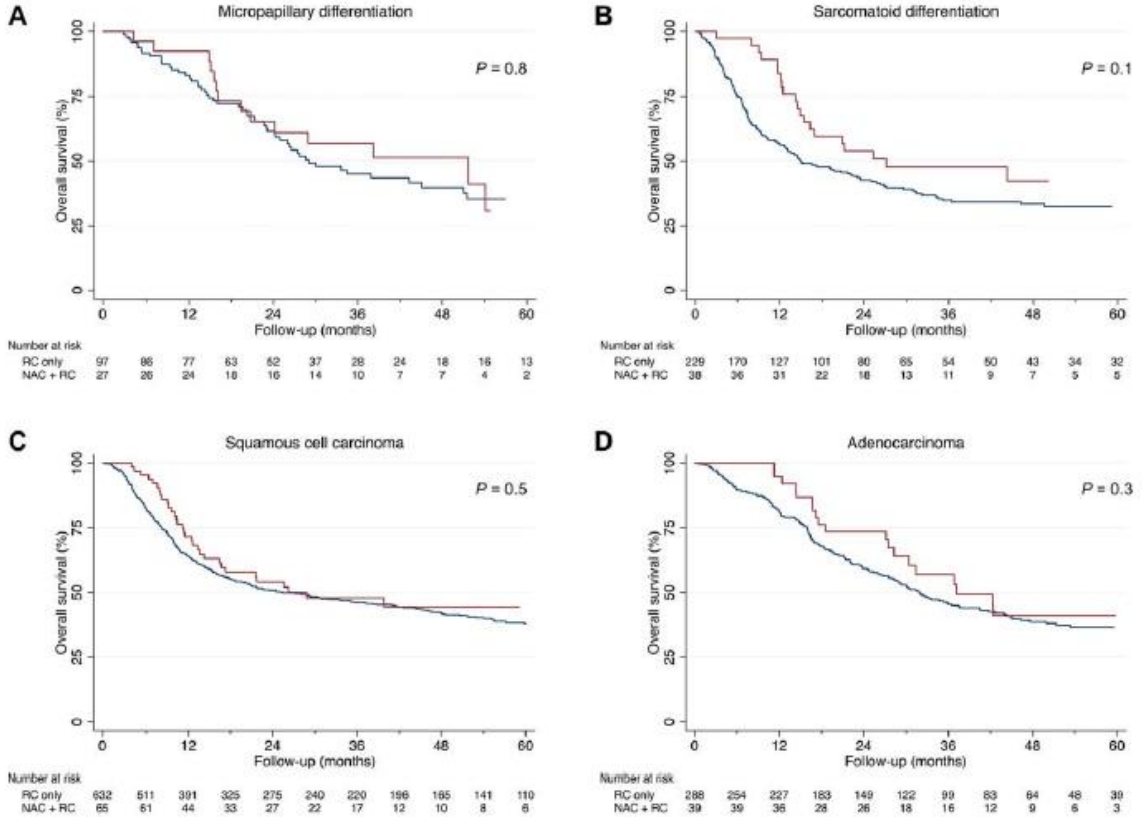
Parts of the results of the current study were accepted and presented in abstract form at the American Urological Association 2017 Annual Meeting, May 12-16, 2017, Boston, MA (https://doi.org/10.1016/j.juro.2017.03.1028).

The National Cancer Data Base (NCDB) is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. The CoC's NCDB and the hospitals participating in the CoC NCDB are the source of the deidentified data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors.

Additional supporting information may be found in the online version of this article.

DOI: 10.1002/cncr.30897, **Received:** April 14, 2017; **Revised:** June 30, 2017; **Accepted:** July 5, 2017, **Published online** July 25, 2017 in Wiley Online Library (wileyonlinelibrary.com)





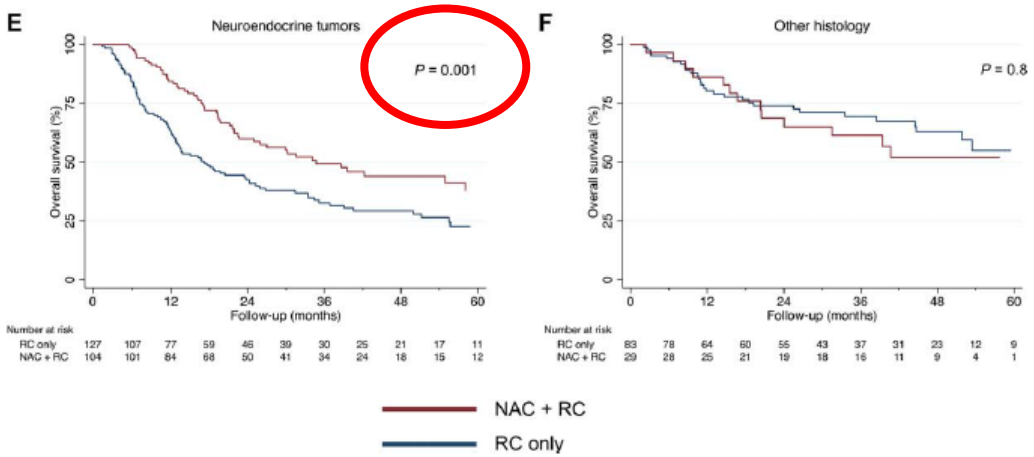


Figure 2. Kaplan-Meier analysis of overall survival in patients who received neoadjuvant chemotherapy (NAC) within 180 days before radical cystectomy (RC) versus RC only for the treatment of bladder cancer with (A) micropapillary differentiation, (B) sarcomatoid differentiation, (C) squamous cell carcinoma, (D) adenocarcinoma, (E) neuroendocrine tumors, and (F) other histology.

VESTFOLD HOSPITAL

Flow chart - MIBC

Willis, Kamat. Hematol Oncol Clin N Am 2015; 29: 237-52

Nonurothelial Bladder Cancer and Rare Variant Histologies

Daniel Willis, MD, FACS, Ashish M. Kamat, MD, MBBS*

KEYWORDS

• Urothelial carcinoma • Variant histology • Micropapillary bladder cancer
• Radical cystectomy • Chemotherapy • Treatment guidelines

KEY POINTS

- At present, radical cystectomy is a mainstay in the management of all bladder cancers, whether of conventional urothelial histology or variant.
- In some variants, it is clearly not enough and multimodal therapy is imperative; in other cases, systemic therapy might be ineffective or even detrimental if it leads to delay in surgery.
- Identification of variant histology is a critical part of bladder cancer staging because such histology may require appropriately tailored therapy.

INTRODUCTION

Although approximately 80% of bladder cancer is caused by "conventional" urothelial carcinoma (UC), the remaining 10% to 25% is the result of nonurothelial and "variants" of UC.[1,2] Although the term "variant histology" can sometimes be used in a variety of different capacities, for the current discussion variant histology refers to any bladder malignancy other than pure UC. This simplification includes UC with aberrant differentiation in which the tumor arises from a common urothelial stem cell as well as "non-urothelial" carcinoma, which is the result of metaplasia. In reality, these histologic descriptions are based on morphologic features from hematoxylin and eosin–stained pathologic sections with little insight into their biologic derivative. Furthermore, mixed histologies are often present (including so-called urothelial and nonurothelial carcinomas), for which the term variant histology is generally used. Box 1 describes the

Disclosure: Dr Kamat: FKD Industries Research Funding, Photocure Advisory Board, Bioniche Consultant, Sanofi Advisory Board, Merck Advisory Board, Abbott Molecular Consultant, Therealese Consultant, Heat Biologics Research Funding.
The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 1373 Houston, TX 77030, USA
* Corresponding author. The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 1373, Houston, TX 77030, USA.
E-mail address: akamat@mdanderson.org

Hematol Oncol Clin N Am 29 (2015) 237–252
http://dx.doi.org/10.1016/j.hoc.2014.10.011 hemonc.theclinics.com
0889-8588/15/$ – see front matter

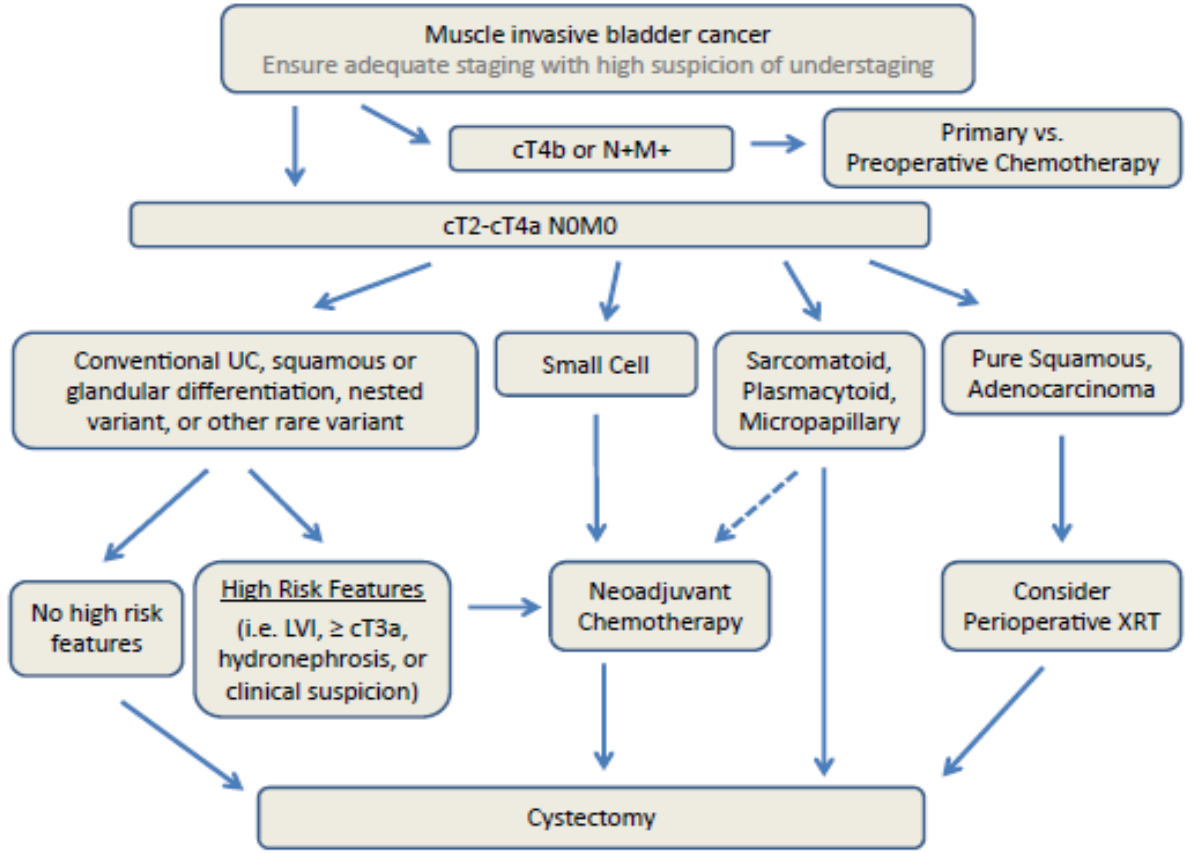


Fig. 2. Management of muscle-invasive bladder cancer and variant histology. Consider neoadjuvant chemotherapy for select patients. LVI, lymphatic invasion; UC, urothelial carcinoma; XRT, x-ray therapy.

VESTFOLD HOSPITAL

Flow chart – Non-MIBC

Willis, Kamat. Hematol Oncol Clin N Am 2015; 29: 237-52

Nonurothelial Bladder Cancer and Rare Variant Histologies

Daniel Willis, MD, FACS, Ashish M. Kamat, MD, MBBS*

KEYWORDS

• Urothelial carcinoma • Variant histology • Micropapillary bladder cancer
• Radical cystectomy • Chemotherapy • Treatment guidelines

KEY POINTS

- At present, radical cystectomy is a mainstay in the management of all bladder cancers, whether of conventional urothelial histology or variant.
- In some variants, it is clearly not enough and multimodal therapy is imperative; in other cases, systemic therapy might be ineffective or even detrimental if it leads to delay in surgery.
- Identification of variant histology is a critical part of bladder cancer staging because such histology may require appropriately tailored therapy.

INTRODUCTION

Although approximately 80% of bladder cancer is caused by "conventional" urothelial carcinoma (UC), the remaining 10% to 25% is the result of nonurothelial and "variants" of UC.[1,2] Although the term "variant histology" can sometimes be used in a variety of different capacities, for the current discussion variant histology refers to any bladder malignancy other than pure UC. This simplification includes UC with aberrant differentiation in which the tumor arises from a common urothelial stem cell as well as "non-urothelial" carcinoma, which is the result of metaplasia. In reality, these histologic descriptions are based on morphologic features from hematoxylin and eosin–stained pathologic sections with little insight into their biologic derivative. Furthermore, mixed histologies are often present (including so-called urothelial and nonurothelial carcinomas), for which the term variant histology is generally used. Box 1 describes the

Disclosure: Dr Kamat: FKD Industries Research Funding, Photocure Advisory Board, Bioniche Consultant, Sanofi Advisory Board, Merck Advisory Board, Abbott Molecular Consultant, Theralese Consultant, Heat Biologics Research Funding.
The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 1373 Houston, TX 77030, USA
* Corresponding author. The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 1373, Houston, TX 77030, USA.
E-mail address: akamat@mdanderson.org

Hematol Oncol Clin N Am 29 (2015) 237–252
http://dx.doi.org/10.1016/j.hoc.2014.10.011 hemonc.theclinics.com
0889-8588/15/$ – see front matter

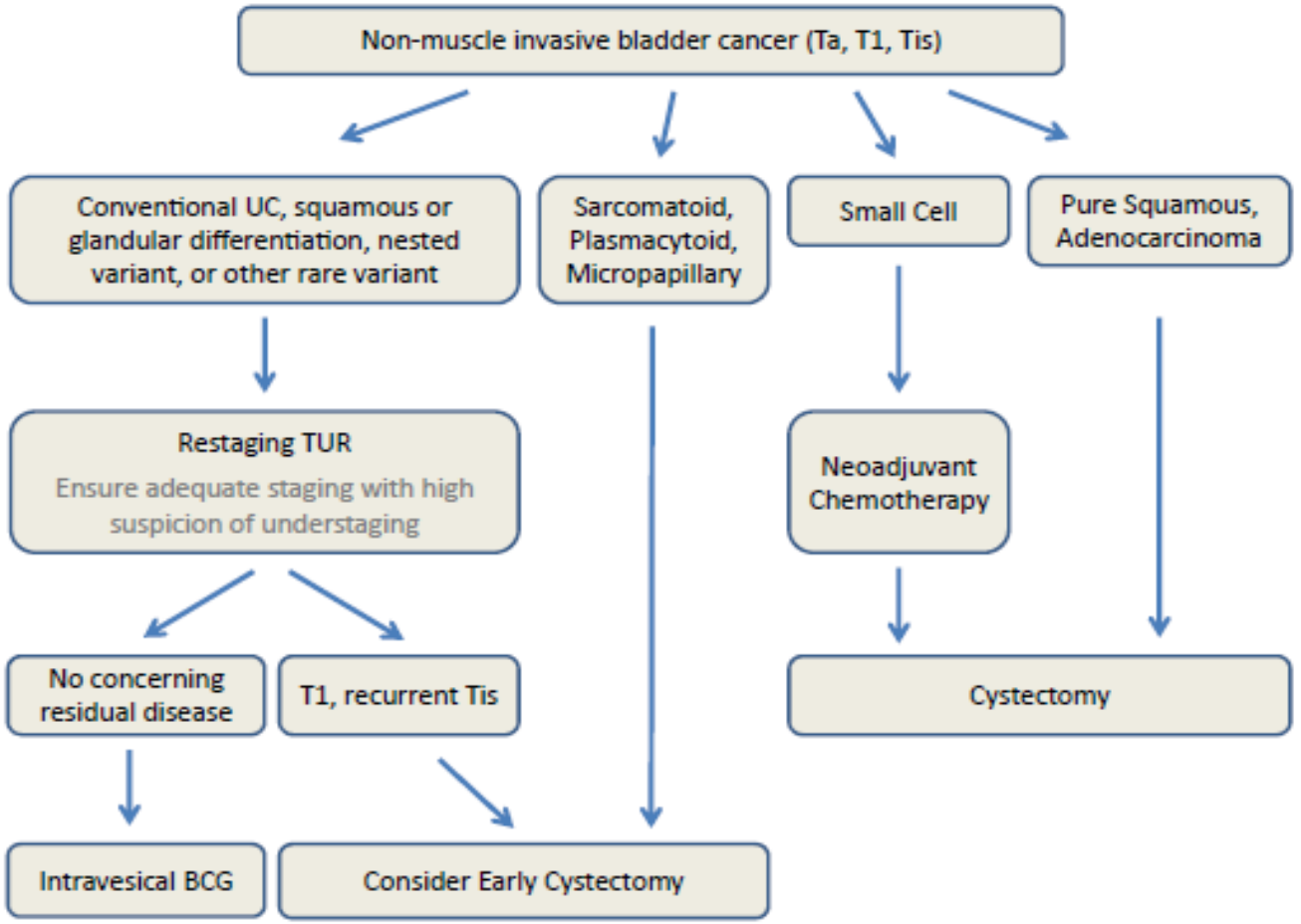


Fig. 1. Management of non–muscle-invasive and variant bladder cancer. BCG, Bacillus Calmette-Guerin; TUR, transurethral resection; UC, urothelial carcinoma.

VESTFOLD HOSPITAL

(chemo)Radiation in mixed histology BCa

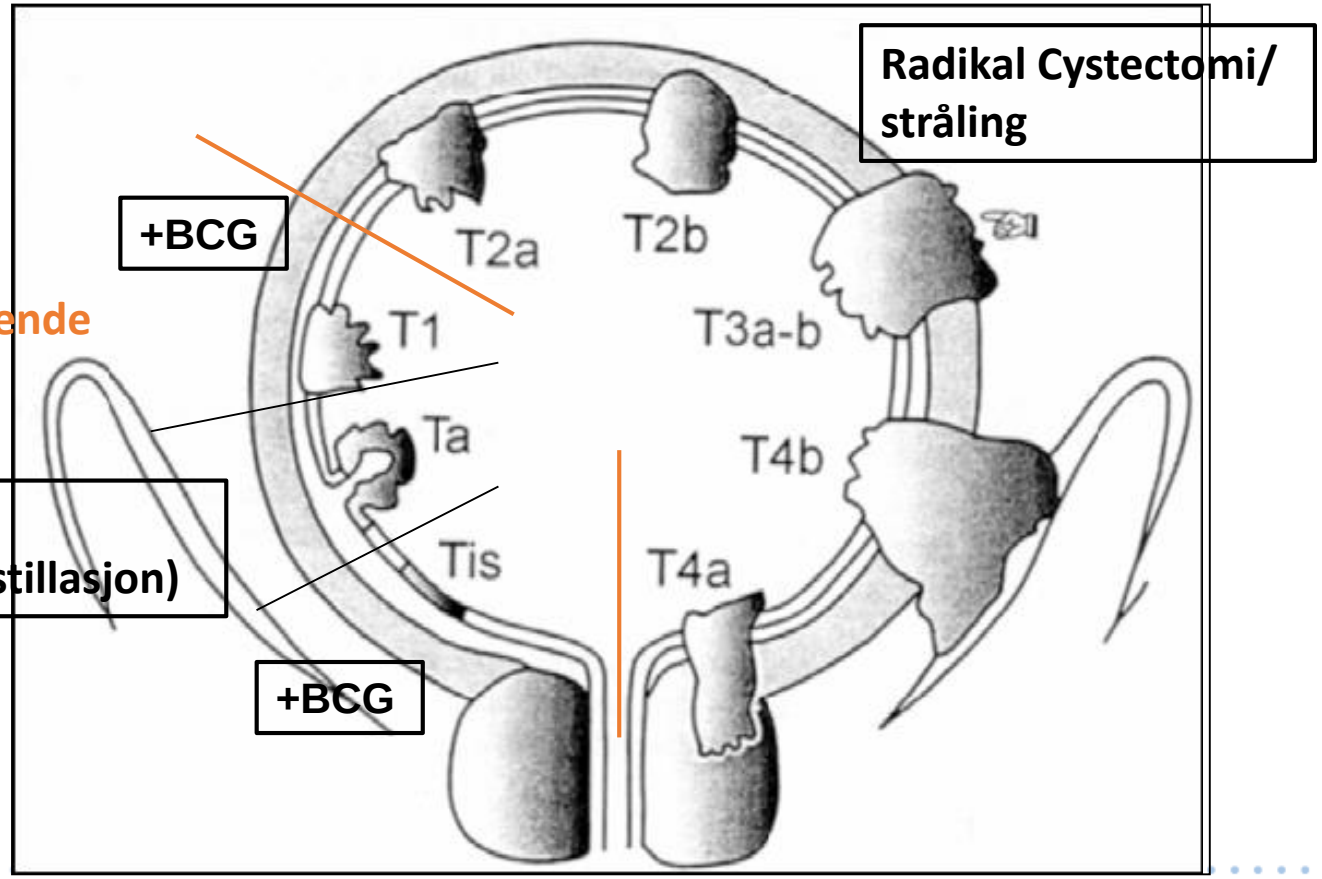
- Hardly mentioned in the reviews
- May be part of bladder preserving strategy in neuroendocrine carcinoma
  - Combined with Ethoposide-Cisplatin based Neo-Adjuvans
  - Trimodal therapy in small cell carcinoma has shown «fairly equivalent outcomes on small retrospective cohorts with short FU»
  - Prophylactic radiation to brain have been proposed, but is not established
- Adjuvant radiation after cystectomi for adenocarcinoma (and squamous) may be of value
  - Predisposition of local recurrence

Behandling av blærekreft

Muskelinfiltrerende

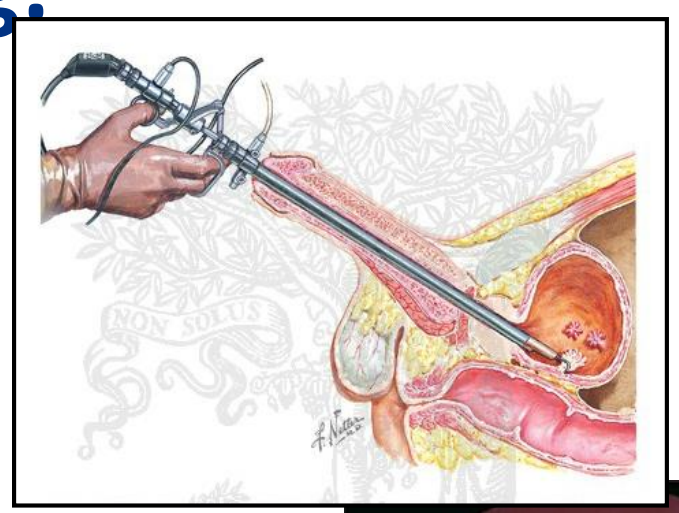
Ikke-muskelinfiltrerende

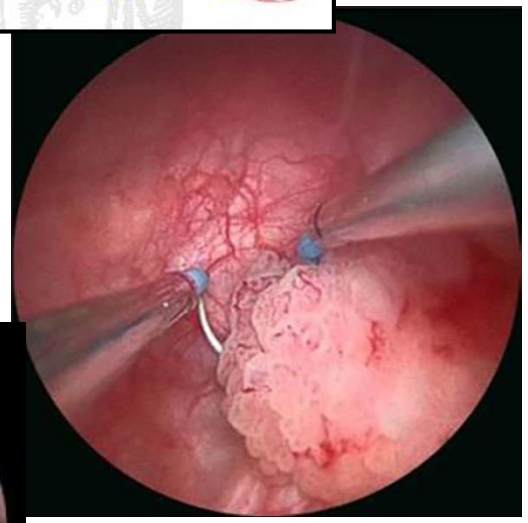
75-85%

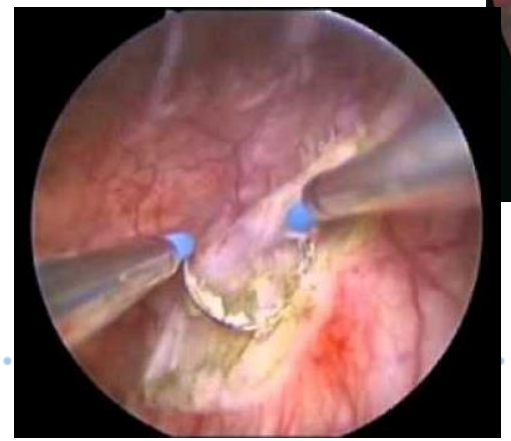


Primær behandling: TUR-B

- **T**rans**U**rethral **R**eseksjon av **B**lære
- 1.linje behandling av «alle» stadier!
- Det vanligste onkologiske inngrepet i Norge
- Utbredt i alle landets urologiske avdelinger
- Et «enkelt» inngrep?
- Også tilbakefall (recurence) identifiseres ved cystoskopi





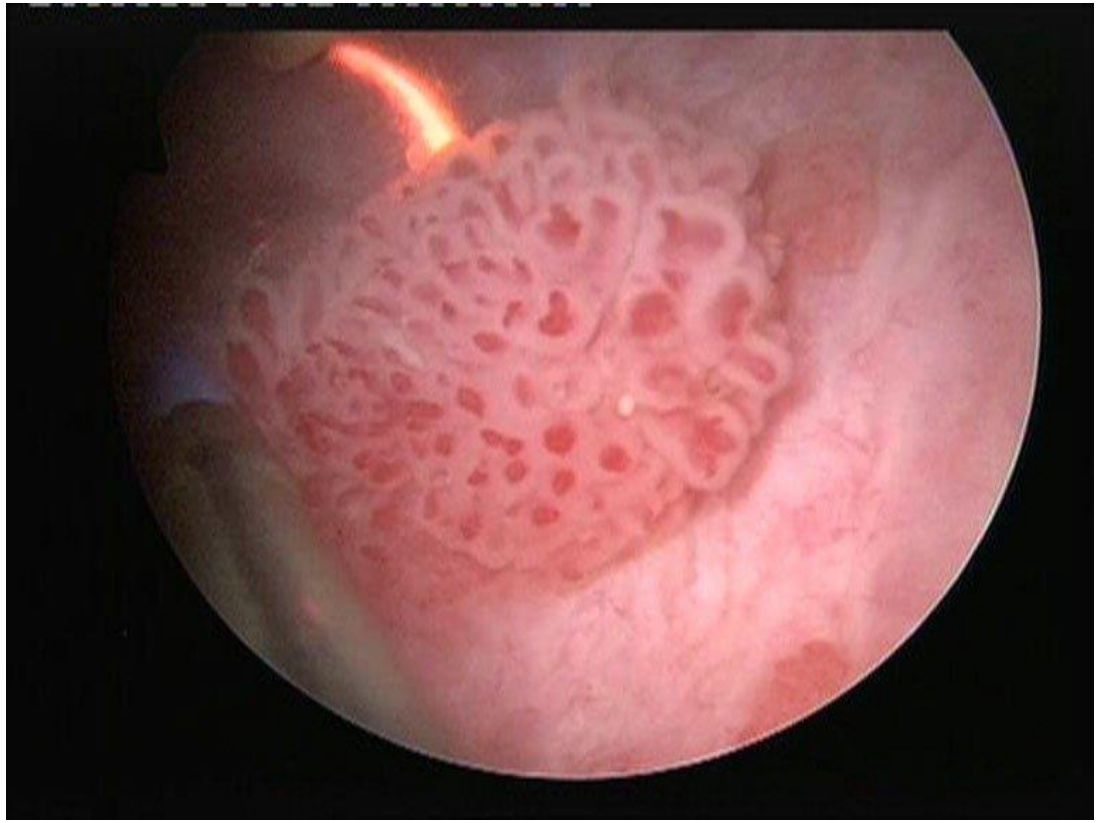


Skagerak blærekreftgruppe: «*<u>30 % av pasientene er pT0</u> i preparatet etter TUR-B utført pga mistanke om recurence»*

TURB - Hensikt

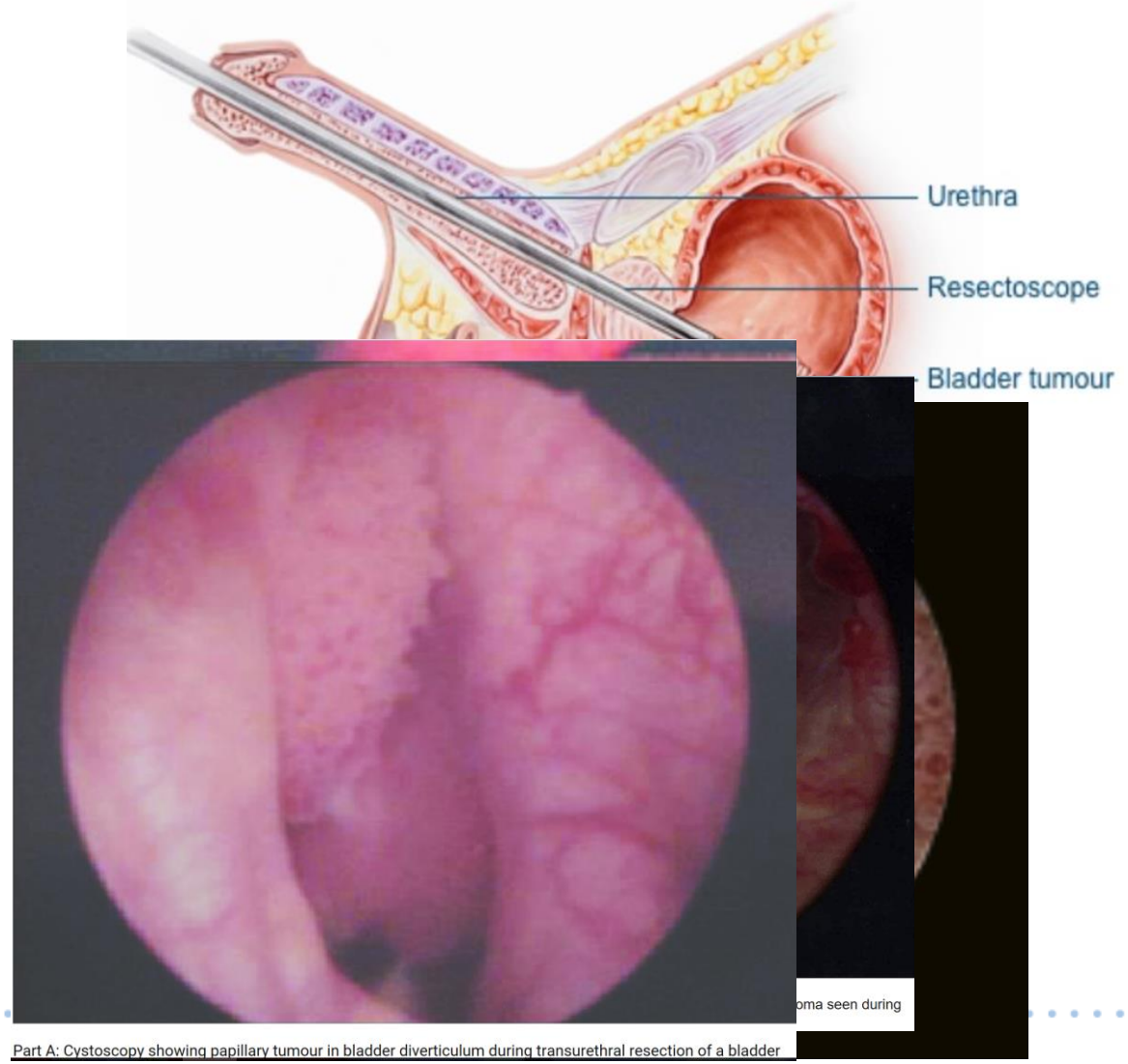
Biopsi & Behandling

- Stille diagnose
- Finne histologisk stadium
- Radikalt fjerne NMIBC
- Palliativ behandling ved MIBC



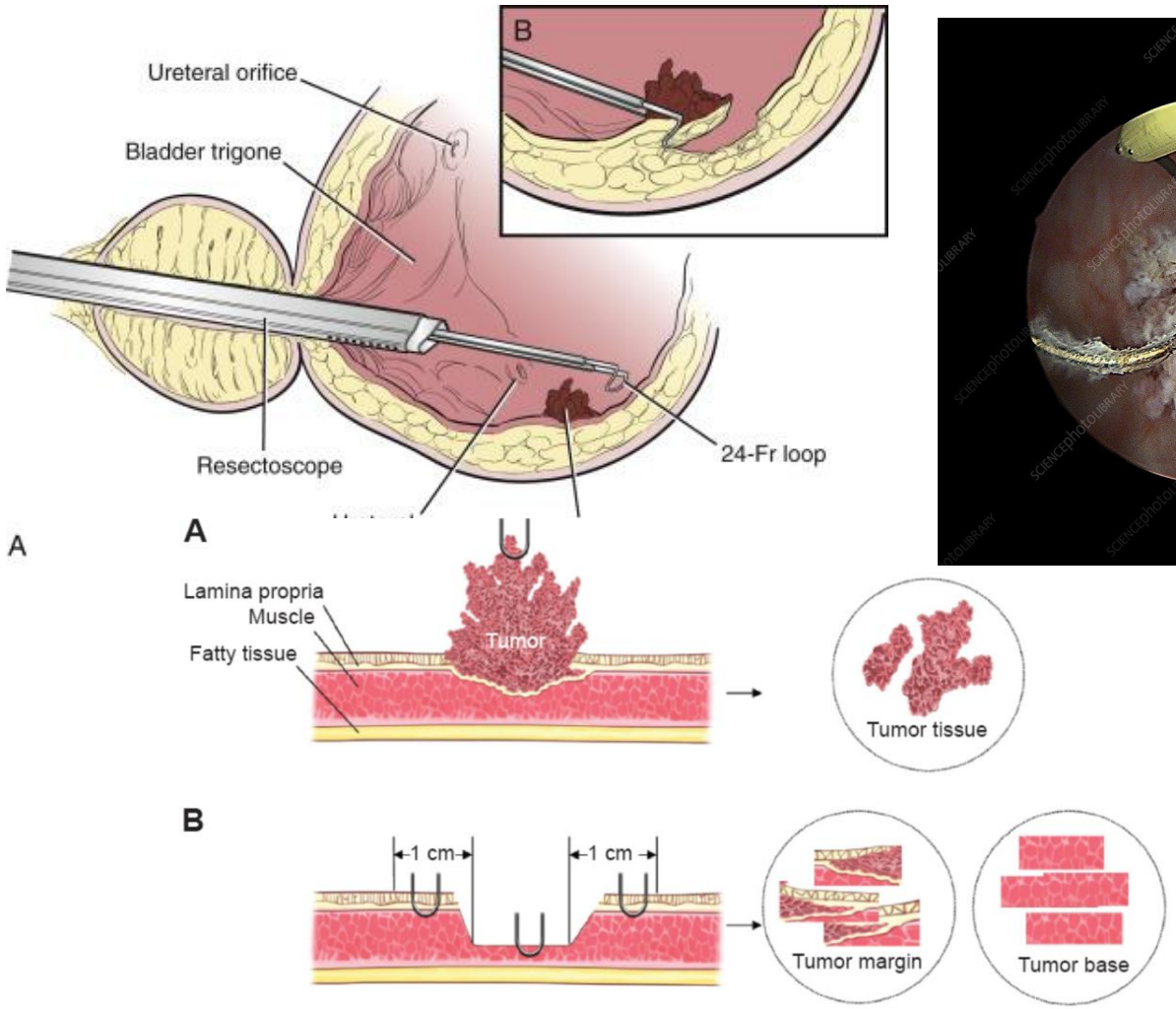
TURB - En krevende prosedyre

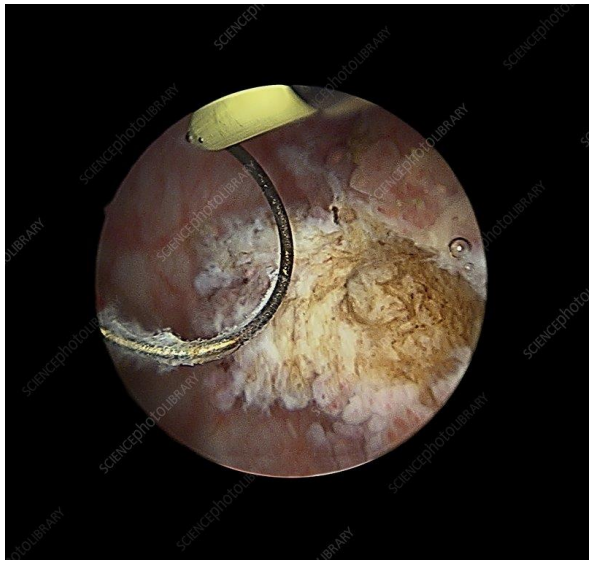
- Prosedyre i narkose evt. spinal
- Muskelrelaksasjon
- Mono eller bipolar strømslynge
- Skjærer tumor i mindre deler
- Evakuere tumor via resektoskopet
- Skjærestrøm og koagulasjonsstrøm
- Bimanuell palpasjon



Part A: Cystoscopy showing papillary tumour in bladder diverticulum during transurethral resection of a bladder

TURB – Brudd med onkologiske prinsipper?





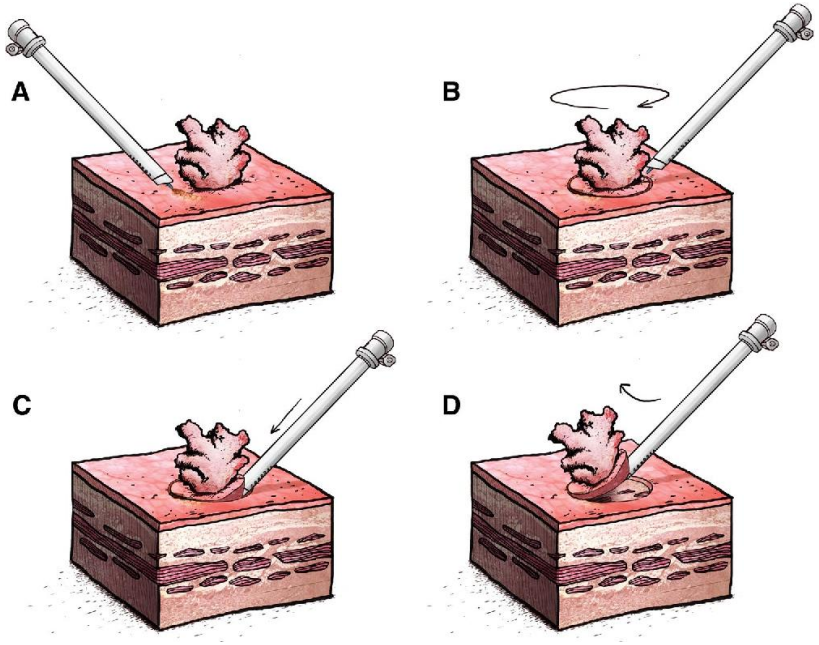
Utfordringer:

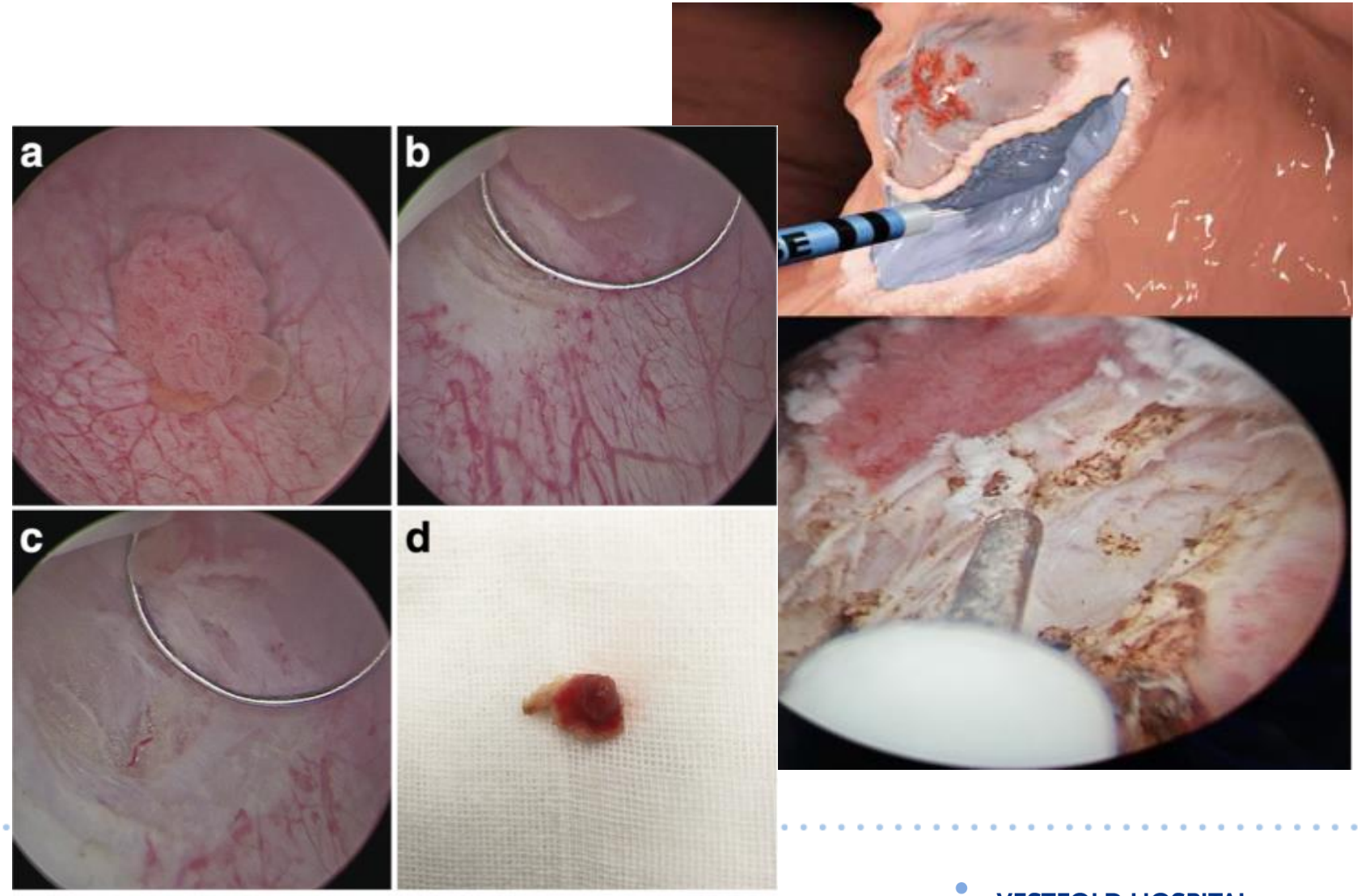
- Fare for perforasjon
  - Implantasjon/ spredning
  - Mitomycin-komplikasjoner
- Ufullstendig reseksjon
  - Større utbredelse enn synlig
- Varmeskadet vev
- Høy rekurrens-rate
  - Sirkulerende tumorvev
  - Residual tumor

Figure 1 A flow chart of the extensive transurethral resection procedure.
Notes: (**A**) Remove the entire visible tumor and then collect all the tumor tissue specimens. (**B**) Get additional specimens of tumor base and margin (tumor margin means at least 1 cm around bladder tumor).

VESTFOLD HOSPITAL

Fremskritt? – En bloc reseksjon





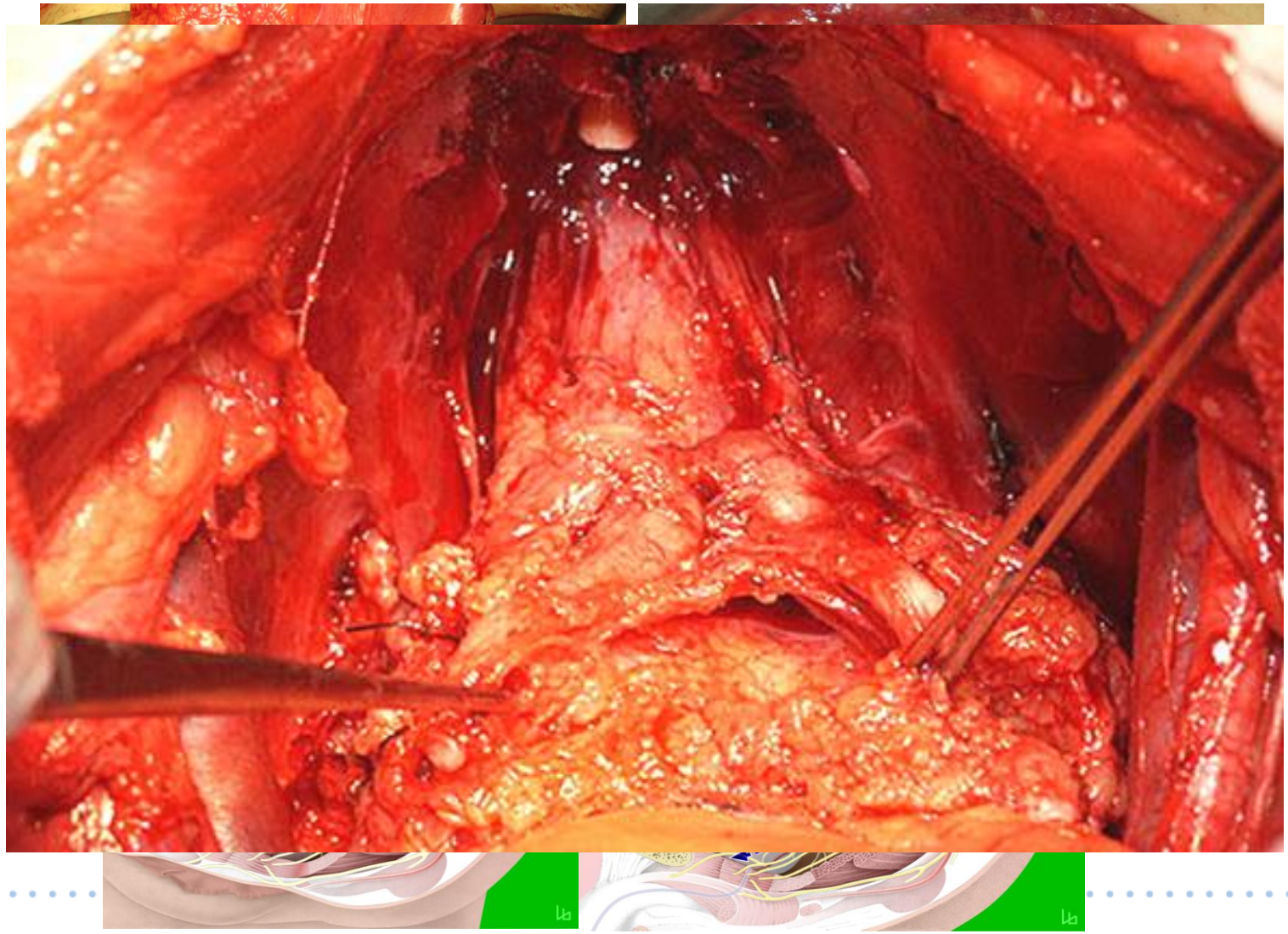
Behandling av muskelinfiltrerende blærekreft

Standard:

- **Radikal cystectomi**
  - Evt. Neo-adjuvant Cisplatin-basert kjemoterapi (MVAC)
  - Lymfeknutedisseksjon
  - Fjerne prostata/ genitalia interna
  - Evt. Nervesparende
  - **En Bloc reseksjon?**
  - Urinavledning

Alternativt:

- **Trimodal behandling**
  - TURB
  - Kjemoterapi
  - Stråling

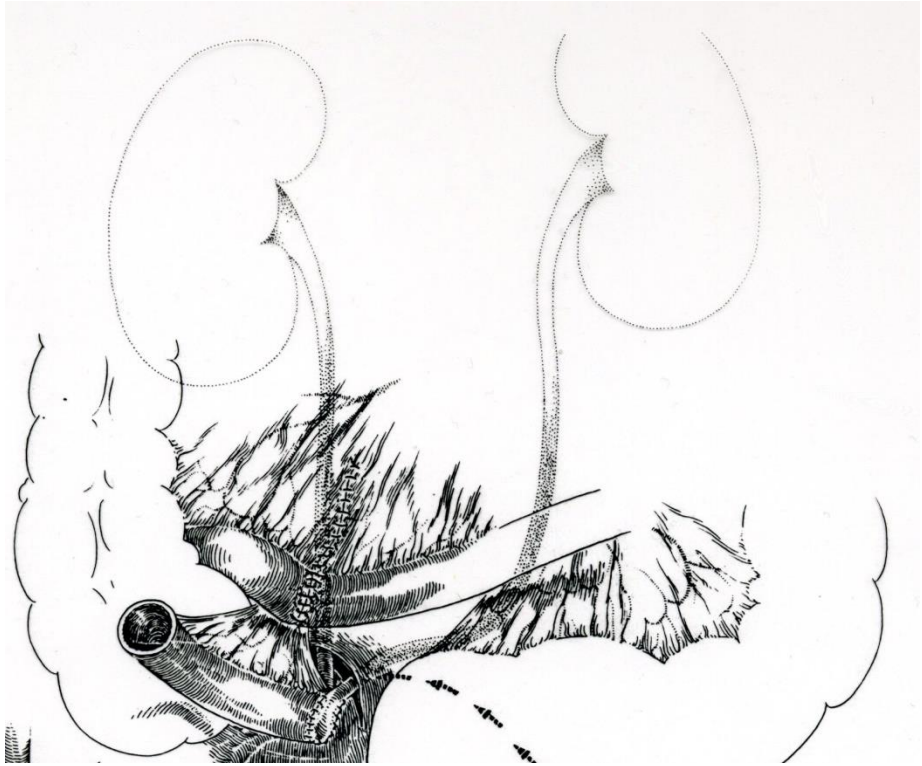


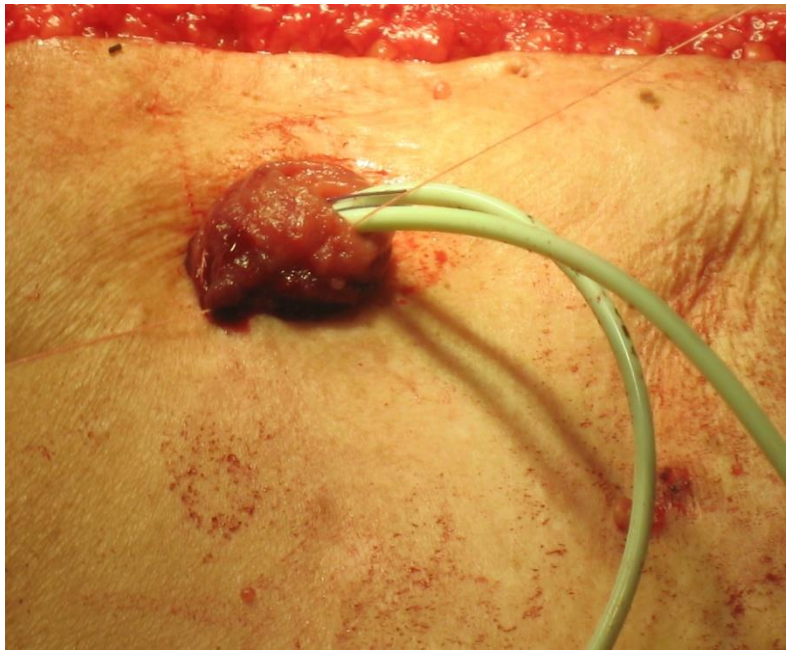
Nervesparende teknikk

VESTFOLD HOSPITAL

Urostomi

«Pasientens begrensinger i forhold til aktivitet sitter i hodet»





Ortotop neoblære a.m. Studer

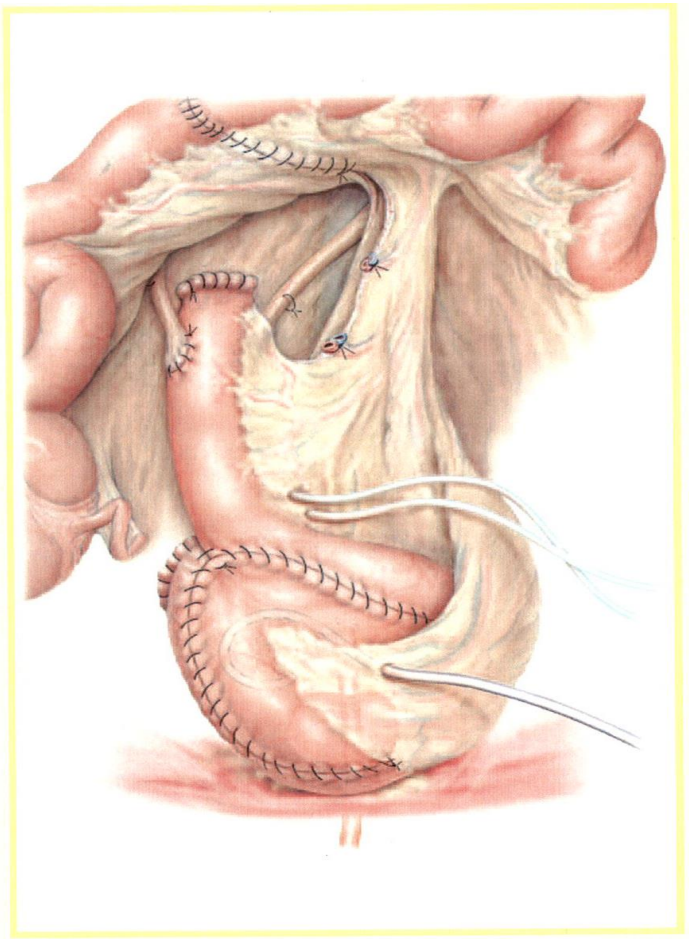
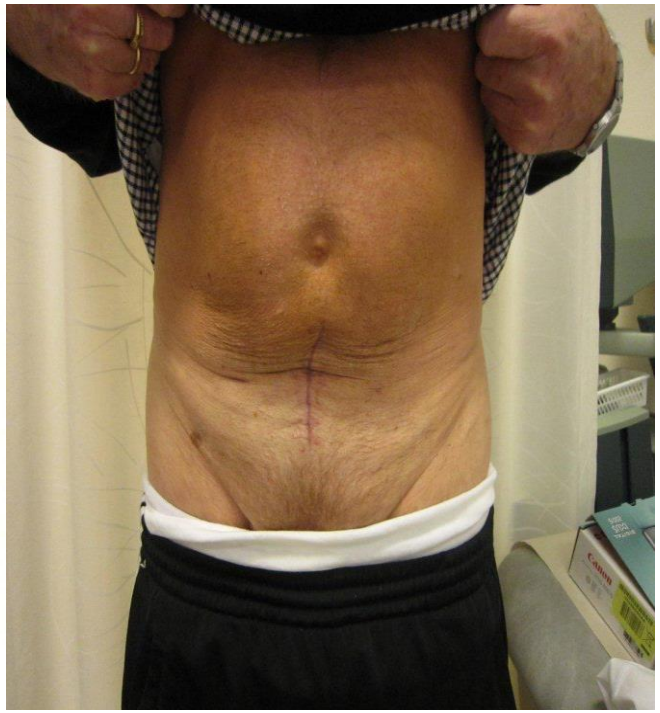


Figure 8

Before completely closing the pouch a 10 F cystostomy tube is placed into the reservoir through the fat of the mesoileum. The reservoir is flushed to remove any clots and checked for leakage.

«Fascinerende - men ny blære er dessverre noe ganske annet enn å bytte eksosanlegg på bilen»



Complications after ORC

- Most resent comprehensive study on complications following ORC (MSK-US):
  - 64 % all-grade (Clavien) 90d-complicationrate
  - 13 % grade 3-5
  - 67 % of complications during hospital stay
  - 58 % also experienced complications after leaving the hospital
  - 70 % of complications related to diversion
  - 30-d mortality 1,5 %, 90-d 2,7 %

EUROPEAN UROLOGY 55 (2009) 164–176

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

European Association of Urology

Bladder Cancer

Defining Early Morbidity of Radical Cystectomy for Patients with Bladder Cancer Using a Standardized Reporting Methodology

Ahmad Shabsigh[a], *Ruslan Korets*[a], *Kinjal C. Vora*[a], *Christine M. Brooks*[a], *Angel M. Cronin*[b], *Caroline Savage*[a], *Ganesh Raj*[a], *Bernard H. Bochner*[a], *Guido Dalbagni*[a], *Harry W. Herr*[a], *S. Machele Donat*[a,*]

[a] Department of Urology, Memorial Sloan-Kettering Cancer Center, New York, NY 10021, United States
[b] Departments of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY 10021, United States

Table 1 – Postoperative complication grading system

Grade	Definition
Grade 0	No event observed
Grade 1	Use of oral medications or bedside intervention
Grade2	Use of intravenous medications, total parenteral nutrition (TPN), enteral nutrition, or blood transfusion
Grade 3	Interventional radiology, therapeutic endoscopy, intubation, angiography, or operation
Grade 4	Residual and lasting disability requiring major rehabilitation or organ resection
Grade 5	Death of patient

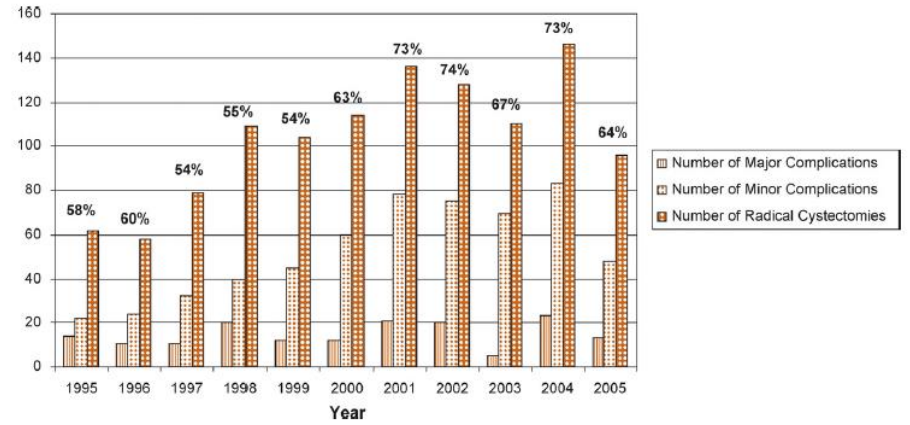


Fig. 1 – Number of major and minor radical cystectomy (RC) complications recorded relative to the number of RCs performed with the percentage of total complications by year.

HOSPITAL

Does robot assisted RC performe better?

Tan WS, et al PLOS ONE 2016. 11:e0166221;

Systemativ review of randomized trials

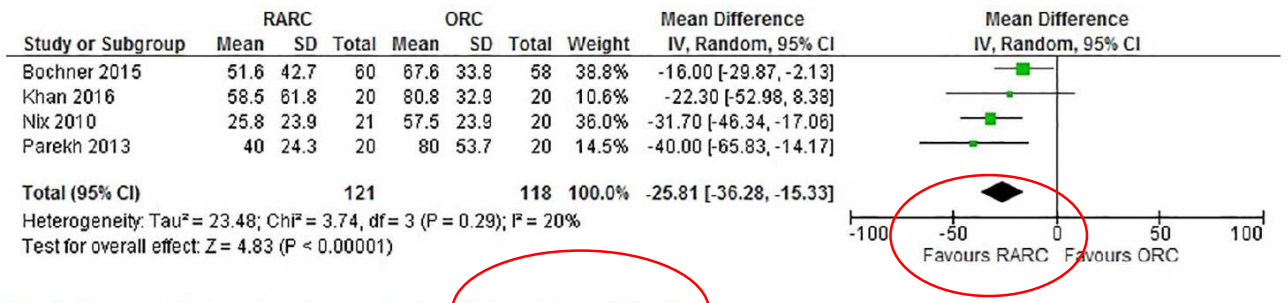
Table 1. Characteristics of included studies.

First author and reference	Recruitment	Country	Primary end point	Number of patients, ORC/ RARC	Male sex, ORC/ RARC	Age, median/ mean, ORC/ RARC	IC patients, ORC/ RARC	NB patients, ORC/ RARC	Match factors
Nix et al. 2010 [16]	April 2008- Jan 2009	USA	Lymph node yield	20/ 21	17/ 14	69.2/ 67.4	14/ 14	6/ 7	1,2,3,4,7,8
Parekh et al. 2013 [14]	July 2009- June 2011	USA	Feasibility study	20/ 20	16/ 18	64.5/ 69.5	NA	NA	1,2,3,4,5,6, 7
Bochner et al. 2015 [17]	March 2010- March 2013	USA	Perioperative complication	58/ 60	42/ 51	65.0/ 66.0	23/ 27	35/ 33	1,2,3,4,5,6,7,8
Khan et al. 2016 [15]	March 2009- July 2012	UK	Perioperative outcomes	20/ 20	18/ 15	66.6/ 68.6	17/ 18	3/ 2	1,2,3,4,5,6,7,8

1 = age, 2 = gender, 3 = BMI, 4 = ASA, 5 = previous abdominal surgery, 6 = neoadjuvant chemotherapy, 7 = clinical stage, 8 = diversion type, ORC: open radical cystectomy, RARC: robotic assisted radical cystectomy, IC: ileal conduit, NB: neobladder

doi:10.1371/journal.pone.0166221.t001

Blood loss, operating time and length of stay

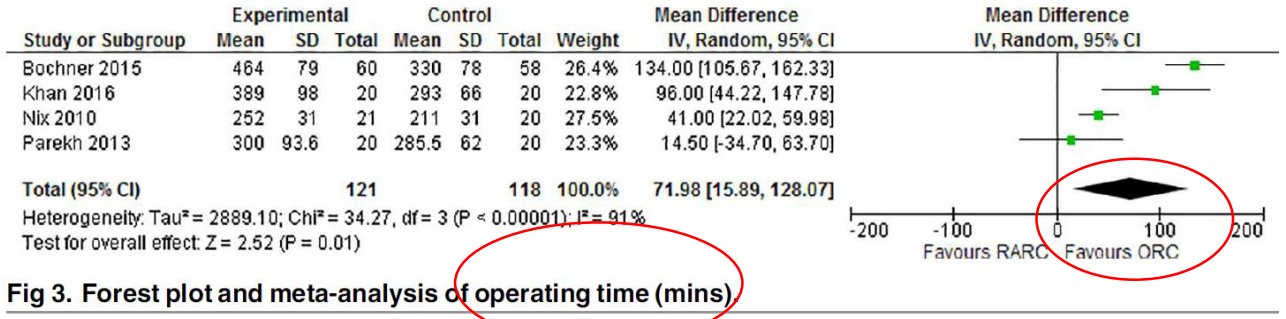


Study or Subgroup	RARC Mean	RARC SD	RARC Total	ORC Mean	ORC SD	ORC Total	Weight	Mean Difference IV, Random, 95% CI
Bochner 2015	51.6	42.7	60	67.6	33.8	58	38.8%	-16.00 [-29.87, -2.13]
Khan 2016	58.5	61.8	20	80.8	32.9	20	10.6%	-22.30 [-52.98, 8.38]
Nix 2010	25.8	23.9	21	57.5	23.9	20	36.0%	-31.70 [-46.34, -17.06]
Parekh 2013	40	24.3	20	80	53.7	20	14.5%	-40.00 [-65.83, -14.17]
Total (95% CI)			**121**			**118**	**100.0%**	**-25.81 [-36.28, -15.33]**

Heterogeneity: Tau² = 23.48; Chi² = 3.74, df = 3 (P = 0.29); I² = 20%
Test for overall effect: Z = 4.83 (P < 0.00001)

Fig 2. Forest plot and meta-analysis of blood loss (10ml).

250 ml less blood loss

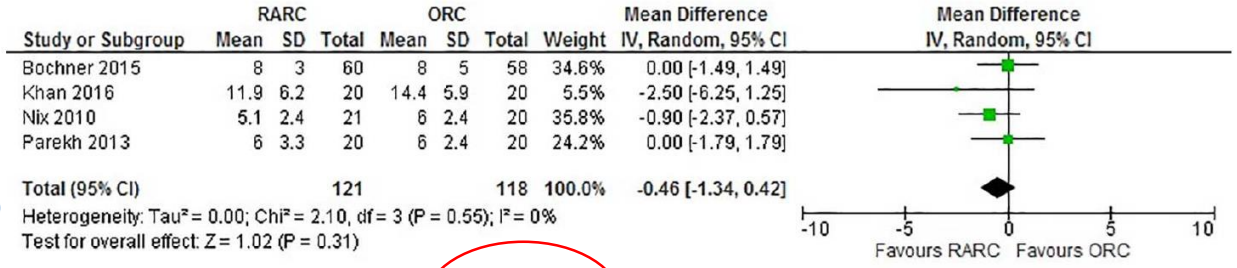


Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Bochner 2015	464	79	60	330	78	58	26.4%	134.00 [105.67, 162.33]
Khan 2016	389	98	20	293	66	20	22.8%	96.00 [44.22, 147.78]
Nix 2010	252	31	21	211	31	20	27.5%	41.00 [22.02, 59.98]
Parekh 2013	300	93.6	20	285.5	62	20	23.3%	14.50 [-34.70, 63.70]
Total (95% CI)			**121**			**118**	**100.0%**	**71.98 [15.89, 128.07]**

Heterogeneity: Tau² = 2889.10; Chi² = 34.27, df = 3 (P < 0.00001); I² = 91%
Test for overall effect: Z = 2.52 (P = 0.01)

Fig 3. Forest plot and meta-analysis of operating time (mins).

72 min longer operating time



Study or Subgroup	RARC Mean	RARC SD	RARC Total	ORC Mean	ORC SD	ORC Total	Weight	Mean Difference IV, Random, 95% CI
Bochner 2015	8	3	60	8	5	58	34.6%	0.00 [-1.49, 1.49]
Khan 2016	11.9	6.2	20	14.4	5.9	20	5.5%	-2.50 [-6.25, 1.25]
Nix 2010	5.1	2.4	21	6	2.4	20	35.8%	-0.90 [-2.37, 0.57]
Parekh 2013	6	3.3	20	6	2.4	20	24.2%	0.00 [-1.79, 1.79]
Total (95% CI)			**121**			**118**	**100.0%**	**-0.46 [-1.34, 0.42]**

Heterogeneity: Tau² = 0.00; Chi² = 2.10, df = 3 (P = 0.55); I² = 0%
Test for overall effect: Z = 1.02 (P = 0.31)

Fig 4. Forest plot and meta-analysis of length of stay.

0,46 days shorter LOS (ns)

Complications

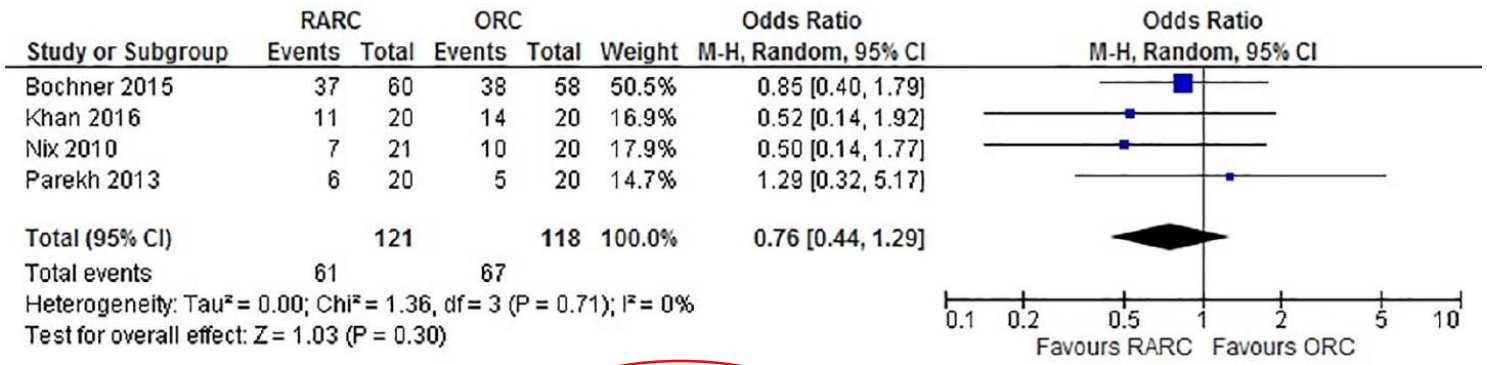


Fig 5. Forest plot and meta-analysis of all complications.

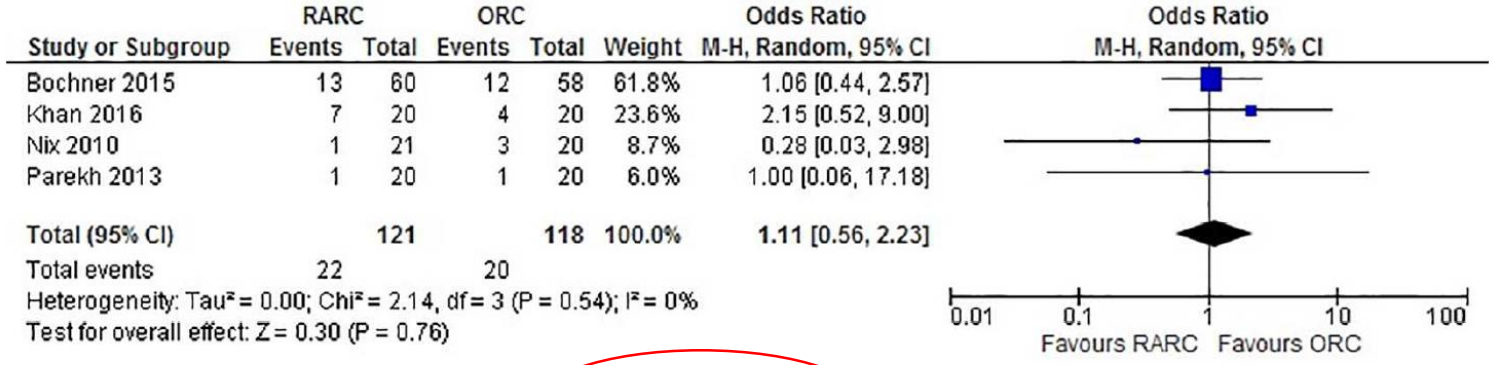


Fig 6. Forest plot and meta-analysis of major complications.

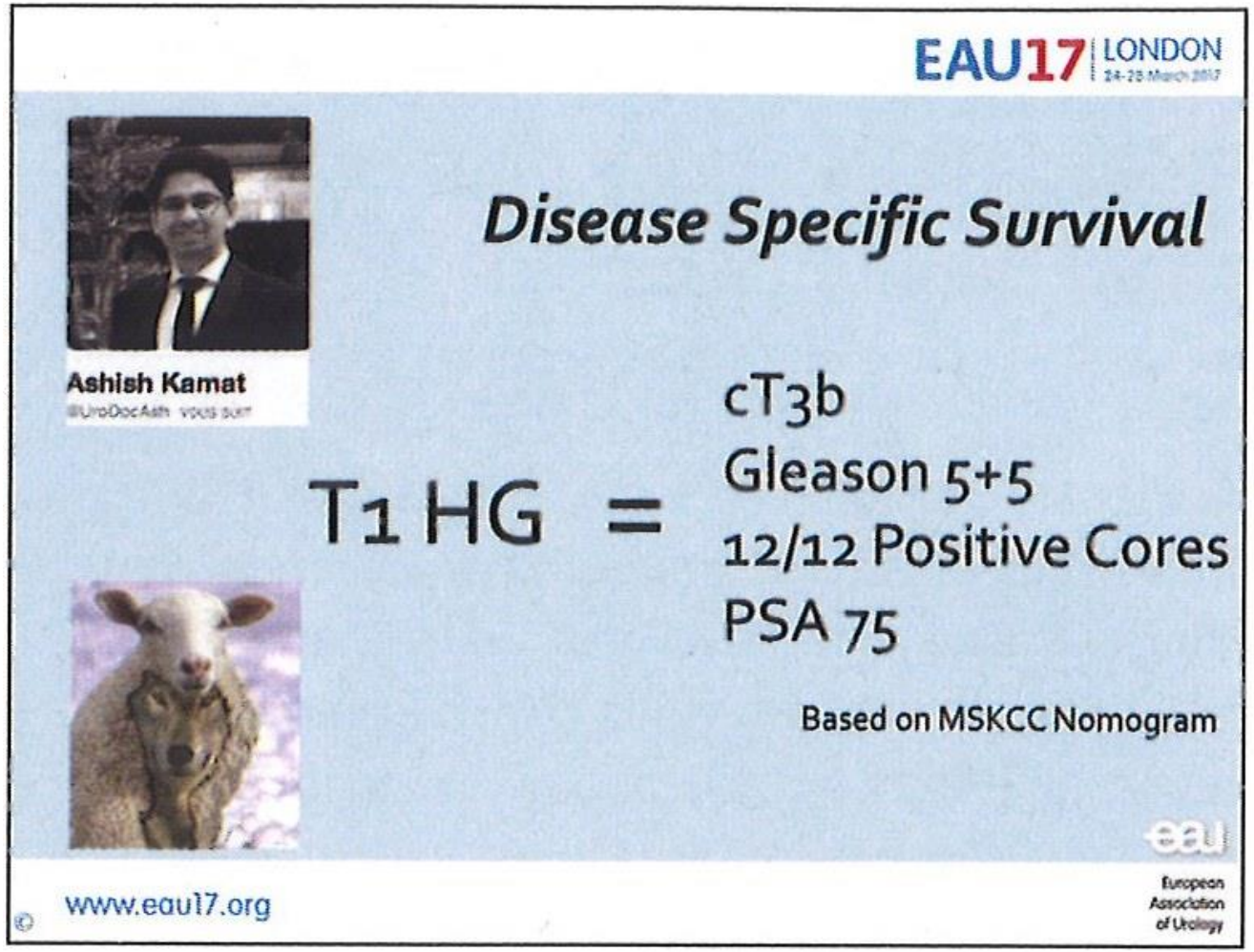
Reduction of risk and morbidity

- Better perioperative service
  - Total intravenous anestesia
  - Frailty assessment
  - ERAS – Enhanced Recovery After Surgery
  - Reduced perioperative risk
- Less invasive tecnique
  - Smaller incisions
  - Laparoscopic access
  - Bladder resection
  - Cutanous ureterostoma

Case;

- Vestfold hospital, male, born ‘57;
  - cT3N0 MIBC
  - COPD – Gold IV, DM-2, schizofrenia
  - Ineligible for MMT and NAC
  - Not suited for Bricker
- Treatment
  - Spinal/epidural anesthesia, sedatives
  - ORC + PLND + Ortotopic bladder
  - 3 hrs 40 min operating time
  - 300 ml Blood loss
  - Uncomplicated

And Finally; early radical treatment?



Stolen from Ashish Kamat's presentation at EAU 2017

Takk for oppmerksomheten!

VESTFOLD HOSPITAL