Debate: multiparametric MRI vs TURBT for staging MIBC

Nicholas James

Marco Moschini

With developments in liquid biomarkers and imaging, should we be moving from TURBT to less invasive staging of bladder cancer?

TURBT essential for all patients

Time to move to a modified pathway

TRANSURETHRAL RESECTION OF BLADDER TUMOR (TURBT)

TURBT essential for all patients

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Importance of TURBT in Urology

1. Diagnostic value
    1. Accurate T stage
    2. Small lesions
    3. CIS
    4. Variant histology
    5. Pathological markers
2. Therapeutic effect

NMIBC vs MIBC

Bladder path (Role of mpMRI)

European Association of Urology

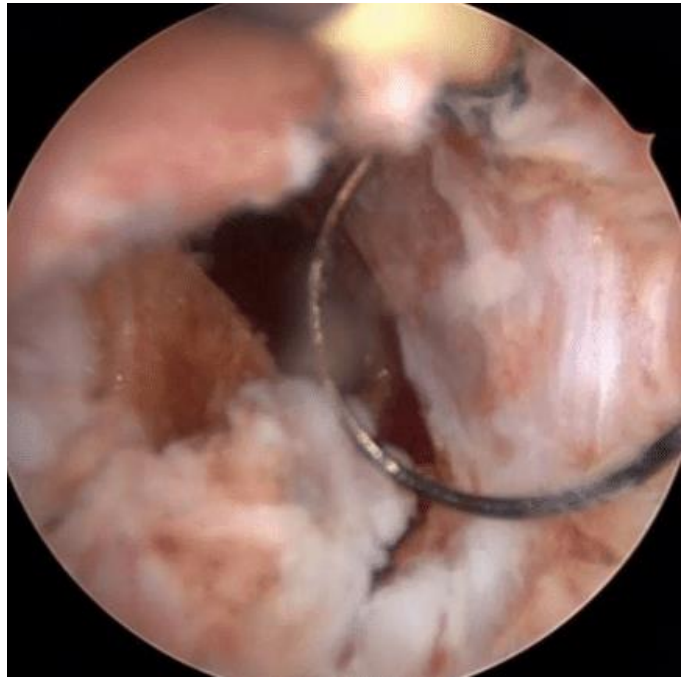
EUO Collaborative Review – Bladder Cancer

Best Practices to Optimise Quality and Outcomes of Transurethral Resection of Bladder Tumours

Hugh Mostafid [a,], Ashish M. Kamat [b], Siamak Daneshmand [c], Joan Palou [d], John A. Taylor III [e], James McKiernan [f], James Catto [g], Marko Babjuk [h], Mark Soloway [i]*

1.1 T Staging- MIBC

- TURBT still the standard of care in diagnose T2 vs T1 disease
  - TURBT superior than mpMRI in diagnosing pT2 disease
- Not necessary/useful in differentiate T2 from T3/T4
  - mpMRI (or CT scan) add information prior radical surgery



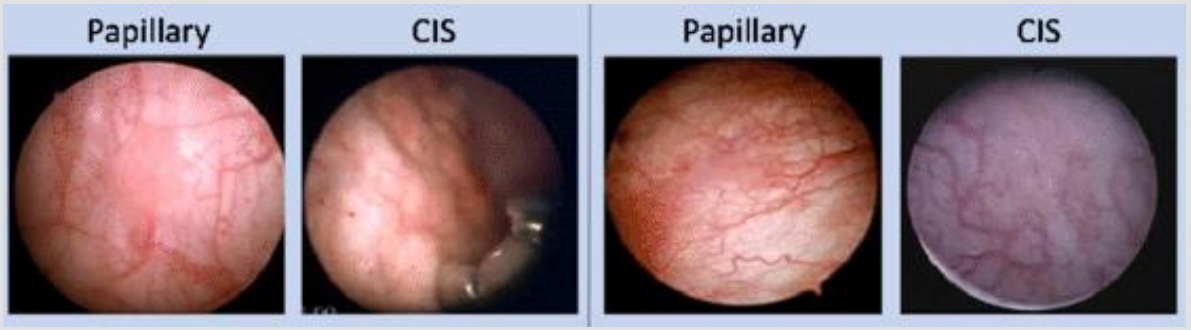
1.2 small lesions

Risk group	
Low Risk	• A primary, single, TaT1 LG/G1 tumour < 3 cm in diameter without CIS in a patient ≤ 70 years
	• A primary Ta LG/G1 tumour without CIS with at most ONE of the additional clinical risk factors (see above*)
Intermediate Risk	Patients without CIS who are not included in either the low-, high-, or very high-risk groups
High Risk	• All T1 HG/G3 without CIS, EXCEPT those included in the very high-risk group • All CIS patients, EXCEPT those included in the very high-risk group
	Stage, grade with additional clinical risk factors: • Ta LG/G2 or T1G1, no CIS with all 3 risk factors • Ta HG/G3 or T1 LG, no CIS with at least 2 risk factors • T1G2 no CIS with at least 1 risk factor

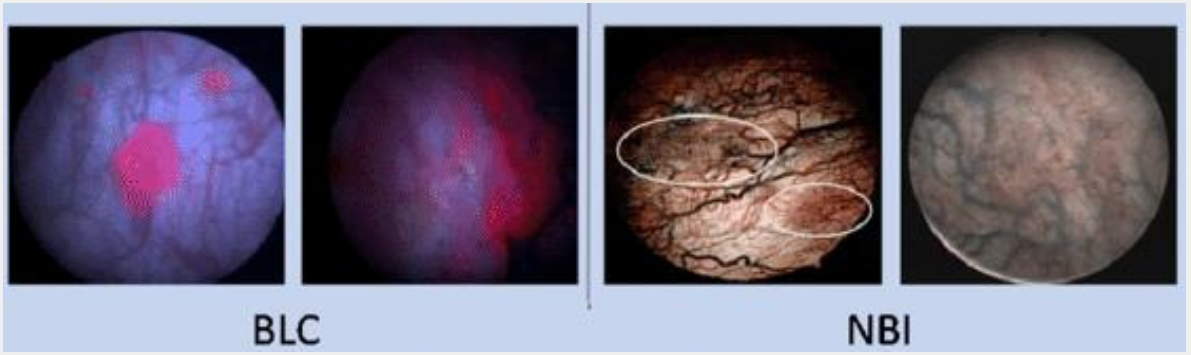
1.2-3. Small lesions/CIS PDD / NBI vs WLC

SUMMARY

SURVEY
WITH WLC…



…SUSPECT
IN PPD OR NBI



Better **SENSITIVITY** than WLC

Better **ONCOLOGICAL** Outcomes

1.2-3. PHOTODYNAMIC DIAGNOSIS (PPD)

DETECTION RATE

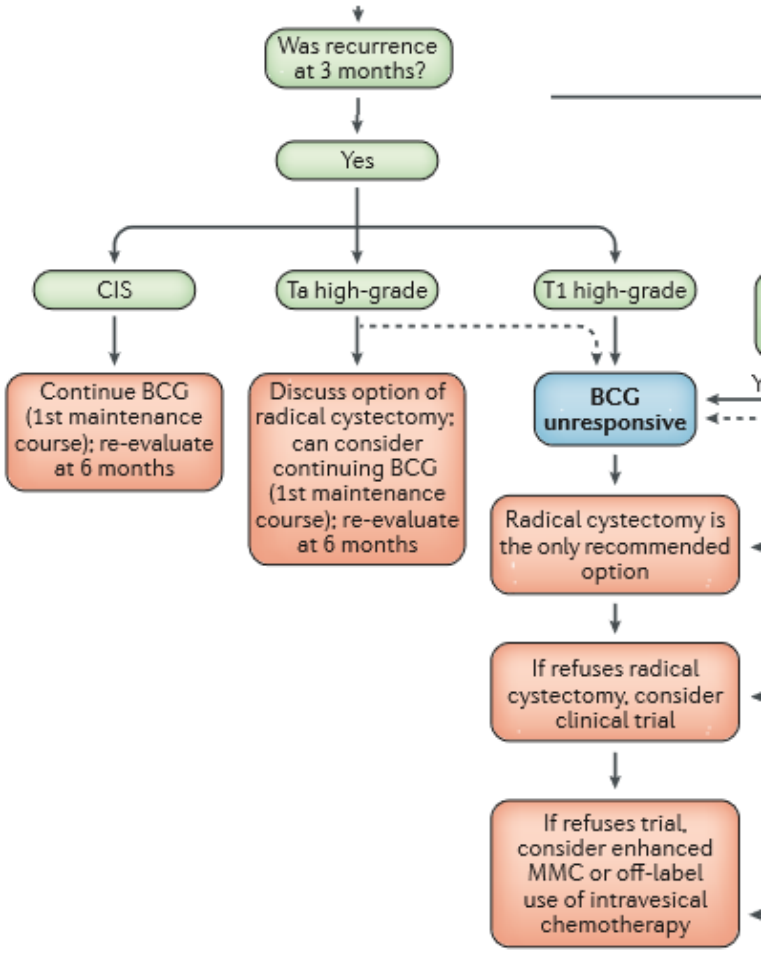
Tumour type	Both methods, *n* (%)	BL only, *n* (%)	WL only, *n* (%)	Total	Odds ratio (CI) in favour of BL	*p* value
Total Ta	1298 (80.1)	239 (14.7)	84 (5.2)	1621	4.898 (1.937–12.390)	<0.001
Ta primary	495 (86.7)	64 (11.2)	12 (2.1)	571	5.146 (2.109–12.554)	<0.001
Ta recurrent	803 (76.5)	175 (16.7)	72 (6.9)	1050	4.637 (1.739–12.364)	0.002
High risk	460 (77.3)	94 (15.8)	41 (6.9)	595	3.635 (1.474–8.966)	0.005
Intermediate risk	674 (79.9)	138 (16.4)	32 (3.8)	844	7.056 (2.376–20.990)	0.005
Low risk	164 (90.1)	7 (3.8)	11 (6.0)	182	0.849 (0.279–2.583)	0.773
Total T1	313 (84.1)	40 (10.8)	19 (5.1)	372	2.253 (0.999–5.081)	0.050
Primary	201 (84.5)	30 (12.6)	7 (2.9)	238	4.478 (1.868–10.737	0.001
Recurrent	112 (83.6)	10 (7.5)	12 (9.0)	134	0.962 (0.315–2.941)	0.946
Total CIS	285 (54.1)	215 (40.8)	27 (5.1)	527	12.372 (6.343–24.133)	<0.001
Primary*	119 (54.6)	94 (43.1)	5 (2.3)	218	21.316 (8.163–55.661	<0.001
Recurrent*	166 (53.7)	121 (39.2)	22 (7.1)	309	7.947 (4.629–13.644)	<0.001

BL = blue light; CI = confidence interval; CIS = carcinoma in situ; WL = white light.
* *Primary* and *recurrent* refer to the diagnosis of the patient at study entry.

BLC detected significantly more Ta/T1 tumours (**14.7%**; P<0.001) and CIS lesions (**40.8%**; P<0.001) than WLC

Burger M., Eur Urol 2013

1.3 CIS



nature REVIEWS UROLOGY

- Assessing pathological response after BCG treatment
- It is mandatory in high risk NMIBC assess type and aggressiveness of recurrence (low grade, high grade, CIS or progression)

BCG-unresponsive non-muscle-invasive bladder cancer: recommendations from the IBCG

Ashish M. Kamat[1], Marc Colombel[2], Debasish Sundi[1], Donald Lamm[3], Andreas Boehle[4], Maurizio Brausi[5], Roger Buckley[6], Raj Persad[7], Joan Palou[8], Mark Soloway[9] and J. Alfred Witjes[10]

nature reviews urology

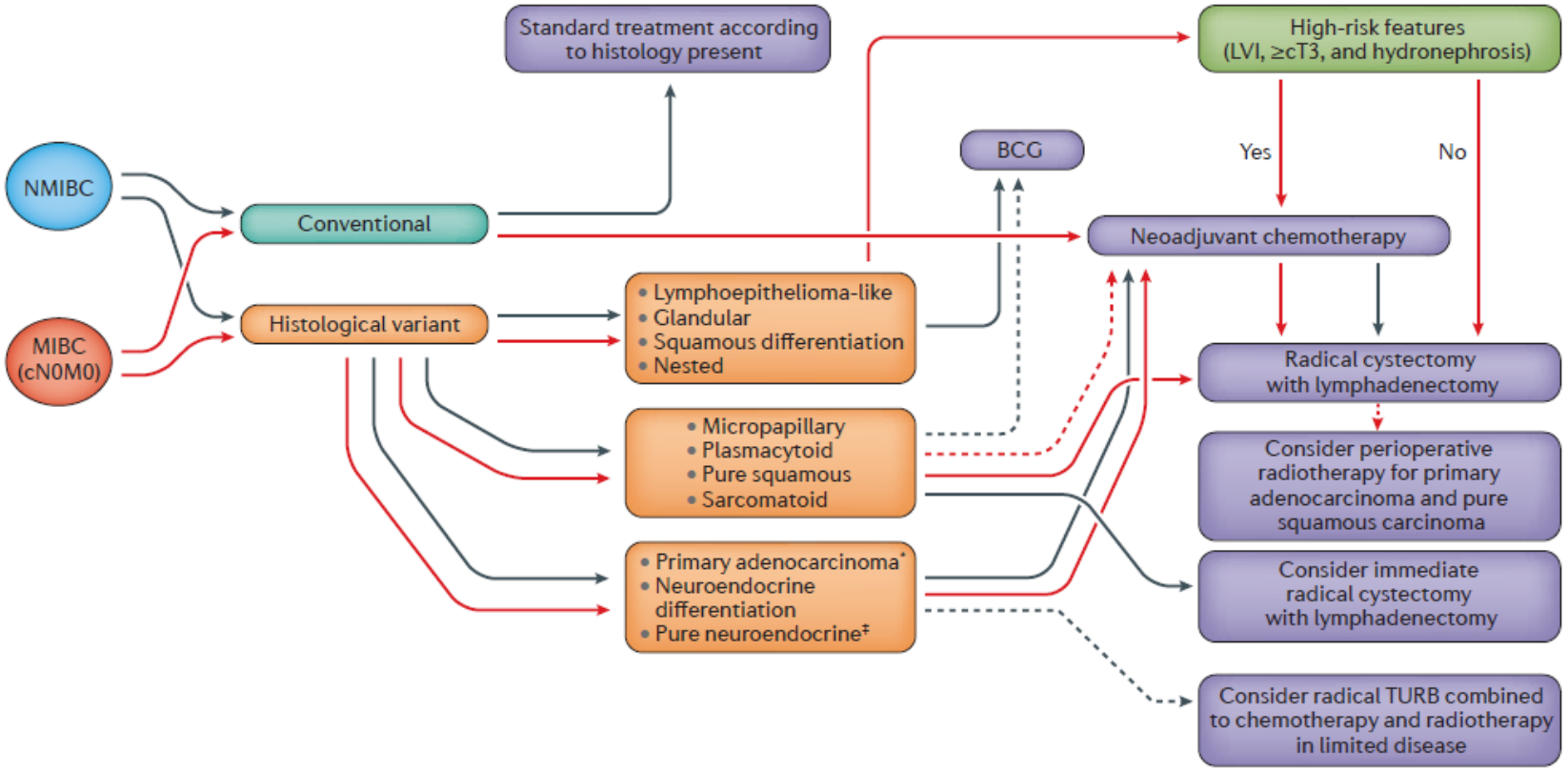
REVIEWS

Characteristics and clinical significance of histological variants of bladder cancer

Marco Moschini[1,2,3], David D'Andrea[1]*, Stephan Korn[1], Yasin Irmak[1], Francesco Soria[1], Eva Compérat[4] and Shahrokh F. Shariat[1,5,6,7]*

- Approximately 75% of instances of these cancers are classified as pure urothelial carcinoma, whereas the remaining 25% consist of other histological variants.
- Diagnosis of histological variants change consistently on the basis of pathologist experience, surgical specimen, geographical variations

1.4 VARIANT HISTOLOGY



Moschini et al. Nature urology reviews 2017

1.5 PROGNOSTIC TISSUE-BASED BIOMARKERS

Molecular markers are promising tools that may give insight into which MIBC patients **will or will not benefit** from neoadjuvant systemic therapy (NAC) before radical cystectomy (RC).

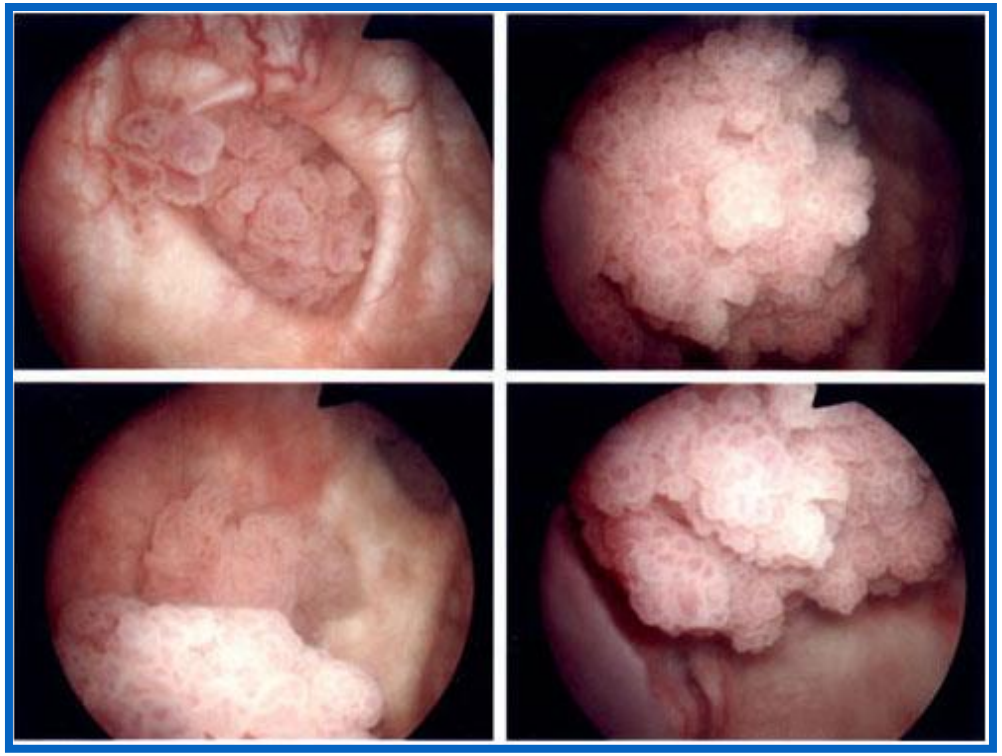
- Specific genomic alterations in **DNA repair genes** (e.g., ATM, RB1, FANCC, and ERCC2) provide predictive value for predicting pathologic response and oncologic outcomes after NAC.
- Quantitative PCR results for the **expression of genes** selected through microarray analysis (e.g., BRCA1) could correctly classify cases with regard to their NAC response.
- A higher pathologic response rate was shown in patients with **PD-L1** positive tumors compared to those with PD- L1 negative tumors undergoing NAI.

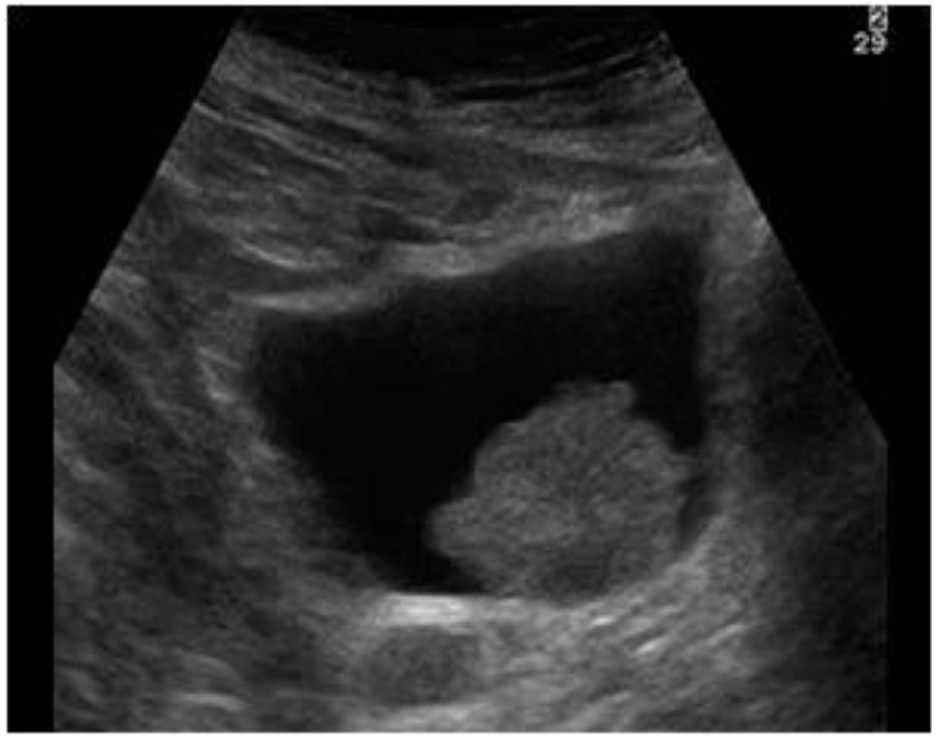
2. THERAPEUTIC EFFECT

- NMIBC: TURBT represents the first step of the treatment
  - NMIBC are the majority of Bca patients (70% at first diagnosis)
  - Mandatory in every patients
  - Do we really need mpMRI in these patients? In my opinion, NO

POTENTIAL DIAGNOSIS OF MIBC

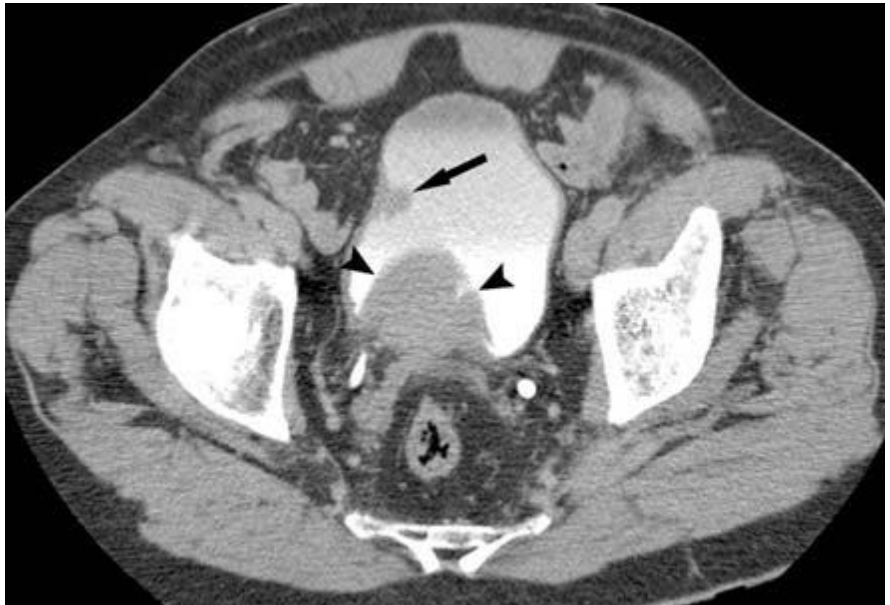
1. Follow up during NMIBC. Patient is already scheduled for TURBT
2. New diagnoses (Hematuria, other symptoms..). Easier to get mpMRI or TURBT?

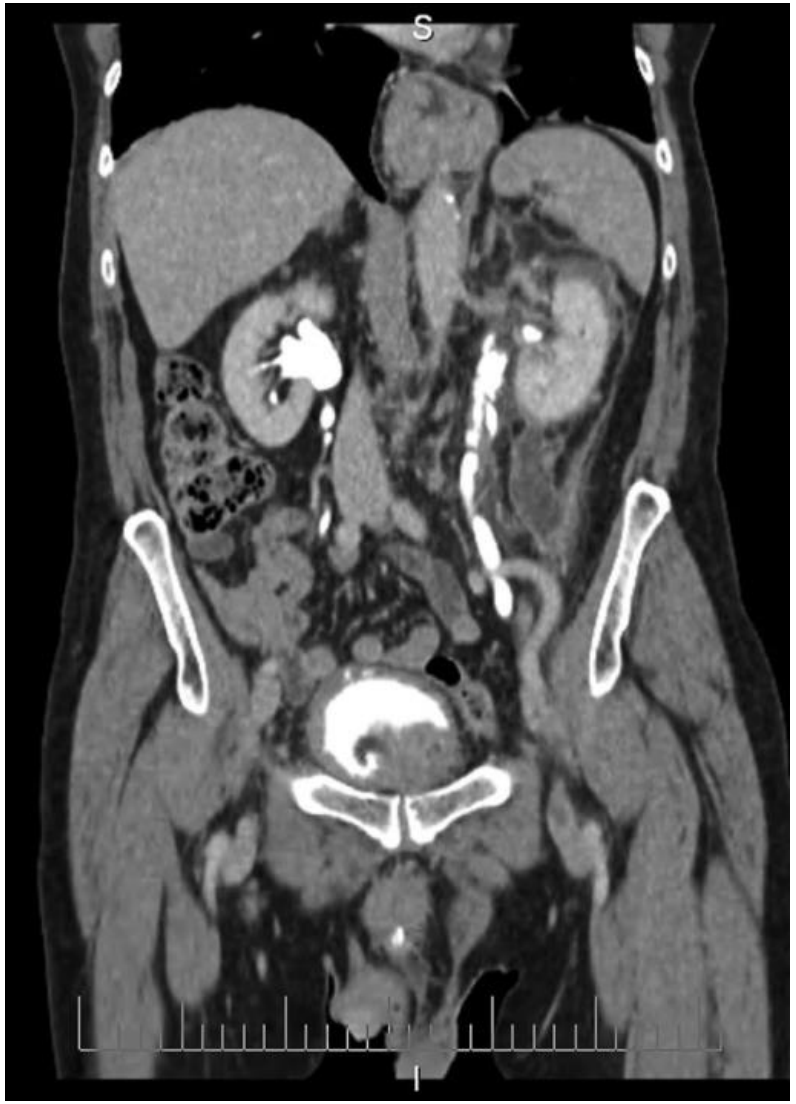




POTENTIAL DIAGNOSIS OF MIBC

1. CT scan not inferior for N and UTUC than mpMRI





2. THERAPEUTIC EFFECT

- MIBC: A complete TURBT in MIBC does not improve patient survival
  - Necessity of biomarker (at least biopsy is necessary, variant histology is often mixed)
  - Should we avoid TURBT in Likert 4-5? (minority of patients)
    - Need for expert radiologist. Might be easier to perform a TURBT.
    - Waiting list for mpMRI sometimes longer than surgery in local hospitals

Zamboni et al 2019

TAKE HOME MESSAGE

- TURBT
  - NMIBC: we need it for every patients
    - For high grade tumors, BCG response
    - Histological variants
    - Biomarker
  - MIBC: we can potentially spare it in some patients
    - TURBT anyway better thant mpMRI in diagnosis
    - Biomarker and Variant histology
    - Necessity of referring patients to expert radiology

How many mpMRI do you need to avoid 1 TURBT?

All NMIBC + All suspicious MIBC + Thrimodal therapy candidates+ histo evaluations/gene

Bladder Cancer – is it time to revise the pathway?

Nicholas James

@Prof_Nick_James

ICR The Institute of Cancer Research

Functions of TURBT?

- Diagnosis
- Staging
- Treatment
- Palliation of symptoms from bladder

Non-muscle invasive bladder cancer – 80% of total

TURBT

- Diagnosis ✔
- Staging ✔
- Treatment ✔
- Palliation of symptoms from bladder ✔

Invasive bladder cancer

TURBT

• Diagnosis	✔
• Staging	✔ - incomplete and inaccurate
• Treatment	No - delayed
• Palliation of symptoms from bladder	Possibly

If we could diagnose and stage a different way, correct treatment could be faster

Ideal new pathway?

NMIBC

- Identify on imaging and biopsy/cytology
- Fast track to TURBT and subsequent therapy

MIBC

- Stage with biopsy and MRI
- Fast track to definitive therapy
- TURBT only if needed

Problem: need to separate NMIBC from MIBC

MRI – Superficial vs invasive

Sensitivity

- T2 – 88%
- T2 + DWI 88%
- T2 + DCE 94%
- All 3 94%

Specificity

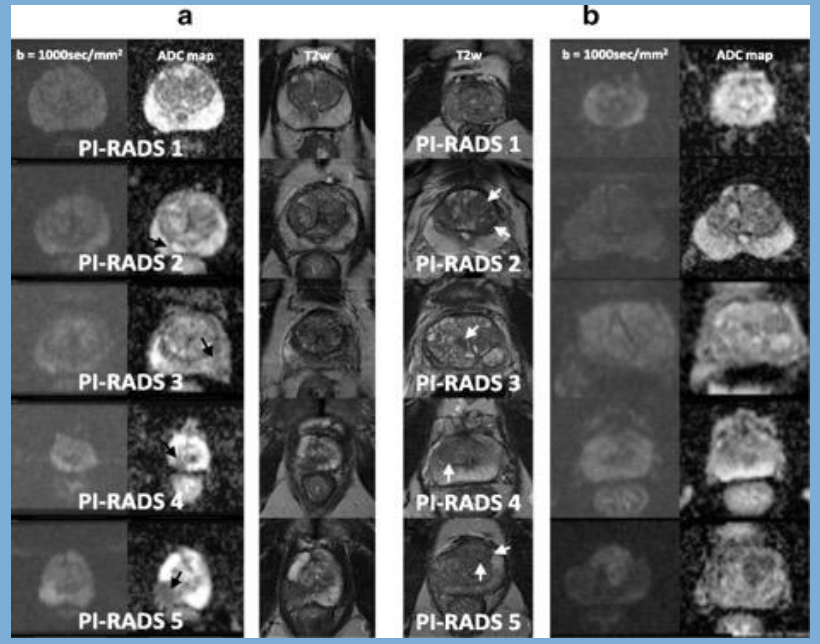
- T2 – 74%
- T2 + DWI 100%
- T2 + DCE 86%
- All 3 100%

TURBT pathological upstaging at cystectomy 40%

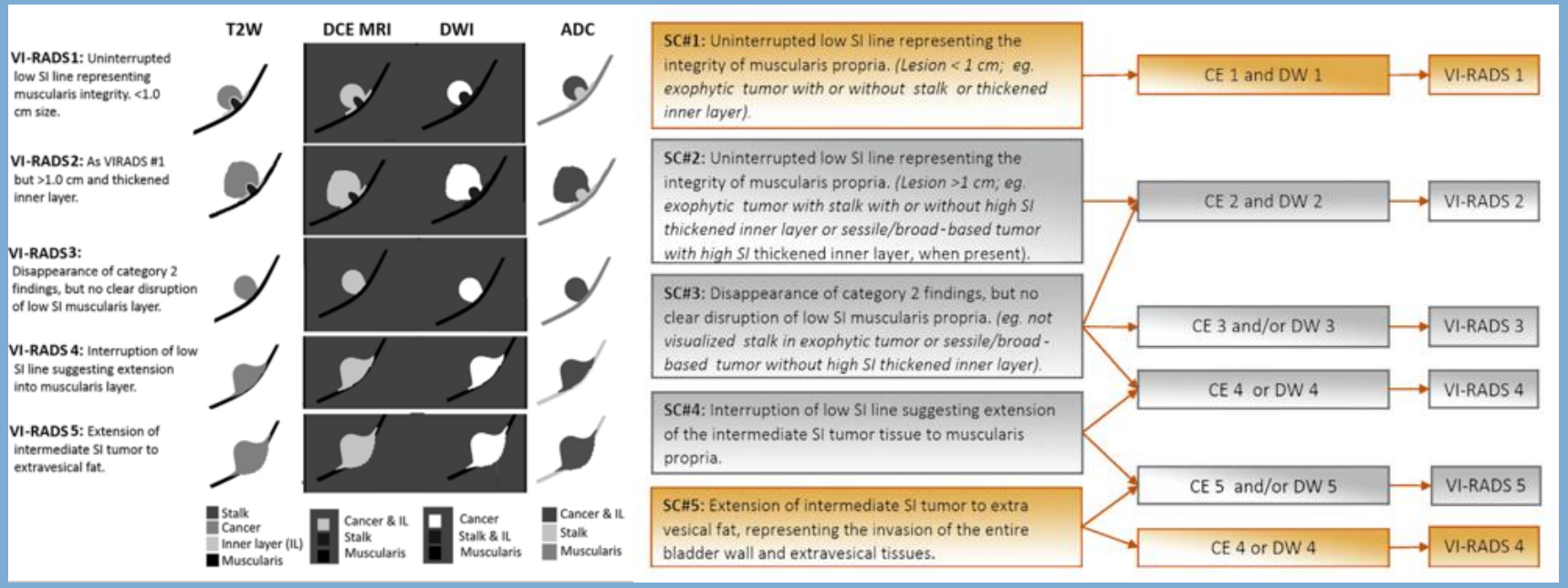
Takeuchi M, Sasaki S, Ito M, Okada S, Takahashi S, Kawai T, Suzuki K, Oshima H, Hara M, Shibamoto Y. Urinary bladder cancer: diffusion-weighted MR imaging--accuracy for diagnosing T stage and estimating histologic grade. Radiology 2009;251:112-21

RADS & Imaging

Prostate cancer: PIRADS



Bladder cancer: VIRADS



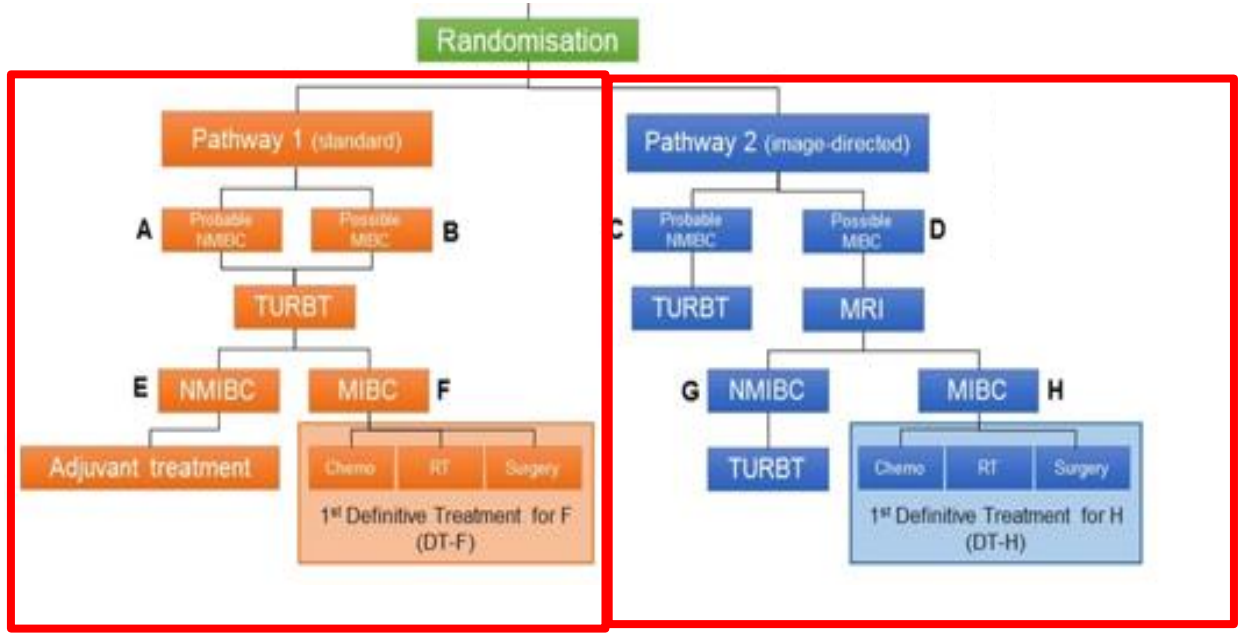
BladderPath key trial design features:

Feasibility stage

- A minimum of **80%** of patients on MRI pathway complete as planned
- Outcome Feasibility: **37/39 95%** CI (83%, 99%) followed protocol

Efficacy stage

- **Primary outcome**
- A reduction of at least **30 days** in time to correct treatment (TTCT) for **muscle-invasive** bladder cancer (MIBC)
- **Secondary outcomes**
- TTCT for all patients
- TTCT for Non-MIBC



Probable non-invasive split from Possible muscle-invasive disease by clinical assessment on 5-point scale:

1. Strongly agree that the lesion is non-muscle-invasive
2. Agree that the lesion is non-muscle-invasive
3. Equivocal
4. Agree that the lesion is muscle-invasive
5. Strongly agree that the lesion is muscle-invasive

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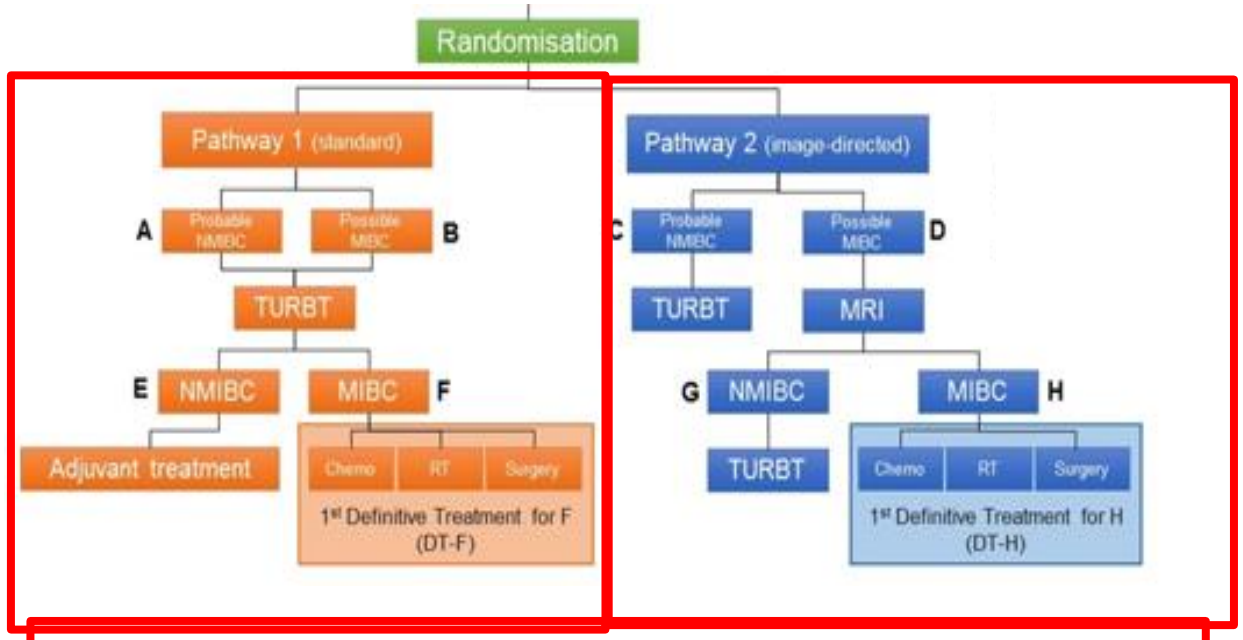

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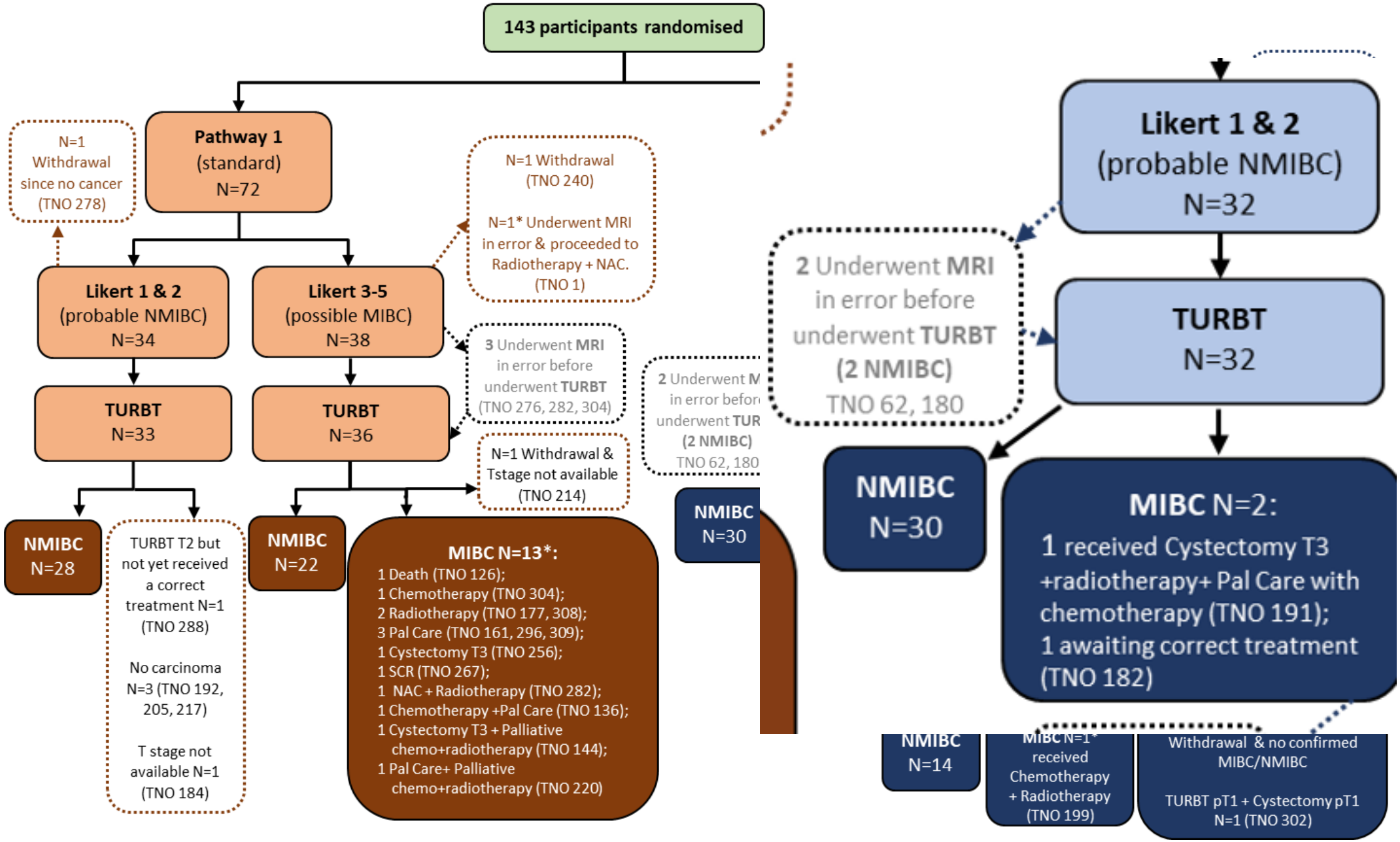
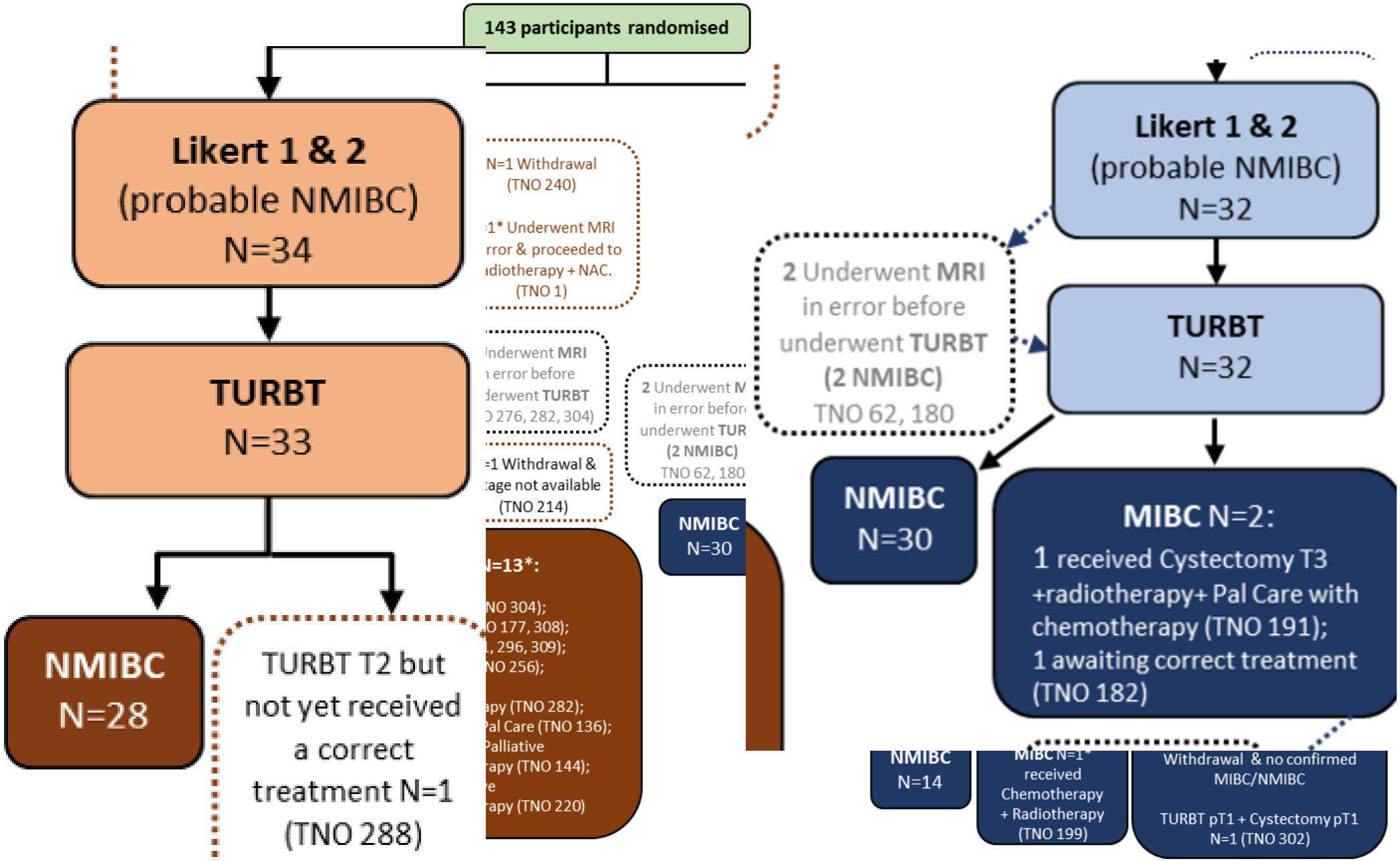

143 participants randomised
N=1 Withdrawal since no cancer (TNO 278)
Pathway 1 (standard) N=72
N=1 Withdrawal (TNO 240)
N=1* Underwent MRI in error & proceeded to Radiotherapy + NAC. (TNO 1)
Likert 1 & 2 (probable NMIBC) N=34
Likert 3-5 (possible MIBC) N=38
3 Underwent MRI in error before underwent TURBT (TNO 276, 282, 304)
TURBT N=33
TURBT N=36
N=1 Withdrawal & Tstage not available (TNO 214)
NMIBC N=28
TURBT T2 but not yet received a correct treatment N=1 (TNO 288)
No carcinoma N=3 (TNO 192, 205, 217)
T stage not available N=1 (TNO 184)
NMIBC N=22
MIBC N=13*:
1 Death (TNO 126);
1 Chemotherapy (TNO 304);
2 Radiotherapy (TNO 177, 308);
3 Pal Care (TNO 161, 296, 309);
1 Cystectomy T3 (TNO 256);
1 SCR (TNO 267);
1 NAC + Radiotherapy (TNO 282);
1 Chemotherapy +Pal Care (TNO 136);
1 Cystectomy T3 + Palliative chemo+radiotherapy (TNO 144);
1 Pal Care+ Palliative chemo+radiotherapy (TNO 220)
2 Underwent MRI in error before underwent TURBT (2 NMIBC) TNO 62, 180
NMIBC N=30
Likert 1 & 2 (probable NMIBC) N=32
2 Underwent MRI in error before underwent TURBT (2 NMIBC) TNO 62, 180
TURBT N=32
NMIBC N=30
MIBC N=2:
1 received Cystectomy T3 +radiotherapy+ Pal Care with chemotherapy (TNO 191);
1 awaiting correct treatment (TNO 182)
NMIBC N=14
MIBC N=1* received Chemotherapy + Radiotherapy (TNO 199)
Withdrawal & no confirmed MIBC/NMIBC
TURBT pT1 + Cystectomy pT1 N=1 (TNO 302)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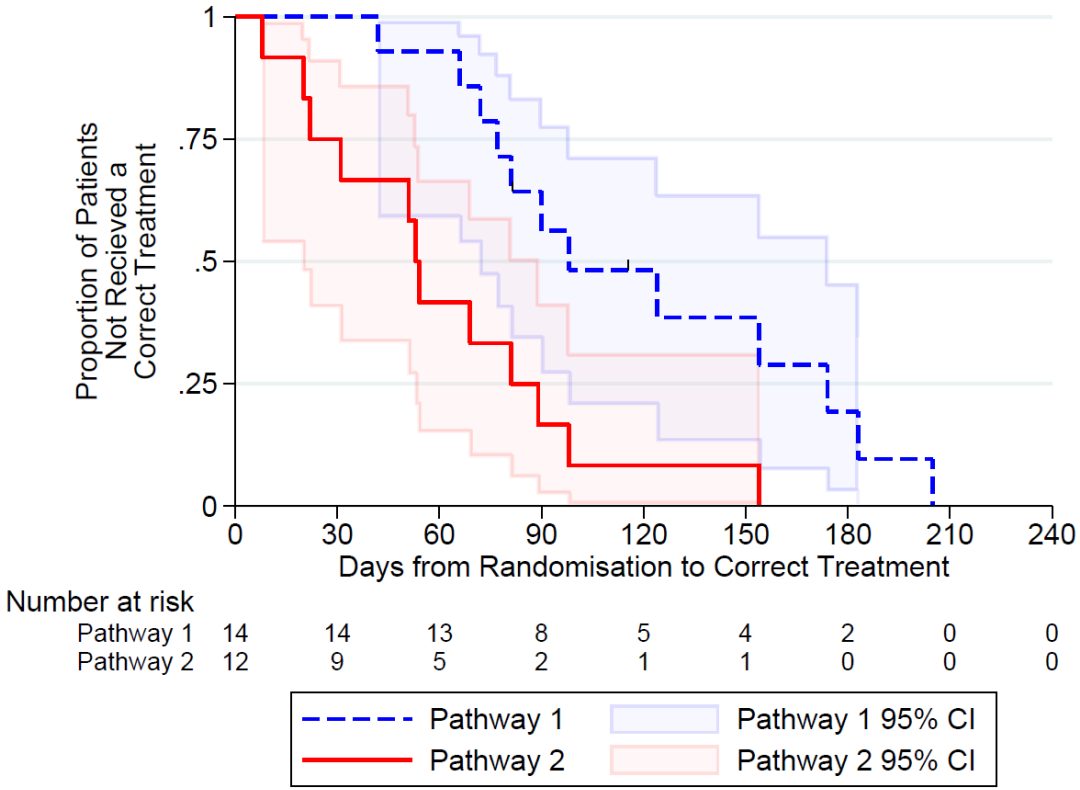
N=14
MIBC N=1*
received
Chemotherapy
+ Radiotherapy
(TNO 199)
Withdrawal & no confirmed
MIBC/NMIBC
TURBT pT1 + Cystectomy pT1
N=1 (TNO 302)

Key Outcomes for efficacy stage

Primary Outcome: Time to correct treatment (TTCT) for patients confirmed to have MIBC

Median TTCT for pathway 1: **98 days** (95% CI. 72, 174) N=14

Median TTCT for pathway 2: **53 days** (95% CI. 20, 89) N=12



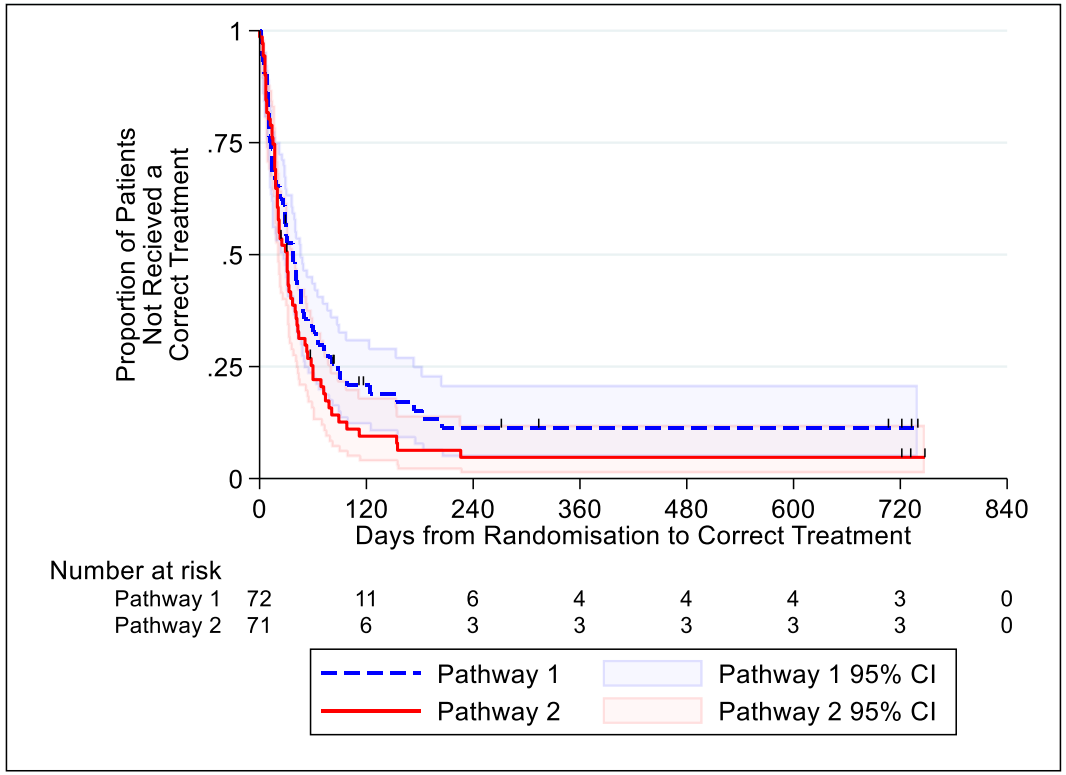
Logrank test: p-value = **0.0046**

Cox model adjusted for gender and age : HR (Pathway 2 vs. Pathway 1) = 3.4 (95% CI. 1.4, 8.3).

Secondary Outcome: time to correct treatment all patients

- Median TTCT for pathway 1: 37 days (95\% CI. 26, 47) N=72
- Median TTCT for pathway 2: 31 days (95\% CI. 20, 37) N=71

Logrank test: p-value= 0.1435
Cox model adjusted for gender and age : HR (Pathway2 vs. Pathway1)=1.3 (95% CI. 0.9, 1.8). Proportional-hazards assumption checked.



Cancer Research UK Clinical Trials Unit @CRCTU

Conclusions: BladderPath

Using a Likert scale at flexible cystoscopy accurately identifies the lower risk non-invasive cases

An image-based pathway substantially accelerated time to definitive treatment for patients with suspected muscle-invasive disease

There was no adverse effect on times to treatment for non-invasive disease

Patients with obvious muscle-invasive disease can potentially avoid the need for TURBT and associated risks

TURBT and subtype histology

Stage at TURBT	Number (%)	Stage at cystectomy		% concordance TURBT vs Cystectomy
Total	1580			
Ta-T1 & CIS	541 (34%)	Ta-T1	238	44%
		T2+	303	
CIS only	132 (8.3%)	CIS	42	31%
		T2+	90	
T2+	1039 (66%)	Ta-T1	106	
		T2+	933	90%

Dyer et al, 2021 Can Urol Assoc J. 2021 Apr; 15(4): 138–140. doi: 10.5489/cuaj.6856

TURBT and subtype histology

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Dyer et al, 2021 Can Urol Assoc J. 2021 Apr; 15(4): 138–140. doi: 10.5489/cuaj.6856

> BJU Int. 2019 Sep;124(3):532-544. doi: 10.1111/bju.14808. Epub 2019 Jun 19.

Targeted deep sequencing of urothelial bladder cancers and associated urinary DNA: a 23-gene panel with utility for non-invasive diagnosis and risk stratification

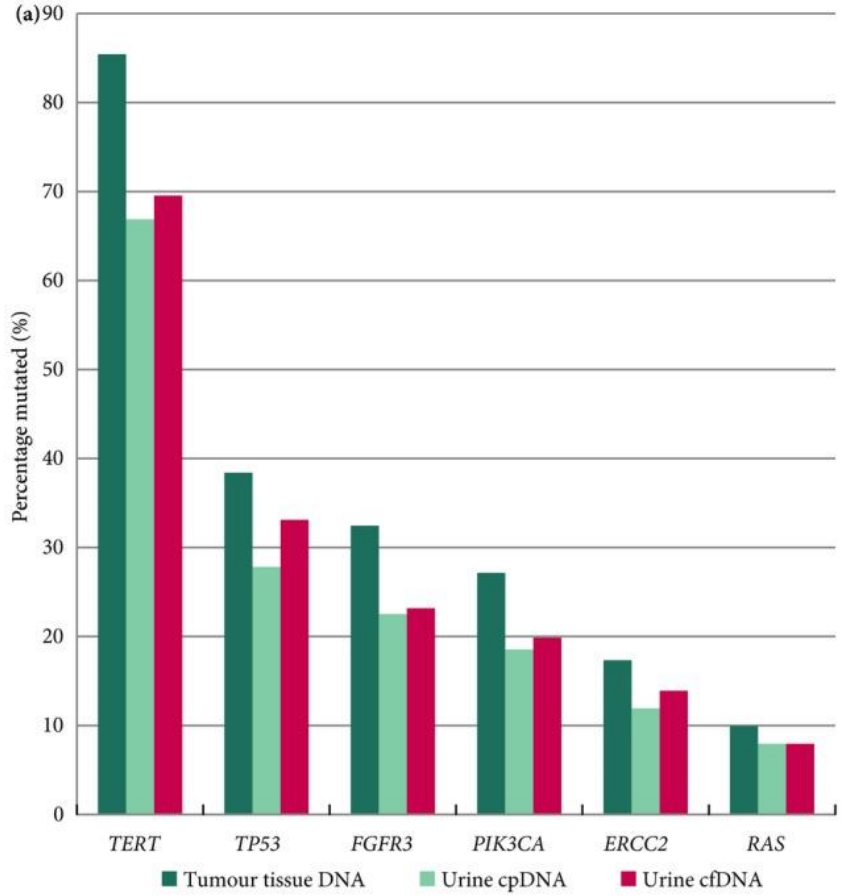
Douglas G Ward [1], Naheema S Gordon [1], Rebecca H Boucher [1], Sarah J Pirrie [1], Laura Baxter [2], Sascha Ott [2], Lee Silcock [3], Celina M Whalley [1], Joanne D Stockton [1], Andrew D Beggs [1], Mike Griffiths [4], Ben Abbotts [1], Hanieh Ijakipour [1], Fathimath N Latheef [1], Robert A Robinson [1], Andrew J White [1], Nicholas D James [1], Maurice P Zeegers [5], K K Cheng [6], Richard T Bryan [1]

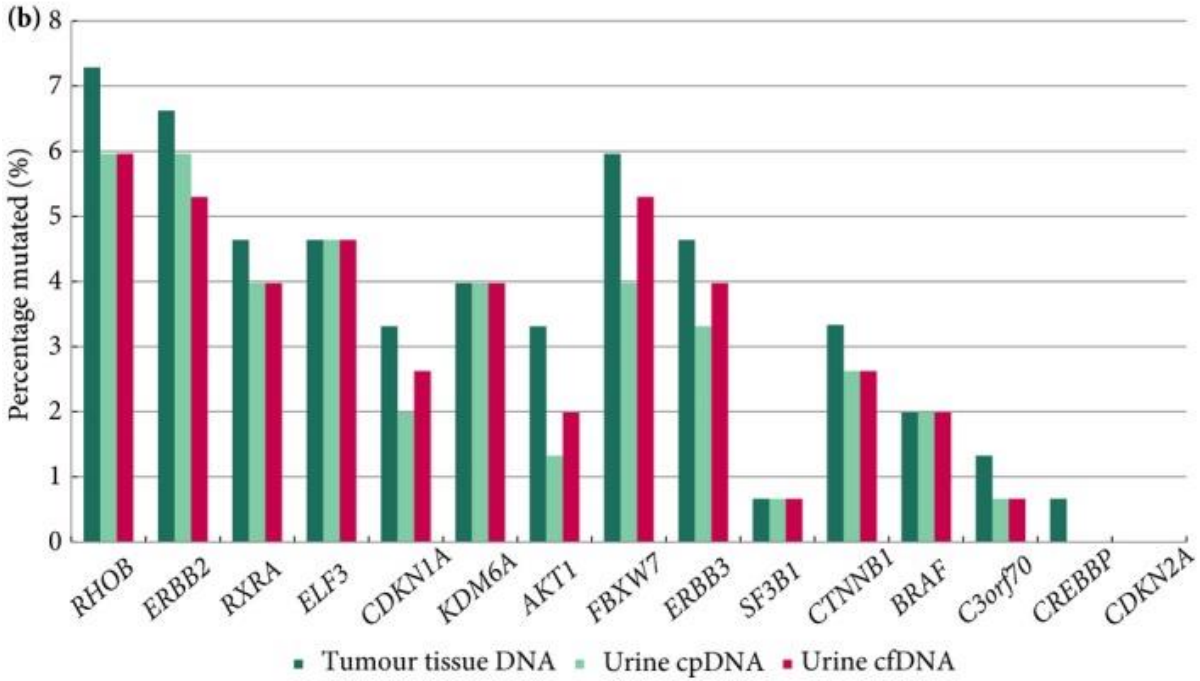
Affiliations + expand

PMID: 31077629 PMCID: PMC6772022 DOI: 10.1111/bju.14808

Free PMC article

Concordance of urine DNA data with tumour sequences





Ward et ap 2019 BJU Int. 2019 Sep;124(3):532-544. doi: 10.1111/bju.14808. Epub 2019 Jun 19.

European Urology
Volume 77, Issue 5, May 2020, Pages 636-643

Urothelial Cancer

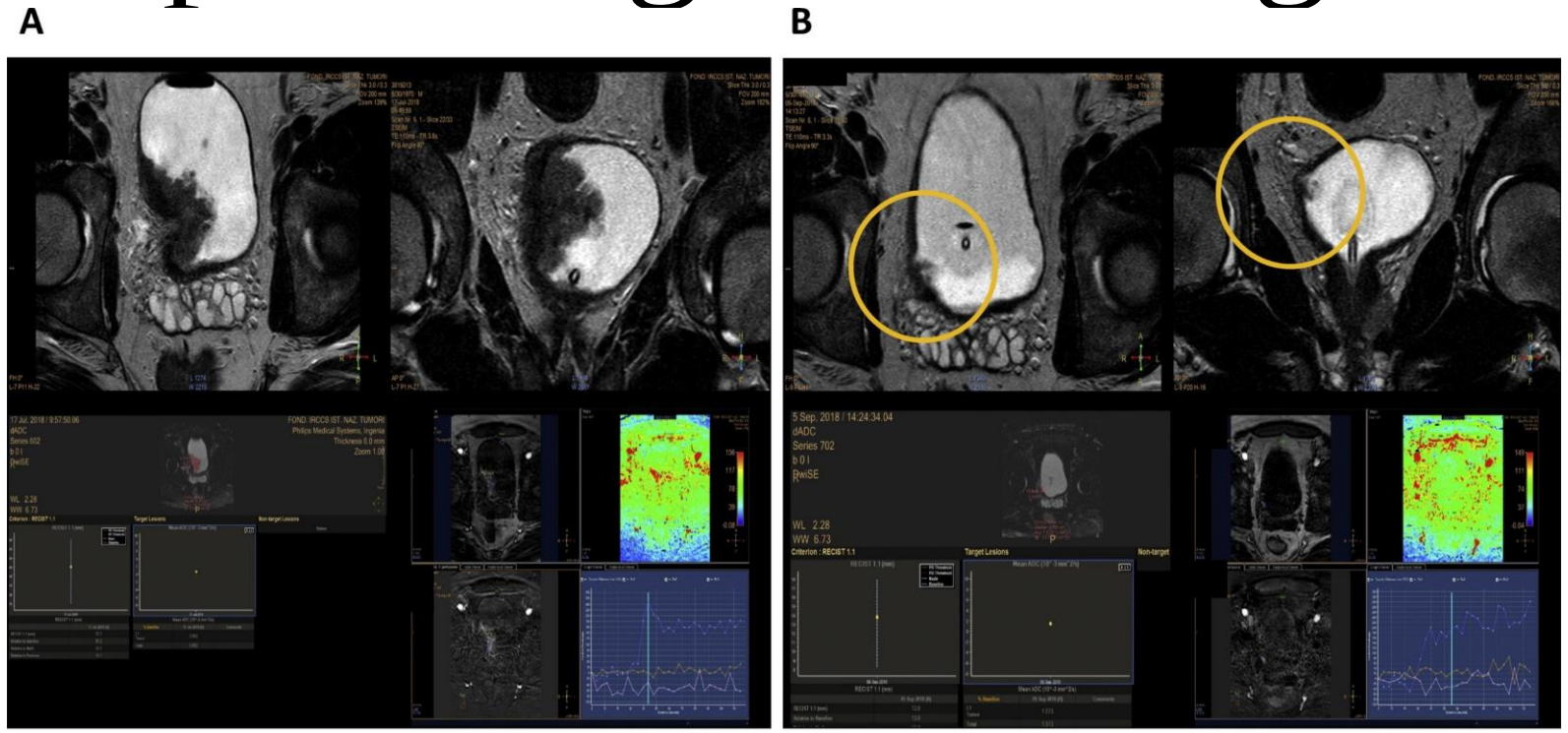
Multiparametric Magnetic Resonance Imaging as a Noninvasive Assessment of Tumor Response to Neoadjuvant Pembrolizumab in Muscle-invasive Bladder Cancer: Preliminary Findings from the PURE-01 Study

Andrea Necchi [a], Marco Bandini [b, †], Giuseppina Calareso [a, †], Daniele Raggi [a], Filippo Pederzoli [b], Elena Farè [a], Maurizio Colecchia [a], Laura Marandino [a], Marco Bianchi [b], Andrea Gallina [b], Renzo Colombo [b], Nicola Fossati [b], Giorgio Gandaglia [b], Umberto Capitanio [b], Federico Dehò [b], Patrizia Giannatempo [a], Roberta Lucianò [b], Andrea Salonia [b] ... Antonella Messina [a, ‡]

Show more

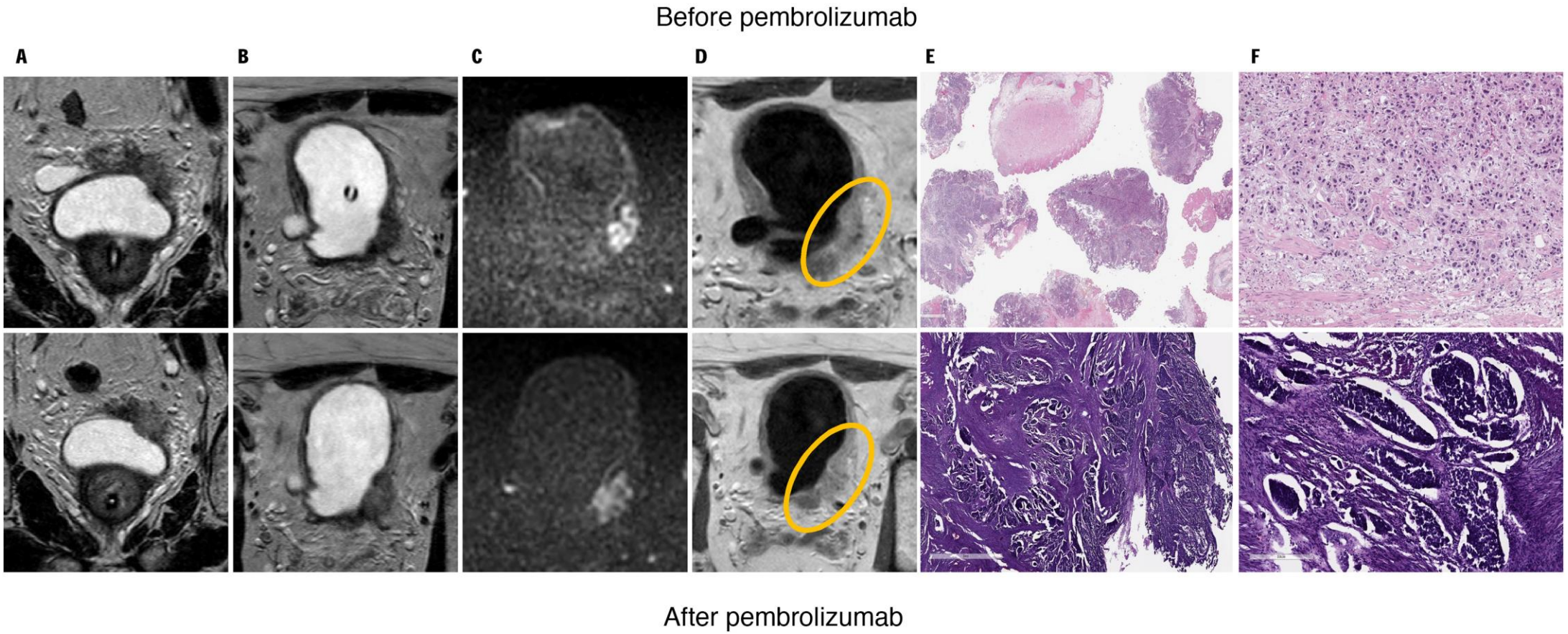
MRI and pathological changes

T2 MRI pre and post pembrolizumab



Necci et al https://doi.org/10.1016/j.eururo.2019.12.016

Non-responding patient



Necci et al https://doi.org/10.1016/j.eururo.2019.12.016

The bladder cancer pathway

- Currently follows a template set down a century ago
- Better image-based management and liquid biomarkers could revolutionise bladder cancer care
- Moving to an MRI-based pathway in MIBC opens up new avenues for disease management
  - More accurate staging
  - Dynamic, non-invasive response assessment

Discussion

With developments in liquid biomarkers and imaging, should we be moving from TURBT to less invasive staging of bladder cancer?

TURBT essential for all patients

Time to move to a modified pathway