Bladder Preservation for muscle invasive disease

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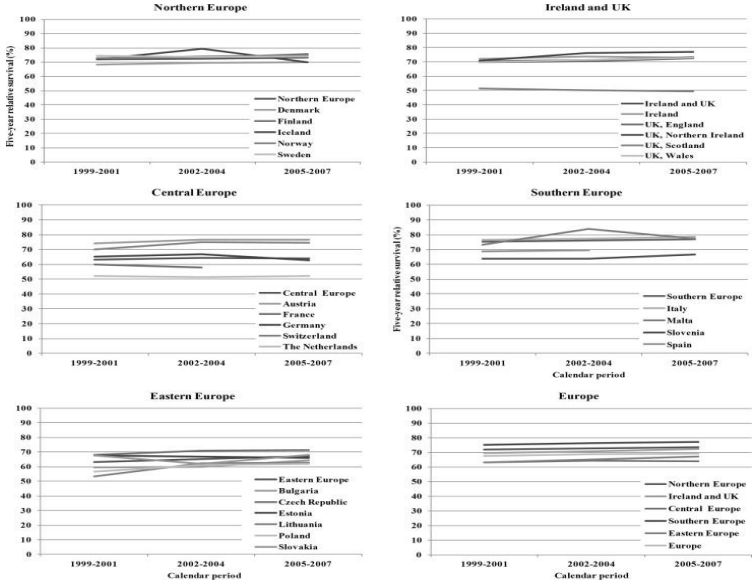
Overview

- Evidence base for bladder preservation as alternative to surgery
- Comparison to other primary sites
- Optimising bladder preservation – diagnostic pathways

Outcomes are static

Age-standardised 5-year survival for bladder cancer 1999—2007

N Europe



Ireland and UK

Central Europe

Southern Europe

Eastern Europe

Europe

Rafael Marcos-Gragera, et al **Urinary tract cancer survival in Europe 1999–2007: Results of the population-based study EUROCARE-5** European Journal of Cancer, Volume 51, Issue 15, 2015, 2217–2230 http://dx.doi.org/10.1016/j.ejca.2015.07.028

Surgery has been optimised

- Bladder cancer outcomes have not significantly improved for 30 years

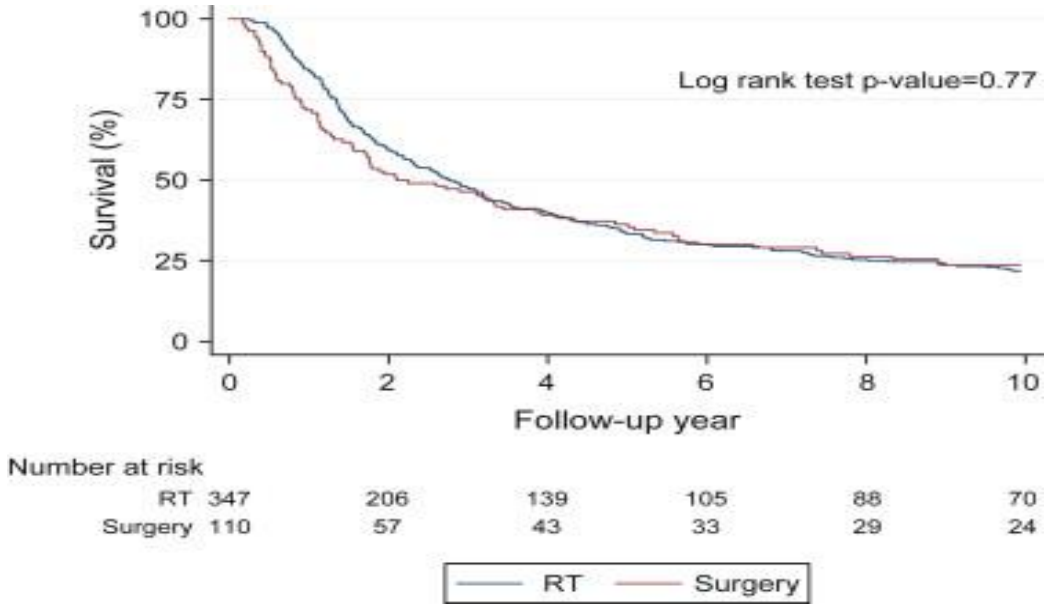
Zehnder P, Studer UE, Skinner EC, Thalmann GN, Miranda G, Roth B, Cai J, Birkhauser FD, Mitra AP, Burkhard FC, Dorin RP, Daneshmand S, Skinner DG, Gill IS. Unaltered oncological outcomes of radical cystectomy with extended lymphadenectomy over three decades. BJU Int 2013;112:E51-8

If you keep doing the same thing you get the same results!

IS SURVIVAL BETTER AFTER SURGERY?

Survival remains poor with death from metastasis

- 453 UK pts, 1993-1996
- Ratio RT:cystectomy 3:1
- 10 year survival RT 22% Surgery 24%



Munro NP, Sundaram SK, Weston PM, et al. A 10-year retrospective review of a nonrandomized cohort of 458 patients undergoing radical radiotherapy or cystectomy in Yorkshire, UK. Int J Radiat Oncol Biol Phys 2010;77:119-24.

Bladder cancer is a systemic disease

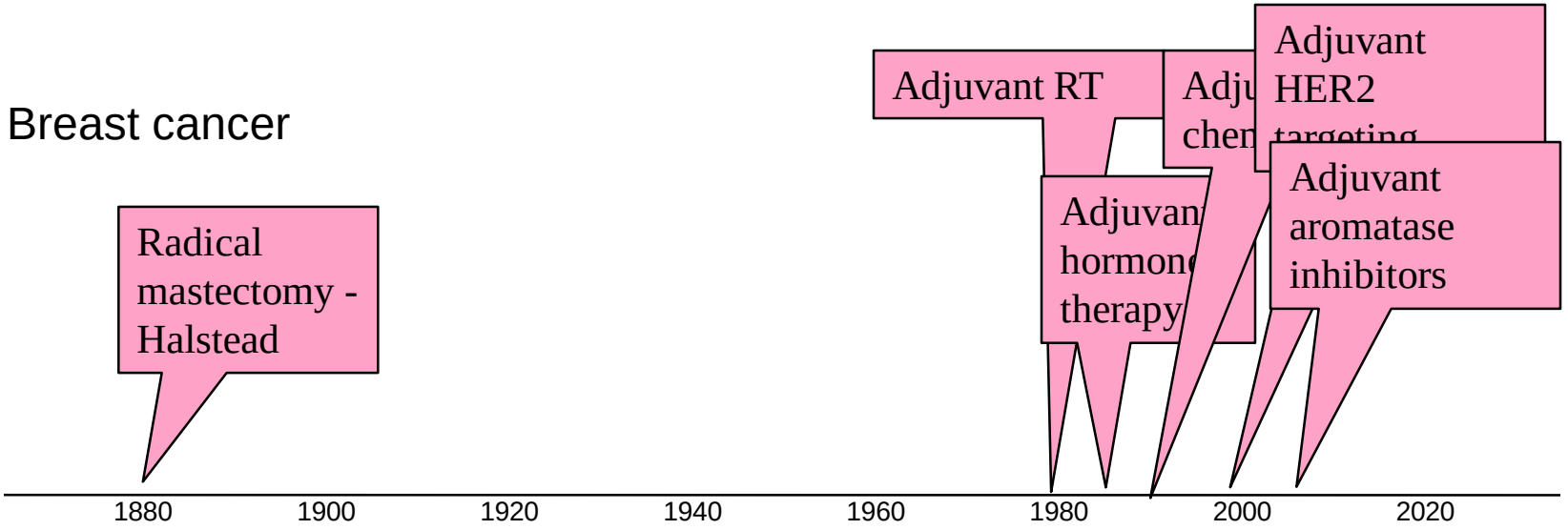
- No plateau in survival curves
  - Patients die from metastases

Treatment needs to address local control and distant metastases:

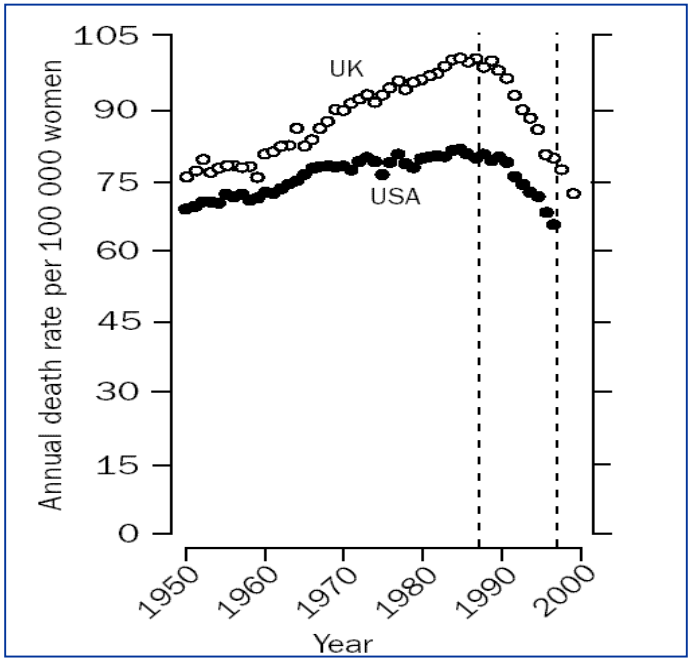
- Local control
  - Surgery or RT
- Metastases
  - Systemic therapy

WHAT CAN WE LEARN FROM OTHER CANCERS – BREAST CANCER?

Breast cancer therapy



Mortality Rates From Breast Cancer



IMPROVED OUTCOMES DEPEND ON NEW SYSTEMIC THERAPIES

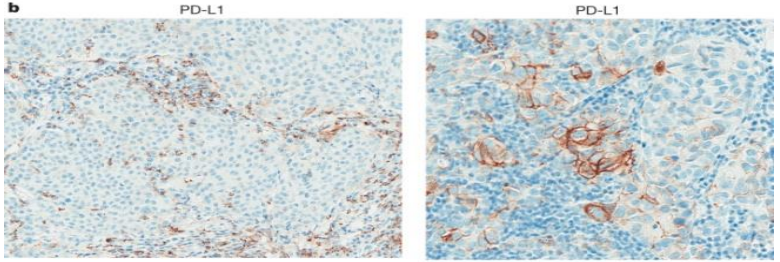
PD-L1 prevalence and response rates in patients with UBC.

a

PD-L1 prevalence in UBC tumours by IHC

n = 205	PD-L1-positive tumour-infiltrating immune cells (no. of specimens (%))	PD-L1-positive tumour cells (no. of specimens (%))
IHC 3	18 (9)	14 (7)
IHC 2	37 (18)	8 (4)
IHC 1	89 (43)	37 (18)
IHC 0	61 (30)	146 (71)

b



c

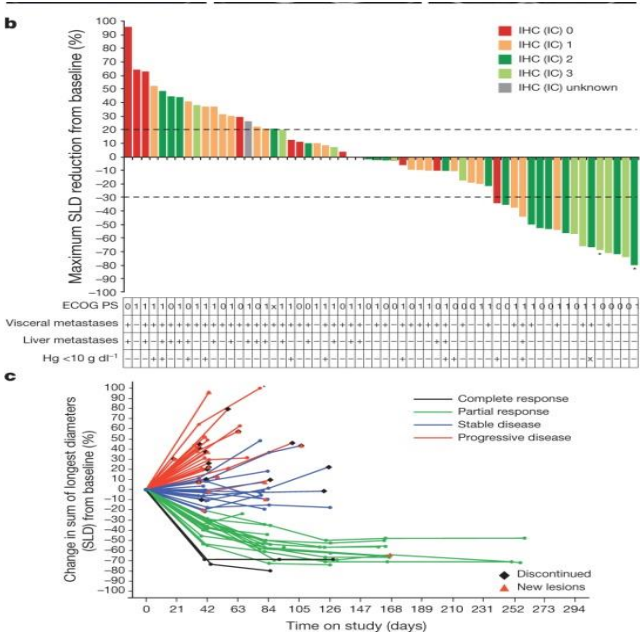
Tumour-infiltrating immune cells and objective response rates

	Objective response rate *n* (%)	Stable disease *n* (%)	Progressive disease *n* (%)
IHC 2/3 (*n* = 30)	13 (43.3) (95% CI: 25.5–62.6)	8 (26.7)	8 (26.7)
IHC 3 (*n* = 10)	5 (50.0) (95% CI: 22.2–77.8)	2 (20.0)	3 (30.0)
IHC 2 (*n* = 20)	8 (40.0) (95% CI: 20.9–63.9)	6 (30.0)	5 (25.0)
IHC 0/1 (*n* = 35)	4 (11.4) (95% CI: 4.0–26.3)	13 (37.1)	13 (37.1)
IHC 1 (*n* = 23)	3 (13.0) (95% CI: 3.7–31.7)	8 (34.8)	8 (34.8)
IHC 0 (*n* = 12)	1 (8.3) (95% CI: 0.4–34.9)	5 (41.7)	5 (41.7)

T Powles *et al. Nature* **515**, 558-562 (2014) doi:10.1038/nature13904

nature

MPDL3280A anti-tumour activity in patients with UBC.



T Powles *et al. Nature* **515**, 558-562 (2014) doi:10.1038/nature13904

nature

WHAT CAN WE LEARN FROM OTHER CANCERS – ANAL CANCER?

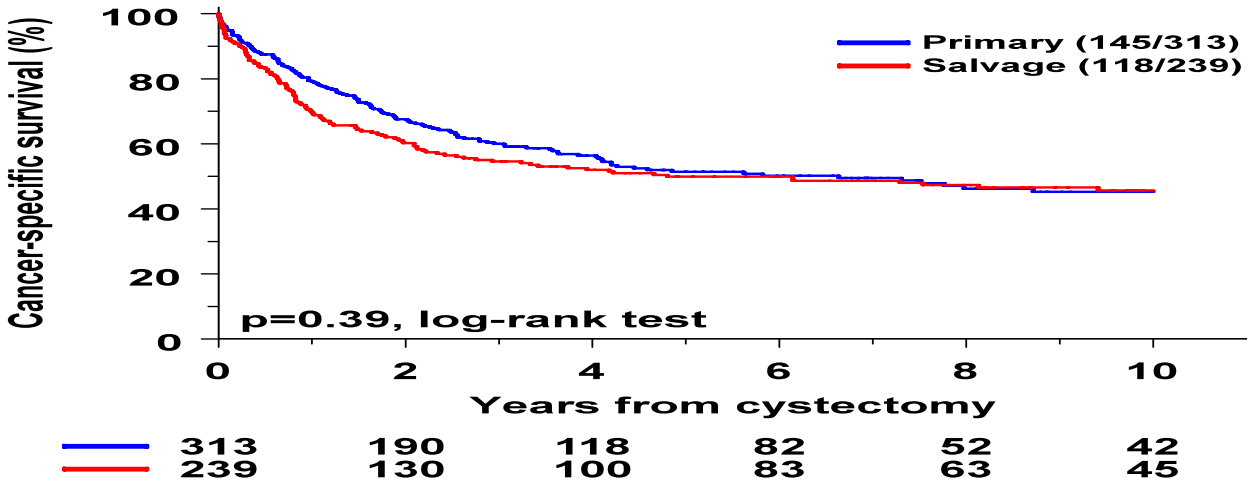
Anal cancer

- Primary therapy was surgery up until mid-1980s
- Various chemo-RT regimens showed high activity with range of agents including 5FU, MMC, cisplatinum during 1970s
- "…surgery as the primary therapeutic modality has been abandoned."

Anal cancer: ESMO-ESSO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up Ann Oncol (2014) 25 (suppl 3):iii10-iii20.doi: 10.1093/annonc/mdu159

CAN WE SALVAGE LOCAL FAILURES?

Primary vs Salvage Cystectomy



Addla et al. The Journal of Urology Vol. 181, Issue 4, Supplement, Page 633

Are complication rates higher with salvage cystectomy?

- 426 primary and 420 salvage cystectomies
- Single institution
- 1970-2005

Differential Complication Rates Following Radical Cystectomy in the Irradiated and Nonirradiated Pelvis
Vijay A.C. Ramani, Satish B. Maddineni, Ben R. Grey, Noel W. Clarke. Eur Urol 57 (2010) 1058–1063

Are complication rates higher with salvage cystectomy?

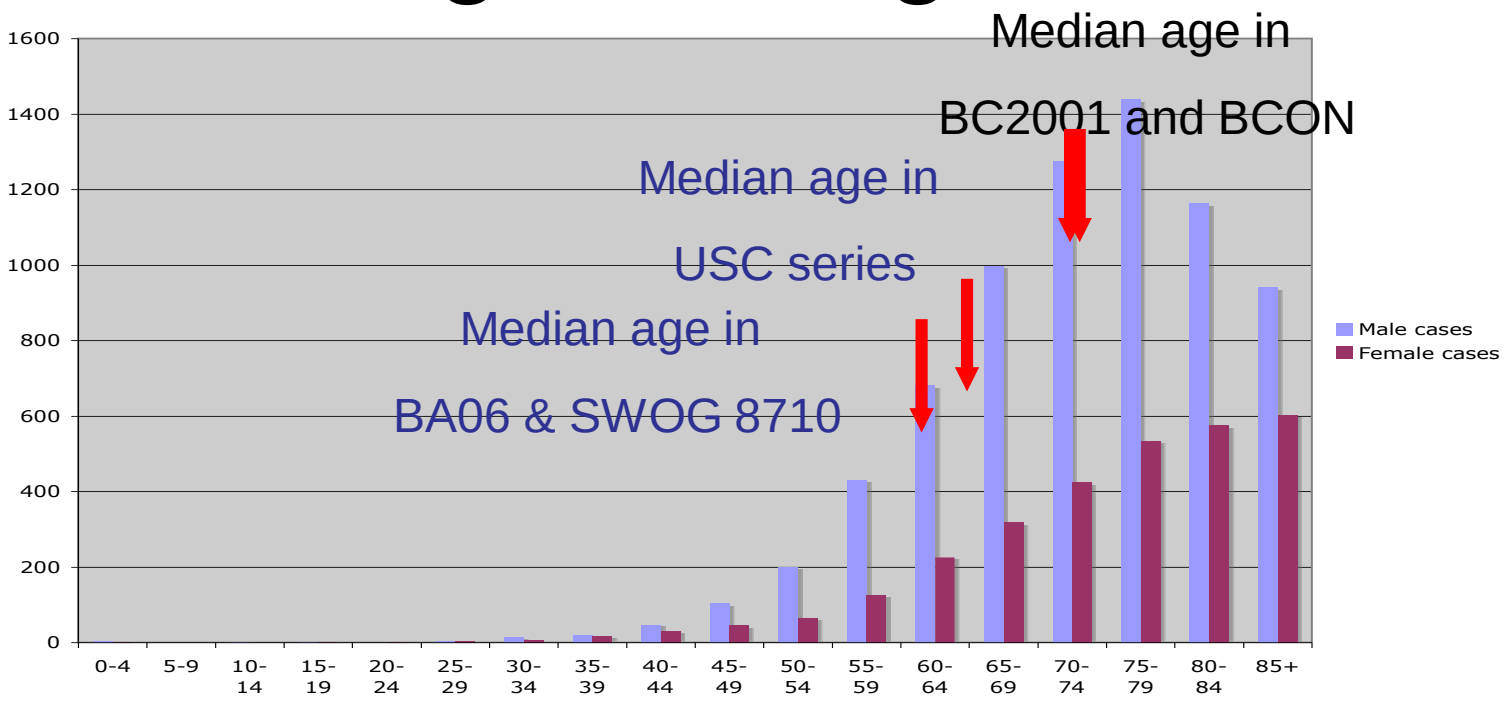
Complication	1970–2005		
	Salvage cystectomy, % (No.)	Primary cystectomy, % (No.)	*p* value
Wound infection	5 (21)	3.8 (16)	0.47
Haemorrhage	1.7 (7)	0.5 (2)	0.17
Anastomotic bowel leak	1.4 (6)	1.1 (5)	0.98
Wound dehiscence	4.8 (20)	4.2 (18)	0.83
Urinary leak	3.8 (16)	4 (17)	0.89

* More than 30 d postoperative; there was no statistically significant difference in either of the groups (χ^2 test).

Differential Complication Rates Following Radical Cystectomy in the Irradiated and Nonirradiated Pelvis
Vijay A.C. Ramani, Satish B. Maddineni, Ben R. Grey, Noel W. Clarke. Eur Urol 57 (2010) 1058–1063

IS SURGERY APPLICABLE TO THE WHOLE POPULATION?

Age at diagnosis



Choice of treatment

- Surgery and radiotherapy data relate to different segments of the population
- Hence age/fitness is important factor in treatment decisions

CHEMORADIOTHERAPY OUTCOMES

Radio-sensitisation

- Numerous phase I/II studies showing feasibility and safety
- Three phase III studies
  - RT vs RT + Cisplatinum (NCIC)
  - RT vs RT + nicotinamide/carbogen (BCON)
  - RT vs RT + 5FU/MMC (BC2001)

Radio-sensitisation

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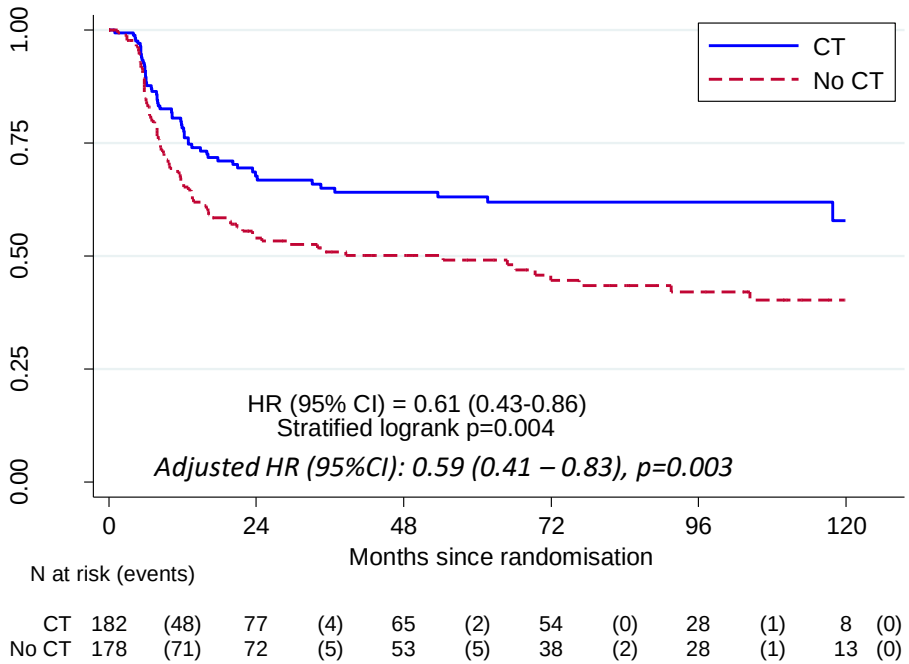
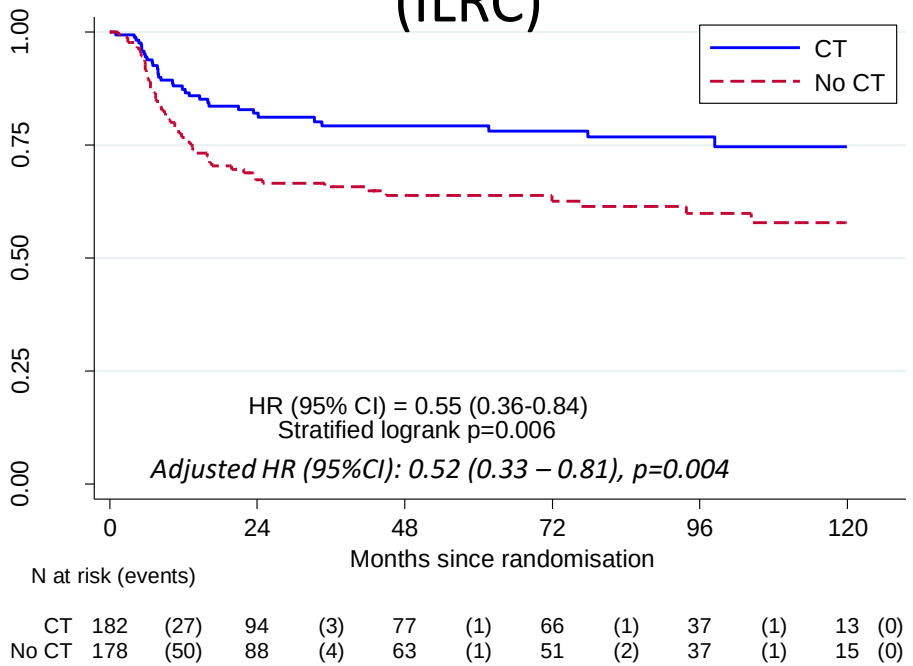
10 YEAR OUTCOMES BC2001

Updated results - CT comparison

Loco-Regional Control (LRC)



Invasive Loco-Regional Control (ILRC)

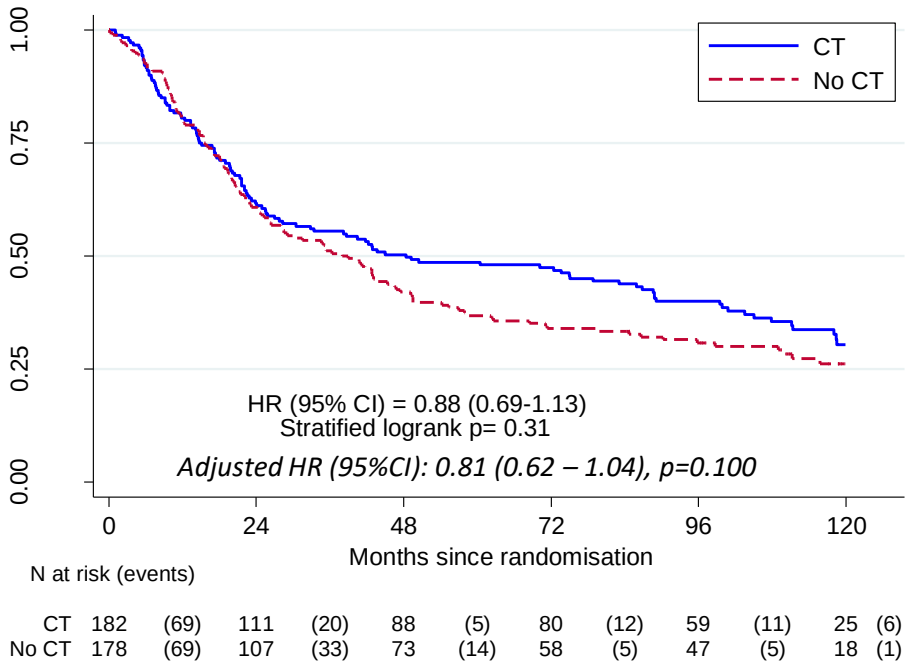


Hall et al Proc ESMO 2016

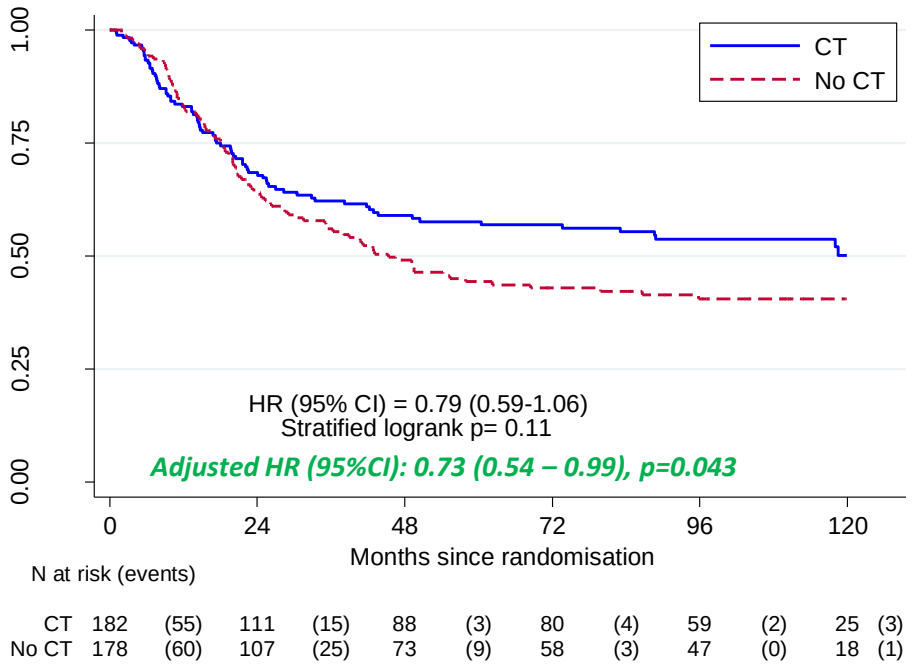
Snapshot of data: July 2016, N=360, Median FUP 117.1 m

Updated results - CT comparison

Overall Survival



Bladder Cancer specific Survival



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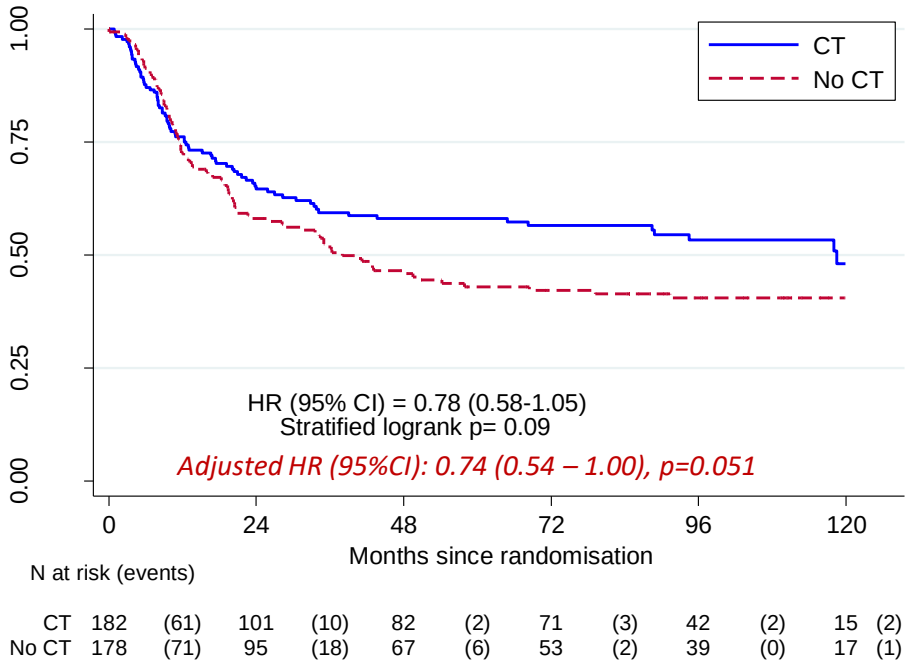
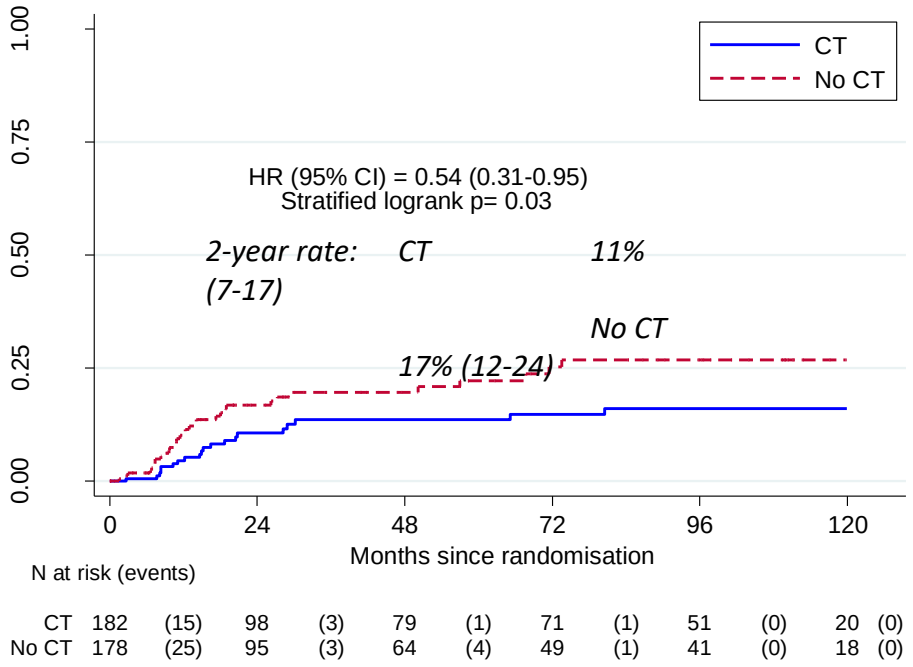
Snapshot of data: July 2016, N=360, Median FUP 117.1 m

Updated results - CT comparison

Metastasis Free Survival



Salvage Cystectomy Rate



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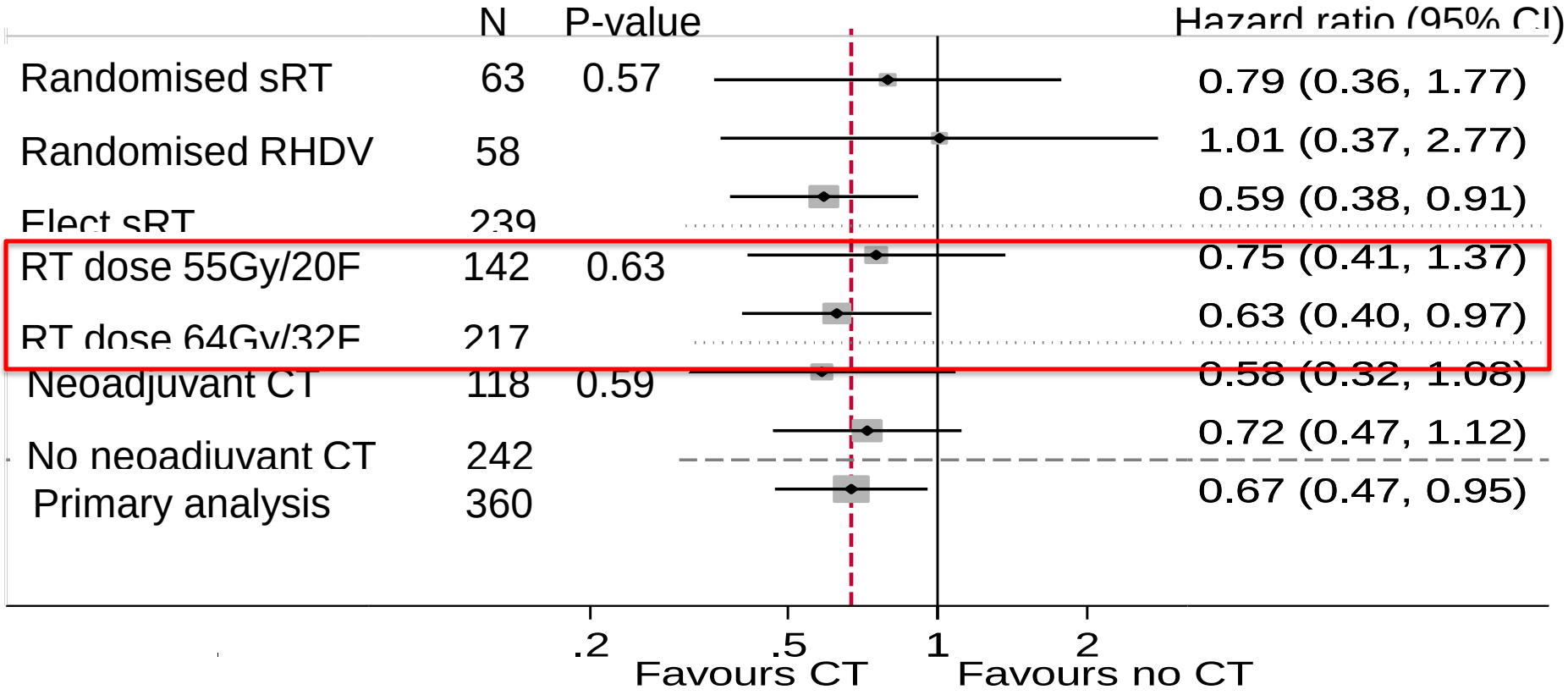
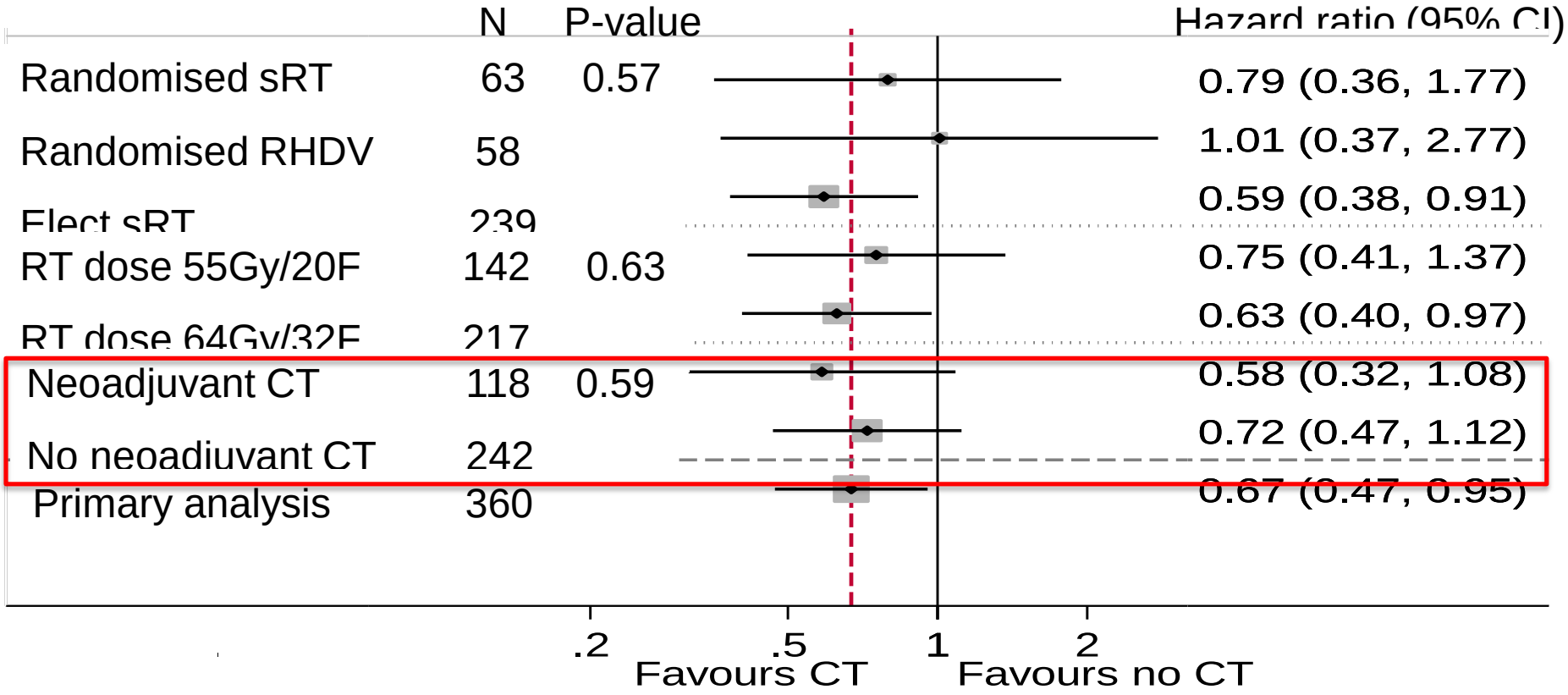
Snapshot of data: July 2016, N=360, Median FUP 117.1 m

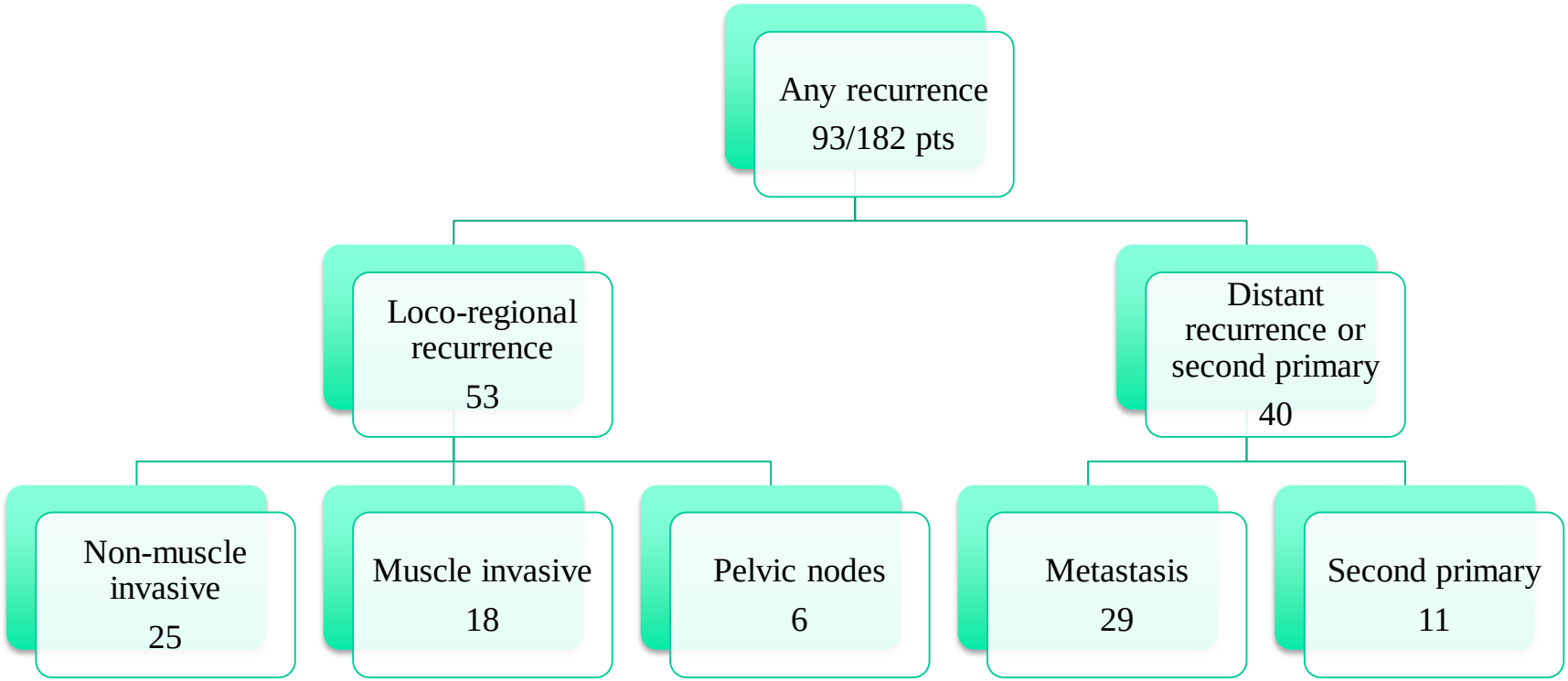
LRDFS - consistency across subgroups



LRDFS - consistency across subgroups



Patterns of recurrence after chemoRT

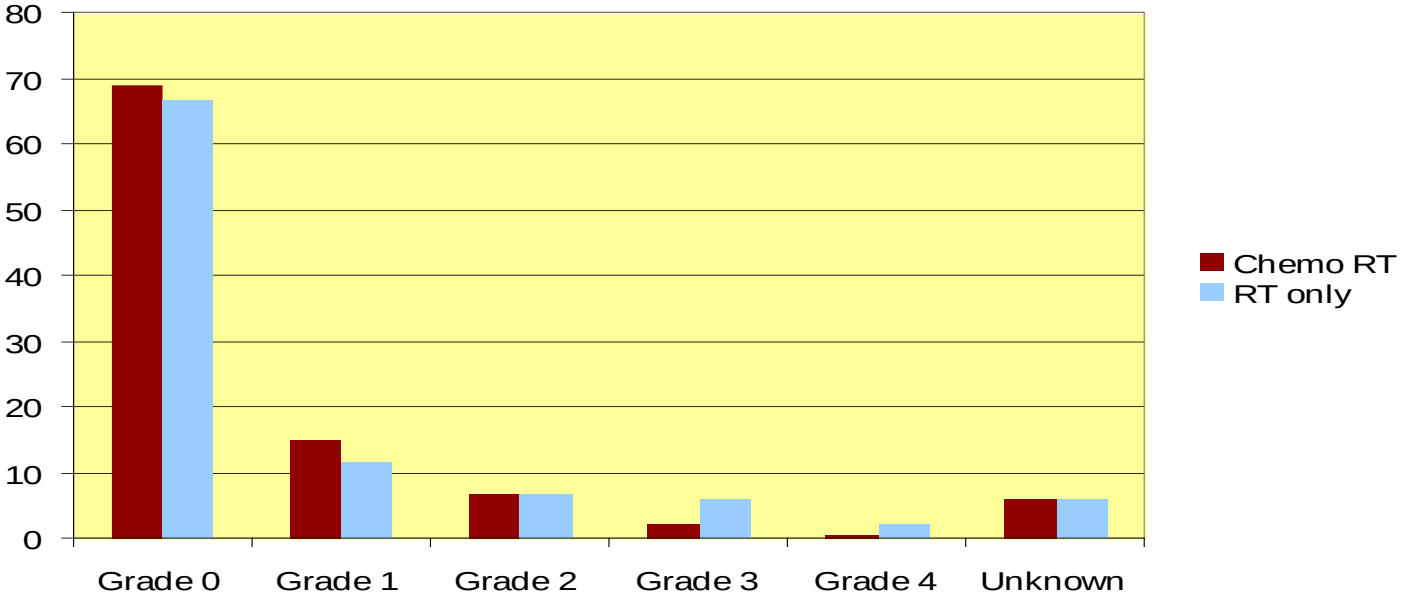


Further trials

- TUXEDO – RT/5FU/MMC + cetuximab
  - Analysis complete, good toxicity, QOL, high rate pelvic control
- RAD-IO - RT/5FU/MMC +/- durvalumab
  - Neoadjuvant, synchronous + adjuvant
  - Multi-stage trial – feasibility, intermediate efficacy, proceed to phase 3 if first 2 stages successful

“But radiotherapy leaves you a small poorly functioning bladder”

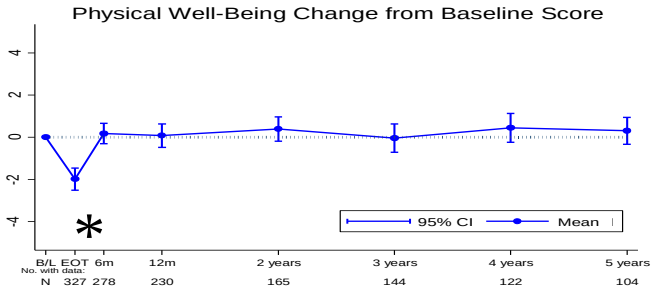
RTOG 6 month toxicity outcomes

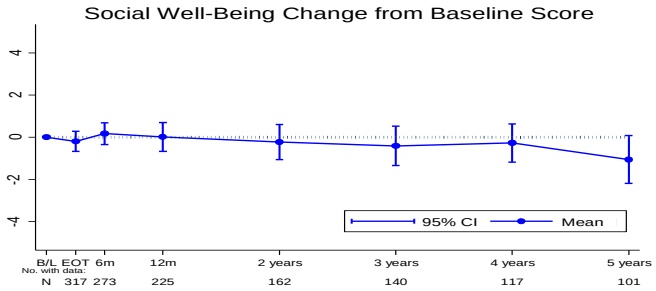


n= 291, 145 RT only, 146 chemo-radiotherapy

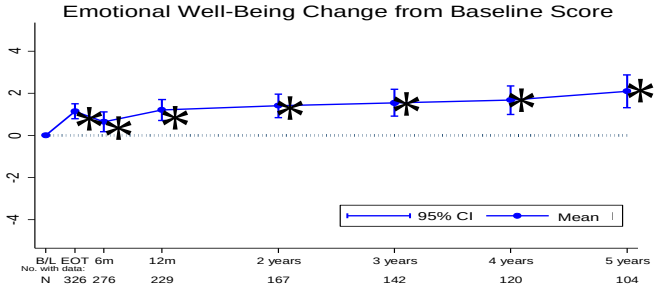
James et al, Radiotherapy with or without chemotherapy for invasive bladder cancer. NEJM 2012 366, 1477-1488

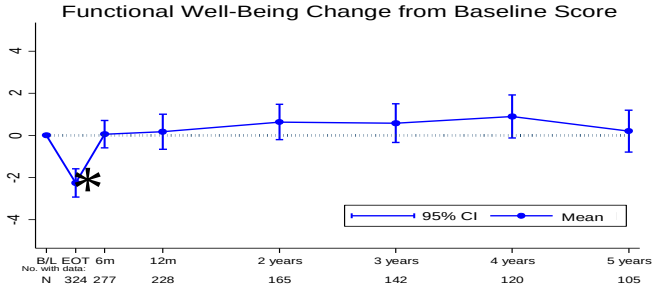
Change in FACT domains (all patients)





*Paired t-test ≤0.01





Hall et al Proc ESMO 2016

CAN WE SELECT PATIENTS FOR CHEMORADIOTHERAPY?

Patients unsuitable for surgery

- Elderly
- Severe cardiovascular or chest problems
- Obese
- Diabetes
- Patients reluctant or unable to cope with stoma
- etc

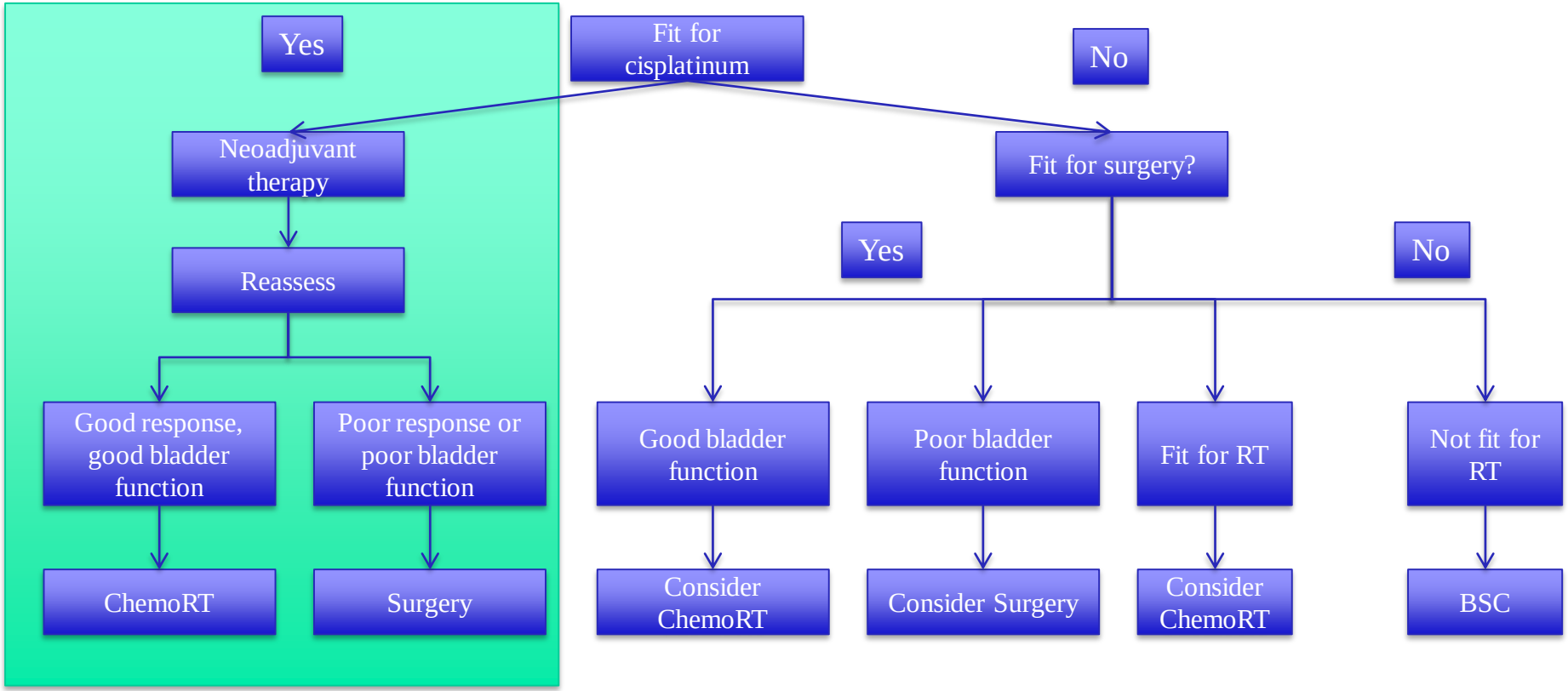
Patients unsuitable for (chemo)RT

- Poor bladder function
- Highly symptomatic bladders
- Extensive CIS
- Prior pelvic RT
- Inflammatory bowel disease
- Certain genetic disorders

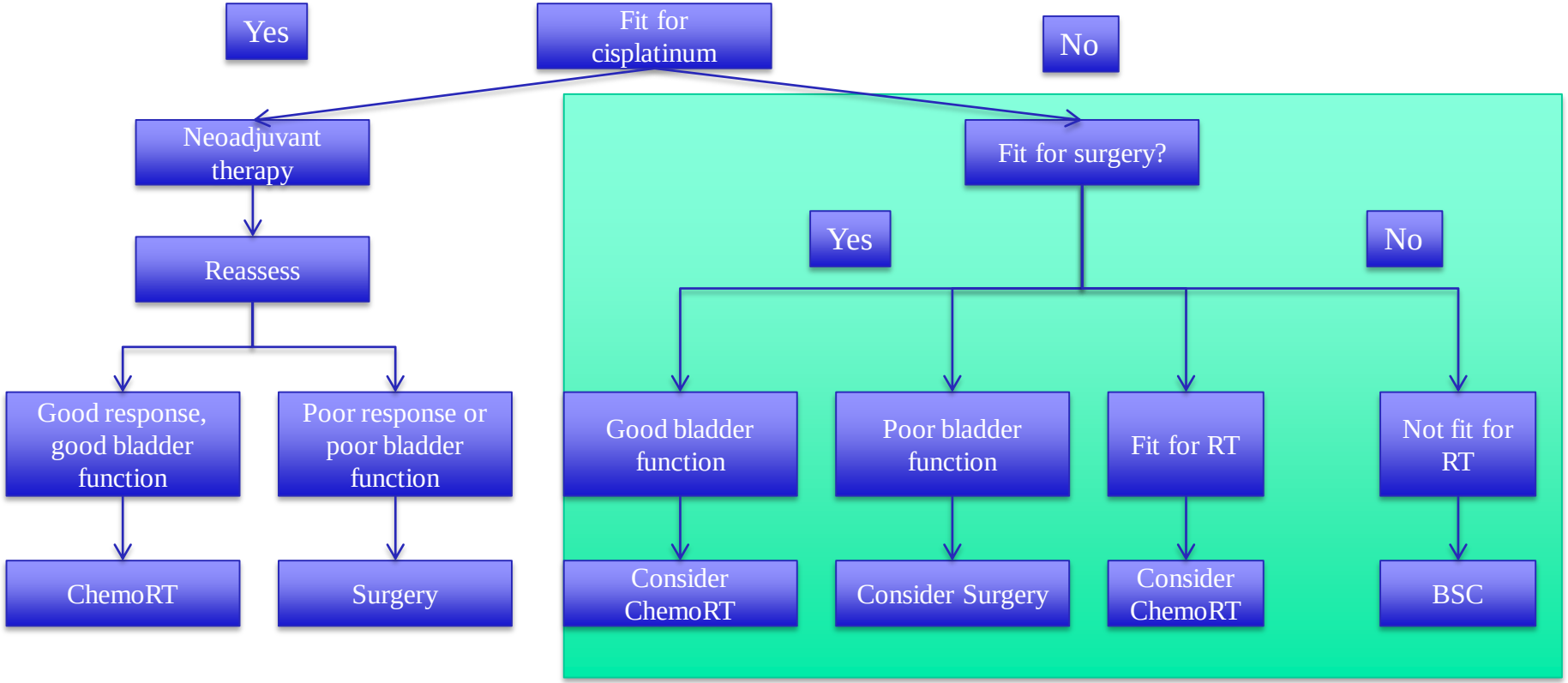
How to decide

- 3 groups:
  - Fit for surgery, fit for cisplatinum
  - Fit for surgery, not fit for cisplatinum
  - Not fit for surgery

How should we make decisions in MIBC?



How should we make decisions in MIBC?



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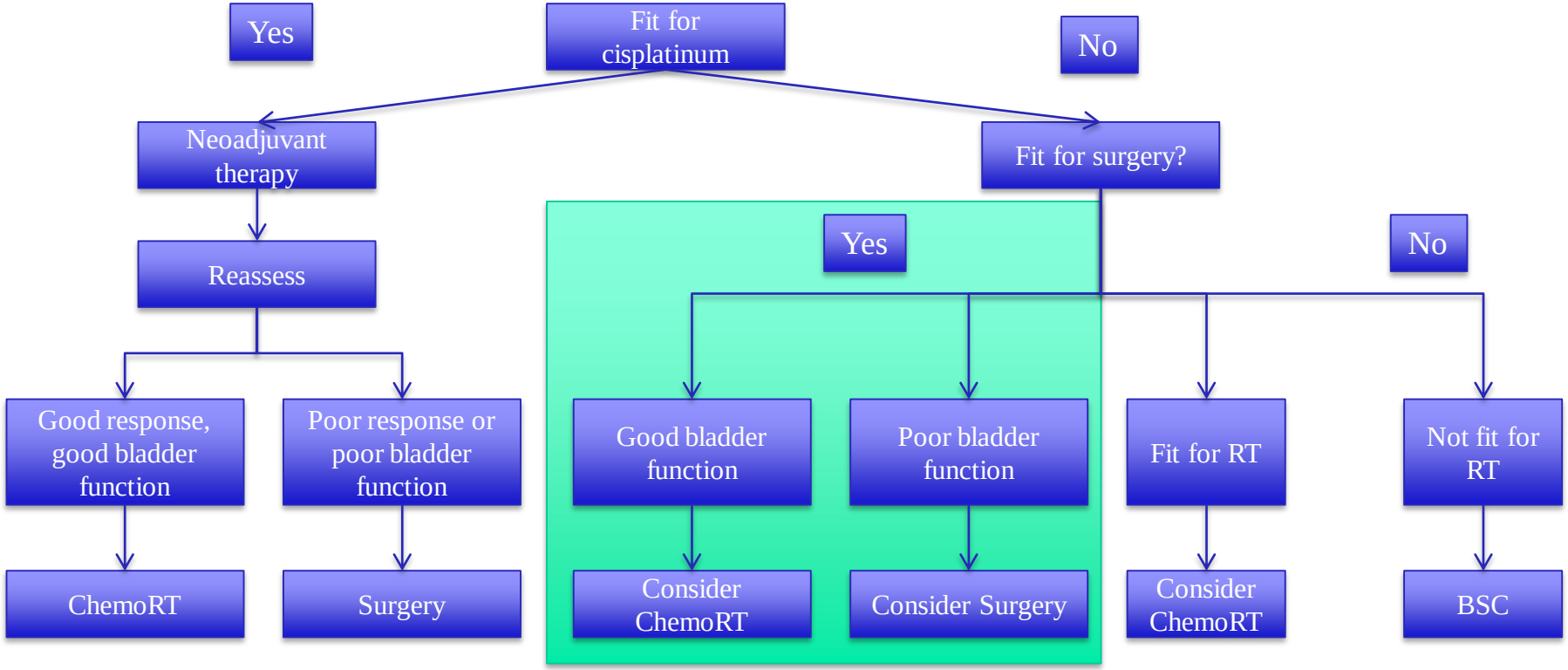

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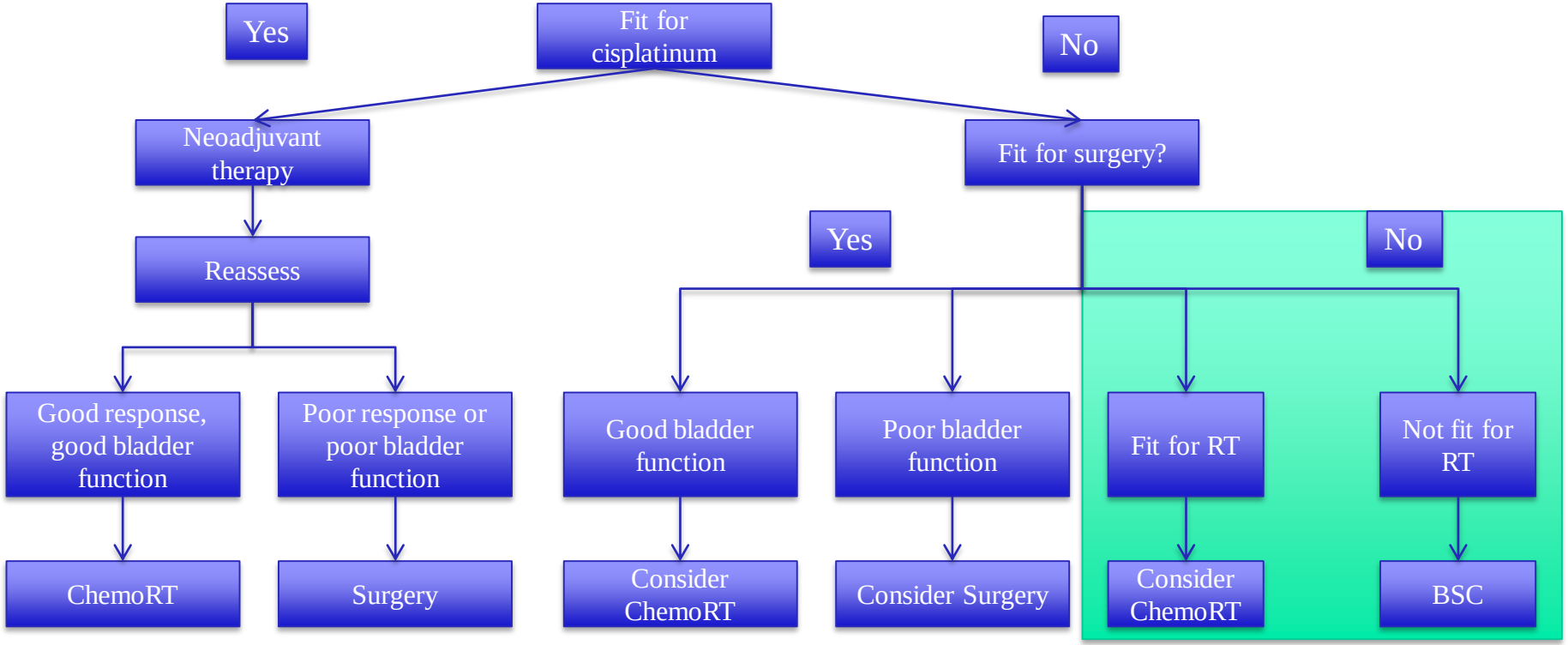
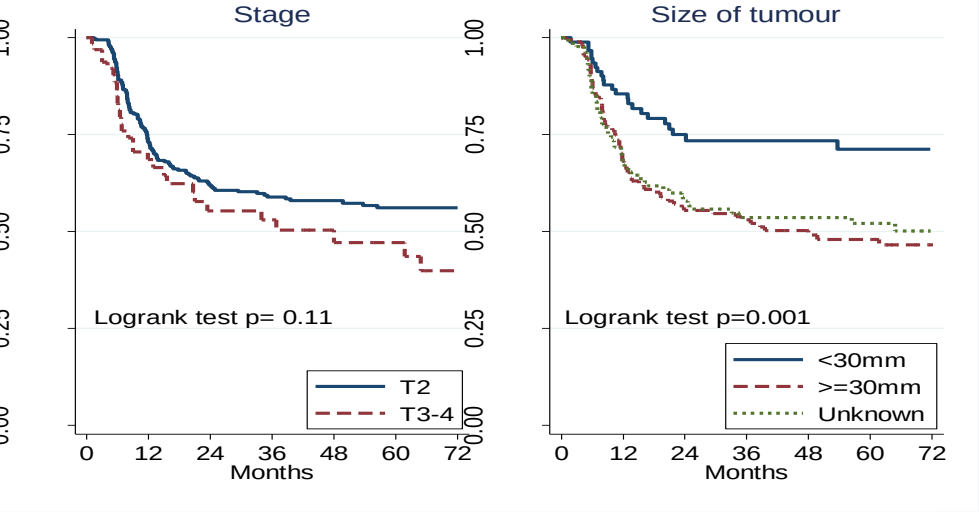
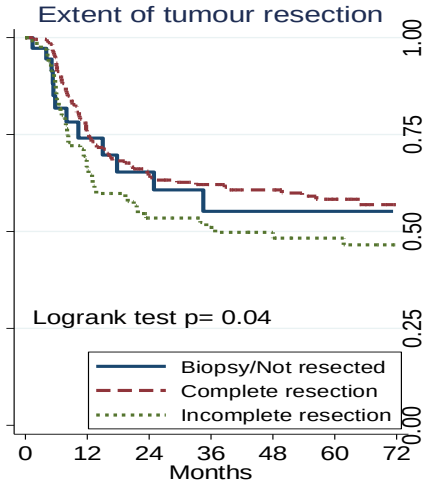
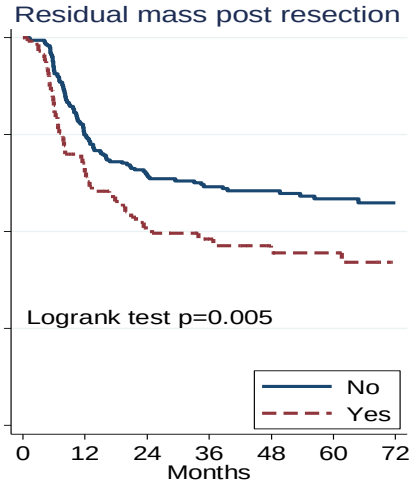


CHEMO-RT IN THE ELDERLY

Presence of residual mass, extent of resection and tumour size are related







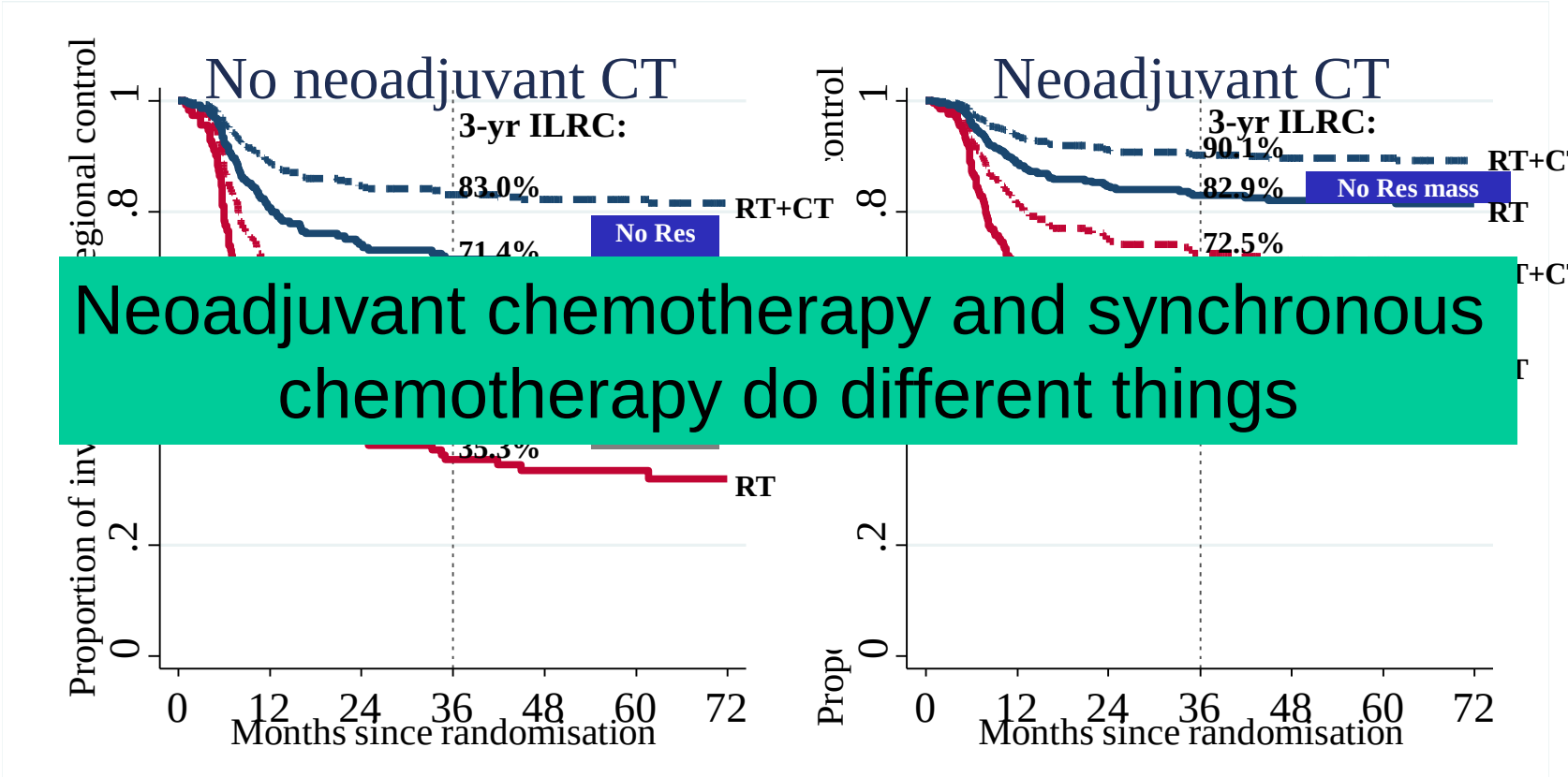
The presence of residual mass was highly correlated with extent of resection

- 96% complete resections without residual mass
- 66% incomplete resections with residual mass

TURBT and residual mass

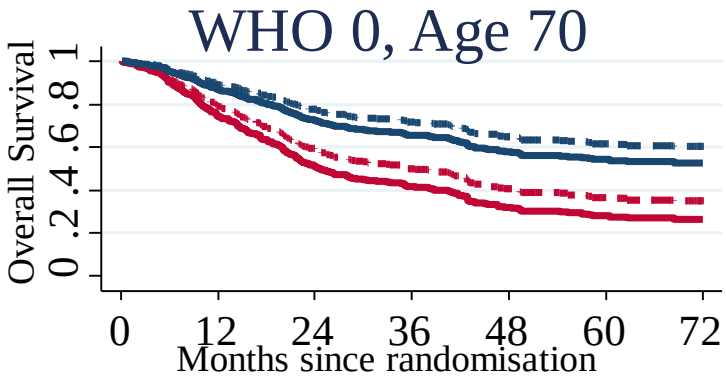
- Residual mass = high stage
- High stage = poor prognosis
- **Therefore does not follow that RT only for patients with no mass post TURBT as these patients will do badly with surgery**
- **Also does not follow that TURBT actually needed**

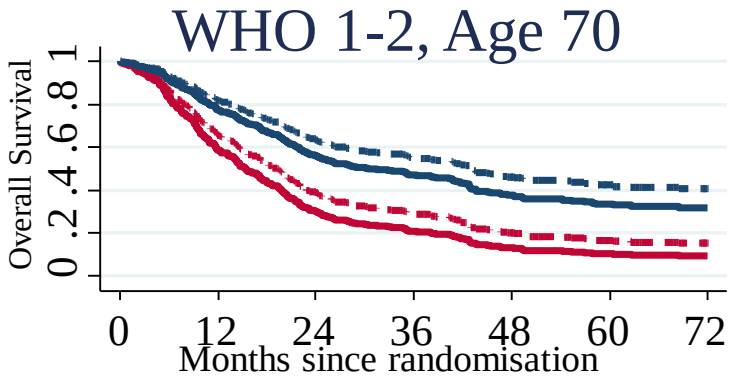
Effect of Multivariate factors on ILRC

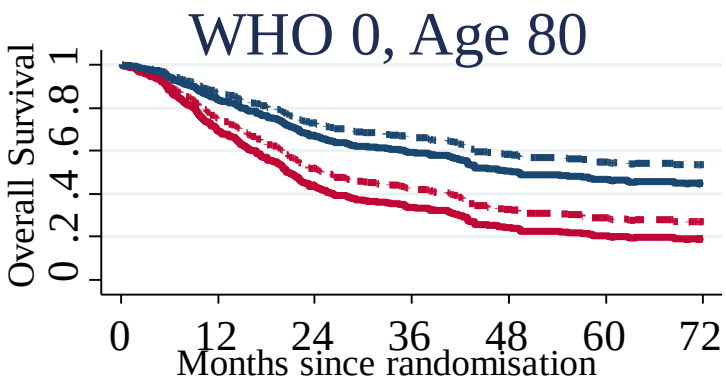


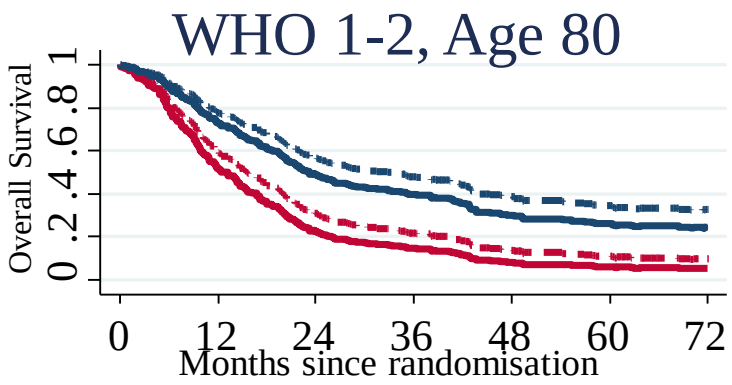
Neoadjuvant chemotherapy and synchronous chemotherapy do different things

Overall Survival









DIAGNOSTIC PATHWAYS

The origin of TURBT

TUMOURS OF THE URINARY BLADDER
WITH DESCRIPTION OF A NEW ENDOSCOPIC TECHNIQUE

By TERENCE MILLIN
SURGEON TO ALL SAINTS' HOSPITAL FOR GENITO-URINARY DISEASES, LONDON

THE last twenty-five years have seen a remarkable change in the outlook for those suffering from tumours of the bladder. Prior to 1910 the prognosis even for the so-called simple papilloma was virtually hopeless, and death brought a happy ending to months of agonizing strangury. A fuller realization of the characters of these bladder growths, and improvement in surgical technique, with introduction of ancillary therapeutic agents—notably high-frequency currents and gamma rays—have all played their part in this creditable chapter of surgical history. Though the picture has thus changed materially, and results are being obtained of which we may well be proud, "we are still far from the goal at which we are aiming" (Beer).

I propose in this paper to review briefly the nature of these bladder tumours and their diagnosis, to consider the most widely used methods of treatment, and to submit a new endoscopic technique employing the endothermy cutting current, which I have found of singular service in dealing with a number of such tumours.

PATHOLOGY

A very great variety of tumours occurring in the urinary bladder have been described. The following list (after Hinman) covers the vast majority :—

A. EPITHELIAL (95 per cent).—
1. Adenoma and endometrioma

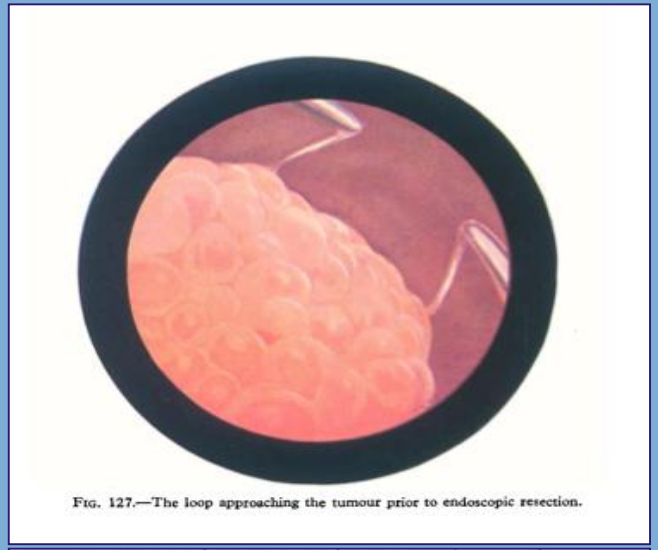


FIG. 127.—The loop approaching the tumour prior to endoscopic resection.

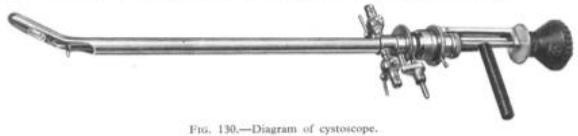
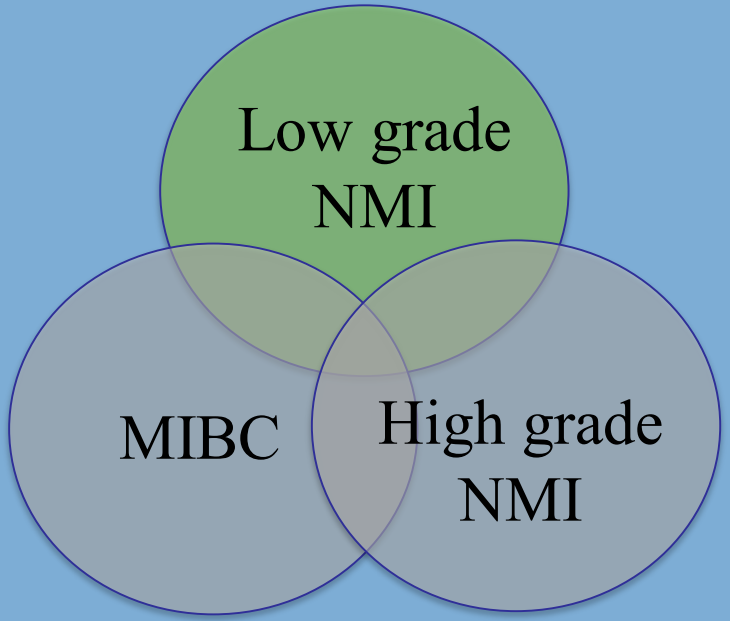


FIG. 130.—Diagram of cystoscope.

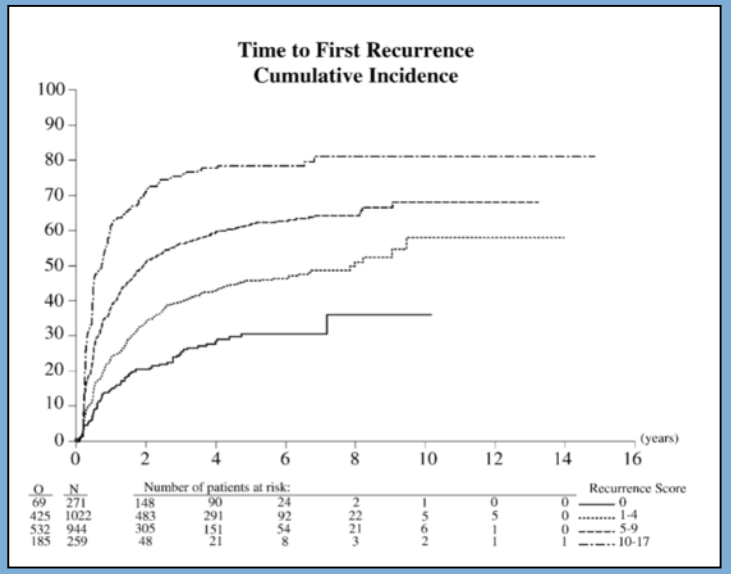
Br. J. Surgery: 1931

1. Does TURBT work?



Low grade NMI Bladder cancer

- High rates of local recurrence



Sylvester et al. EORTC data: Eur Urol 49 (2006) 466–477

What if breast cancer specialists behaved like urologists?

- Breast cancer would be diagnosed by 6 random needle cores in each breast
- Initial treatment would use a hot wire to scrape the middle of the tumour out, leaving the invasive bits round the edge to grow for several weeks while staging proceeds

Debulking in cancer care

- Very few disease sites use primary surgical debulking as staging for bulky disease
- Where this has previously been the practice, now abandoned for primary systemic therapy e.g.
  - Anal cancer
  - Breast cancer
  - Head and neck cancer

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
• Treatment	No - delayed
• Palliation of symptoms from bladder	Possibly

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

Do we need TURBT for histology?

- Flexible cystoscopy can give accurate histology

Can we replace TURBT for staging?

- TURBT is frequently inaccurate and operator dependent – 25-40% NMIBC upstaged at cystectomy
- Repeat TURBT in G3pT1 delays MIBC therapy if upstaged
- A test that distinguished <=T1 vs >=T2 could speed correct MIBC therapy

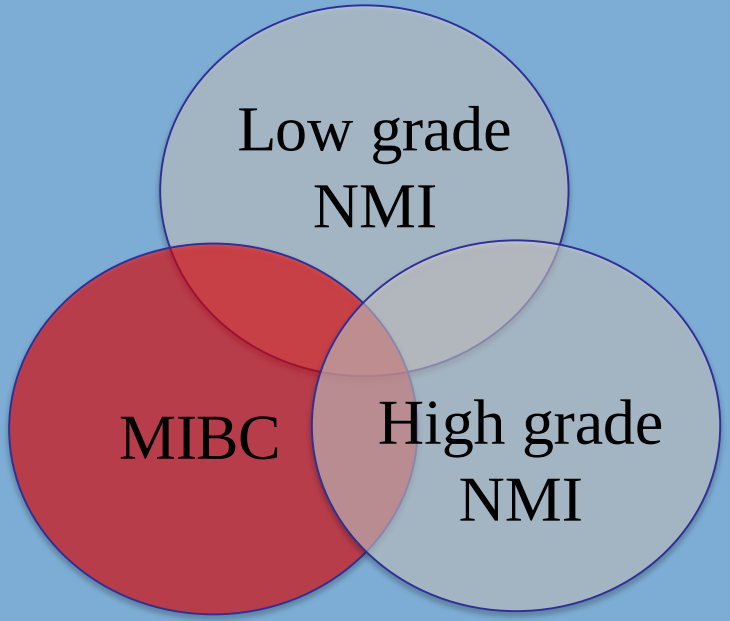
TURBT in MIBC

- 5% overt bladder perforation rate
- 50% occult bladder perforation
- Large increase in circulating tumour cells
- Around 10% of MIBC M+ at diagnosis but half of these get metastasis
- Could TURBT be actually spreading the cancer?

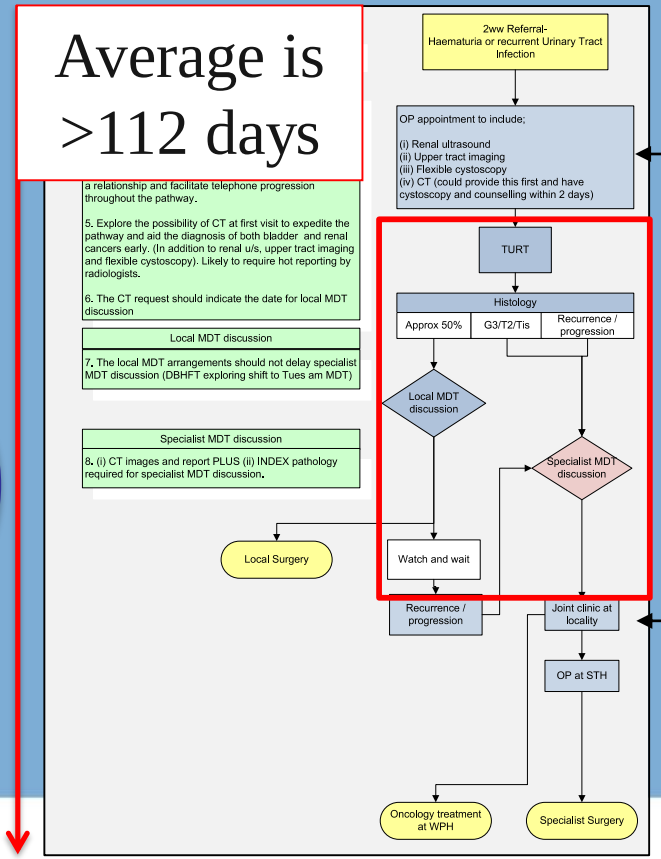
Is TURBT an essential component of MIBC treatment?

- If planning cystectomy why is it needed?
- No randomised data in bladder preservation

2. Does TURBT delay definitive treatment?



Average is >112 days



New lesion

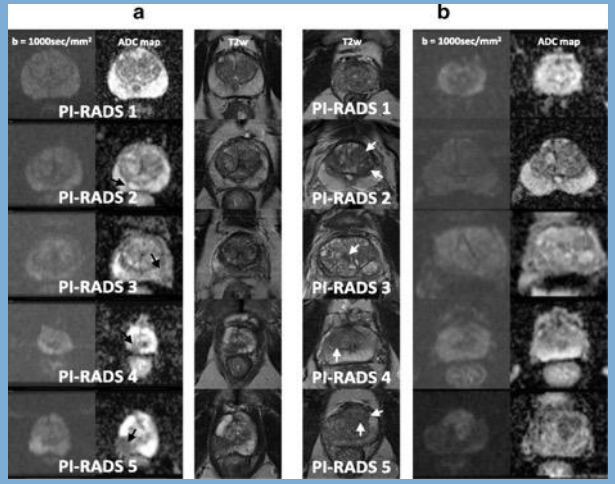
- TURBT 2-4 weeks
- Pathology +2 weeks
- Clinic +1-2 weeks
- ?Re-Resect +6 weeks
- Decision to Radical Rx +2-4 weeks

Total = 7-18 weeks

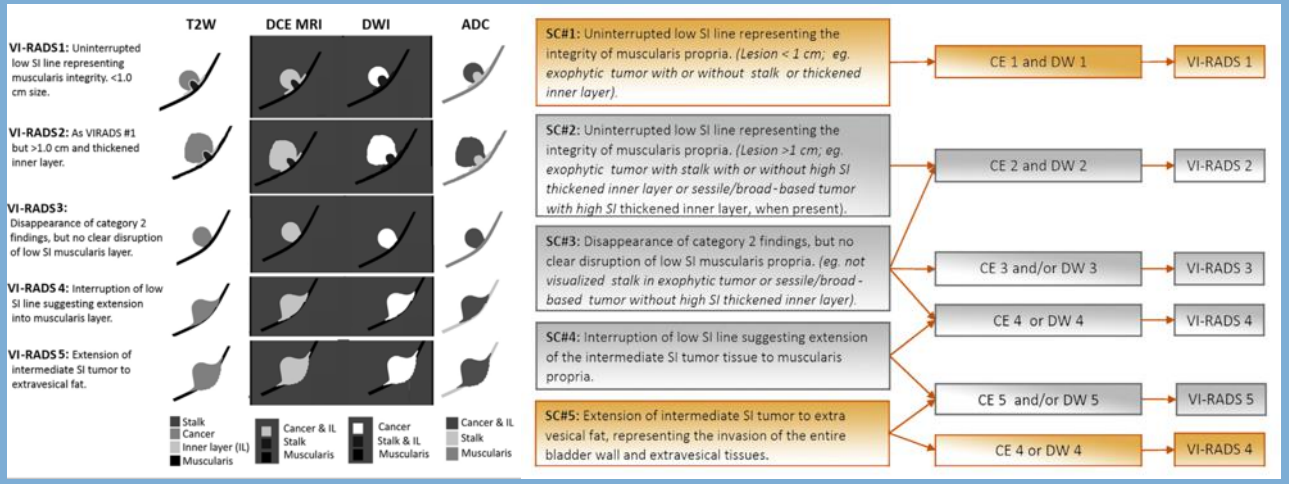
Radical treatment

RADS & Imaging

Prostate cancer: PIRADS



Bladder cancer: VIRADS



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 urgently needed for symptoms e.g. intractable bleeding

Problem: need to separate NMIBC from MIBC

MRI – Superficial vs invasive

Sensitivity

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

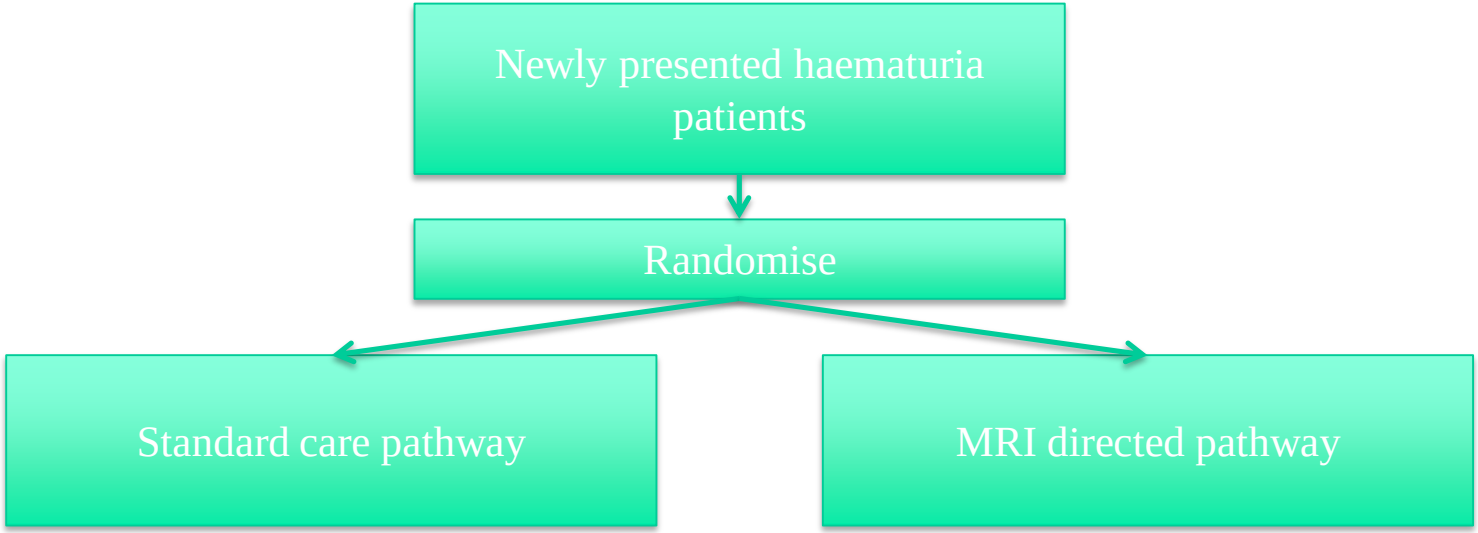
Specificity

- 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

BladderPath Trial



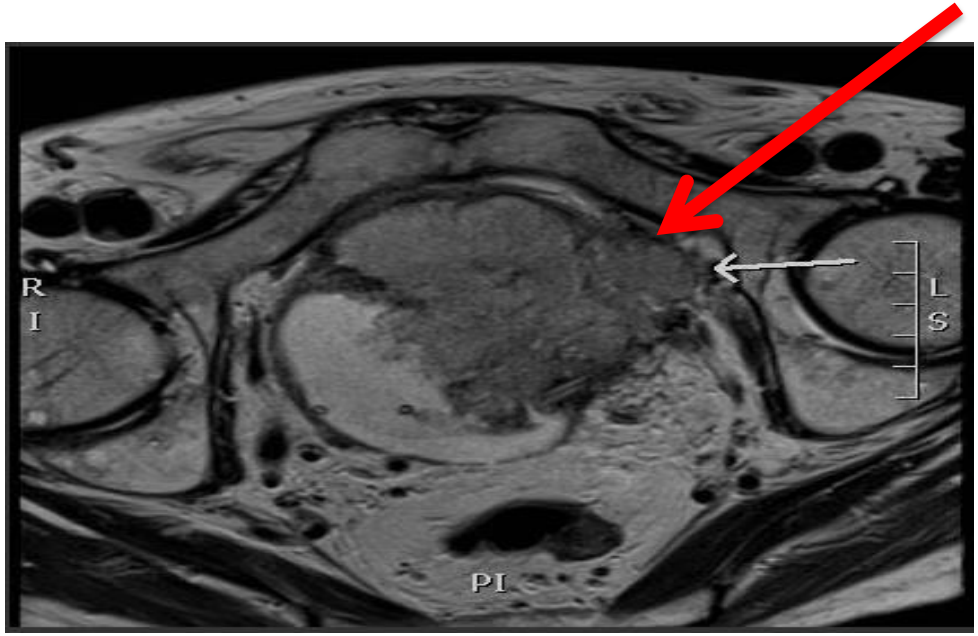
Outcome measures:
Stage 1: Feasibility, safety
Stage 2: Time to primary treatment
Stage 3: Failure free survival

BladderPath

- Feasibility stage – 150 patients
- Intermediate stage – event driven, at least 20 MIBC patients (approximately 80-100 patients will need to be recruited overall).
- Final clinical stage – event driven, (approximately 950 patients)

Patient 1

- Presented with haematuria
- Large mass on flexible cystoscopy
- Biopsy – G3TCC
- Proceeded direct to chemotherapy

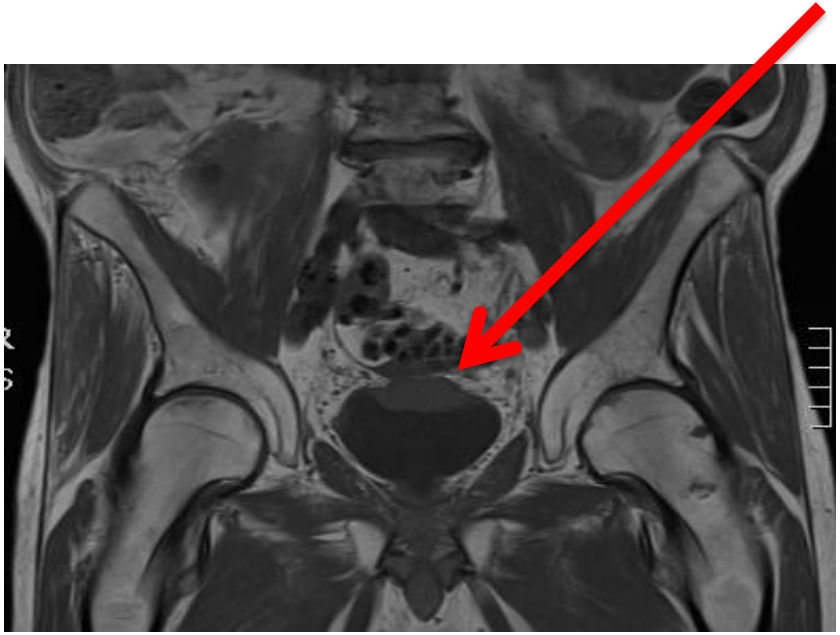


Patient 2

- Haematuria
- Flexible cystoscopy:
- 1.5 cm papillary tumour on left lateral wall
- Histology G2 TCC
- Stage T1N0M0

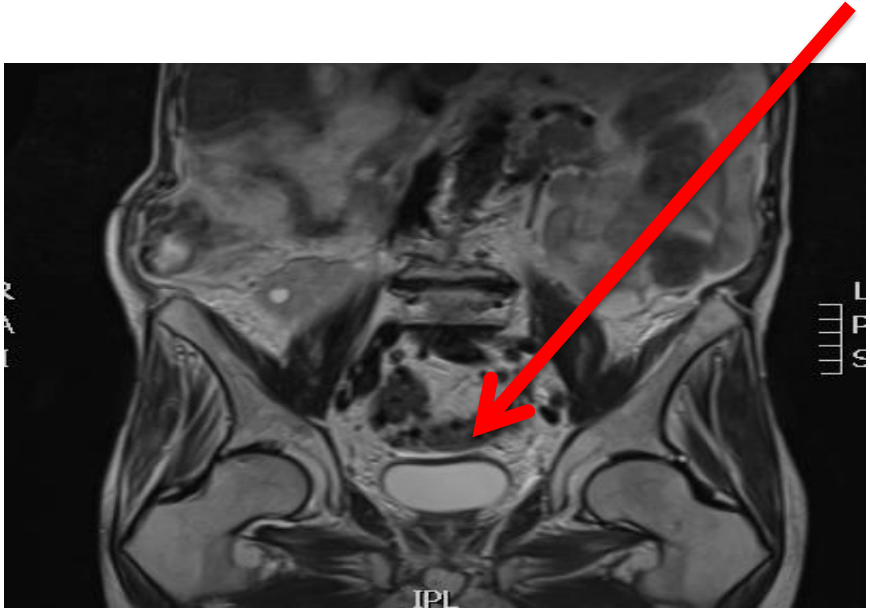
Patient 3

- Transplant pt
- Solid mass at dome of bladder, partial TURBT done
- T4 on MRI with bowel infiltration
- Lower bowel defunctioned



Patient 3 (cont)

- Completed 55Gy/20 fractions + 5FU/MMC
- Post RT cystoscopy – pathological CR
- MRI gives accurate response assessment



Conclusions

- No convincing evidence surgery superior to primary bladder preservation with salvage surgery
- Improved chemoradiotherapy schedules increase pelvic control compared to RT alone and reduce metastasis
- Improved systemic therapies should start to reduce deaths from metastasis