Chemotherapy in Upper Urinary Tract TCC (UUT-TCC)

Dr Alison Birtle MRCP FRCR MD

Honorary Clinical Senior Lecturer & Consultant Oncologist

Rosemere Cancer Centre.

What do we know

- Rare
- Poor prognosis
- Minimal data

What do we know
What do we need to know

- Rare
- Poor prognosis
- Minimal data

Improve outcome

Collect new data

Gold standard

Upper Urinary Tract Transitional Cell Carcinoma (UUT-TCC)

- Low prevalence 0.3%
- 13% patients with bladder carcinoma-in-situ (CIS)
- 2-4% patients with new bladder TCC
- Older age group (mean 65, peak 70's)
- Male:female 2:1
- Haematuria
  - Macroscopic 77%
  - Microscopic 23%

(South West Public Health Observatory, 2012)

Pattern of Failure

- Metastases:
  - Retroperitoneal 34%
  - Distal nodes 17 %
  - Liver 17%
  - Axial skeleton 13%
  - Lungs 9%

(Huben, 1988. Cancer 631:198)

Survival UUT-TCC

- Overall 12 month disease-free survival (DFS) of 75%
- T3/T4 overall survival (OS) of 37 months
- T4 median survival 6 months

(Raman et al., 2011. BJU International; 107(7))

Prognostic Factors

- T stage
- Nodal status
- Grade
  - G1-2 Recurrence rate 5%
  - G3 50% *(*Zincke Urol Clin North Am 1984;11:717*)*
  - Median survival G3 14 months

83 % BCR patients G2/3 (SWPHO/BCR)

(Genega & Porter. 2002. Am J Clin Pathol; 117 Suppl.)

347 Pelvic/Ureteric Tumours - Staging in 58.5% (BCR)

Known Staging	Total Known N	 %
Stage 0a (Ta N0 M0)	**65**	***32.0***
Stage 0is (Tis N0 M0)	**3**	***1.5***
Stage I (T1 N0 M0)	**43**	***21.2***
Stage II (T2 N0 M0)	**29**	***14.3***
Stage III (T3 N0 M0)	**39**	***19.2***
Stage IV (T4 N0 M0 Any T N1, N2, N3 M0 Any T any N M1)	**24 including 14 with metastases**	***11.8*** ***6.9***

45.3%

(c.f. 20.4% for bladder cancer)

Data
Adjuvant Chemotherapy

- Muscle-invasive bladder cancer (MIBC) - 9% difference in absolute survival at 3 years (11% with cisplatin)
- 25% reduction in risk of death
- Meta analysis - underpowered studies
- Chemotherapy given on relapse
- Different regimes
- Cochrane: negative
- USA/Europe-standard therapy

(Cochrane Database Syst Rev, 2006(2): p. CD006018)

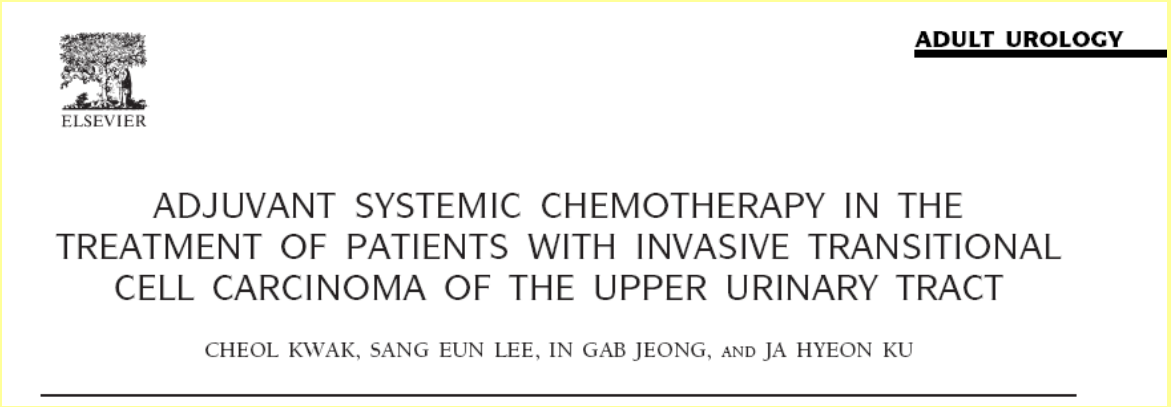
Adjuvant Chemotherapy in UUT-TCC

- Retrospective studies / abstracts
- Low patient numbers

Dufresne et al ASCO 2006 Abstract 14611

Single centre retrospective review (1993-2005)

- 66 patients: 41 pT2-pT4, pN0-2 M0
- Adjuvant treatment:
  - None: 25
  - Chemo: 6
  - Radiotherapy: 1
  - Chemo and radiotherapy: 9
- 27 patients relapsed - median time 12 months
- Response rate to chemotherapy in metastatic disease - 40%



ELSEVIER

ADULT UROLOGY

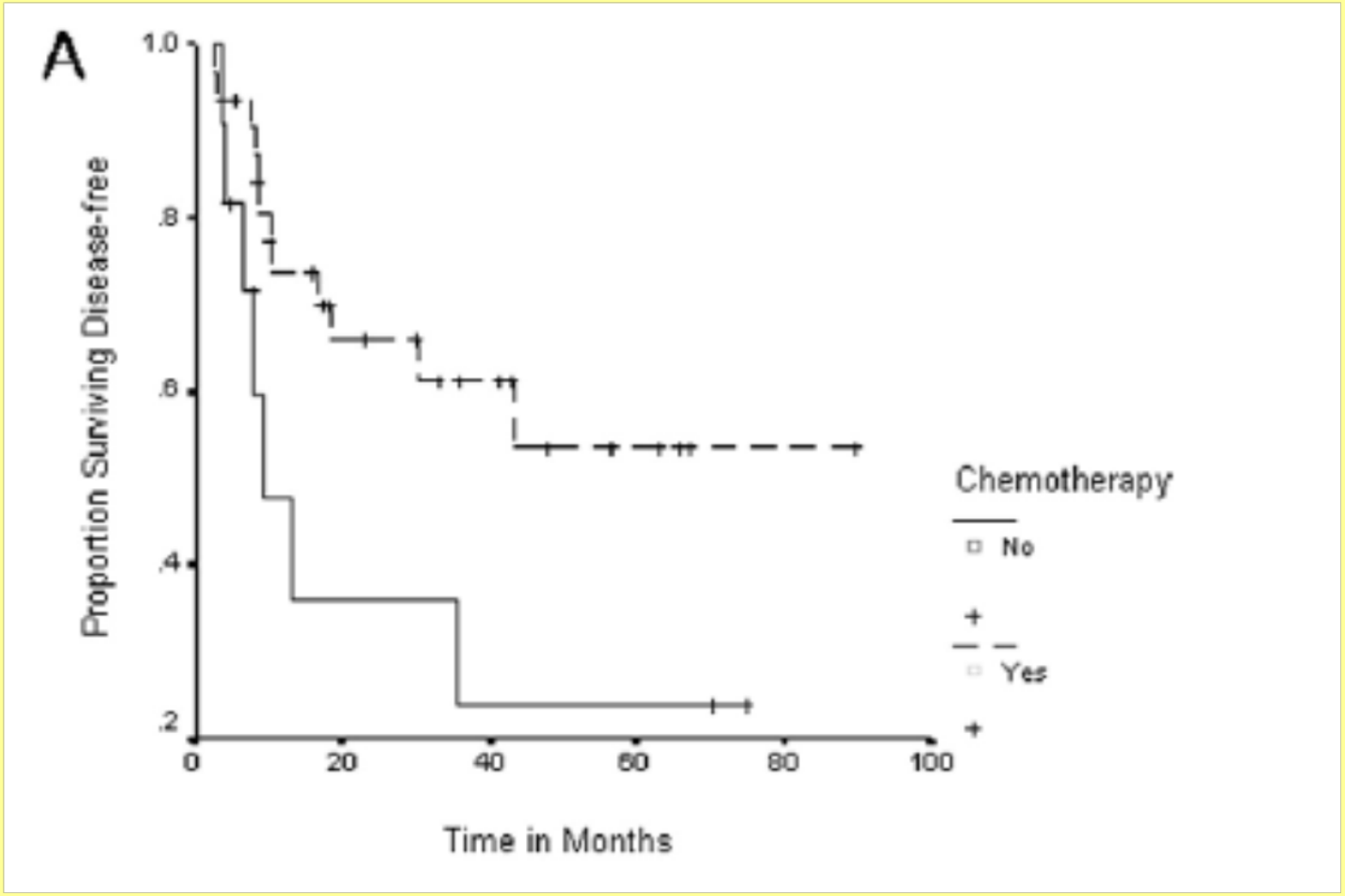
ADJUVANT SYSTEMIC CHEMOTHERAPY IN THE TREATMENT OF PATIENTS WITH INVASIVE TRANSITIONAL CELL CARCINOMA OF THE UPPER URINARY TRACT

CHEOL KWAK, SANG EUN LEE, IN GAB JEONG, AND JA HYEON KU

- 43 patients 1991-2001
- 39 patients T3
- 11 patients N+
- Median follow up 30 months
- Adjuvant chemo versus observation

(Urology 2006 68(1):53-7)

Disease Free Survival



Overall Survival

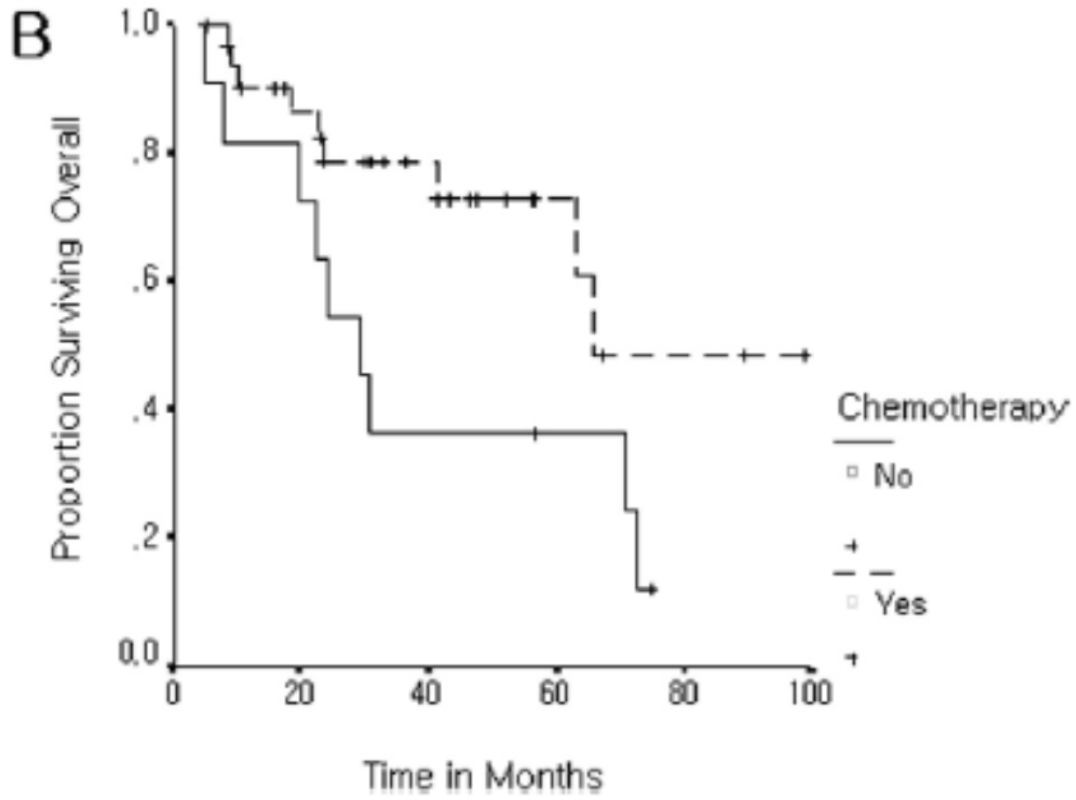


FIGURE 1. *(A) Disease-free survival by adjuvant chemotherapy (P = 0.0439, log-rank test for trend). (B) Overall survival by adjuvant chemotherapy (P = 0.0362, log-rank test for trend).*

Upper Tract Urothelial Carcinoma Collaboration ASCO 2009 Abstract 5075

- Collaboration MD Anderson, Ann Arbor, Montreal, South Western, Sacramento, Mannheim, Graz, Milan.
- 1390 patients nephro-ureterectomy (1992-2006)
- 542 (39%) high risk pT3N0, pT4N0, N+

Upper Tract Urothelial Carcinoma Collaboration

- Adjuvant chemotherapy 121 (22%) of high risk patients
- Given to patients with higher grade and stage more frequently
- No difference in OS, Cancer specific survival
- Median survival 24 months

(Hellenthal, N.J., et al., 2009. The Journal of Urology; **182**(3))

Rest of the World

- NCI Dana Faber Phase II
  - Neo-adjuvant study dose dense MVAC
  - Bladder/ureteric/urethral tumours
  - Grade 3, mass on CT imaging
- Lahey Clinic Burlington Phase II
  - T1-T3 NxMx
  - G3 GFR > 60mls
- ***Reservations…..***

Neo-adjuvant Treatment

- No definitive pathology pre–op
- Over treatment
- No tumour

(Chitale et al. 2008. Ann R Coll Surg Eng; 90(1))

Current UK Practice

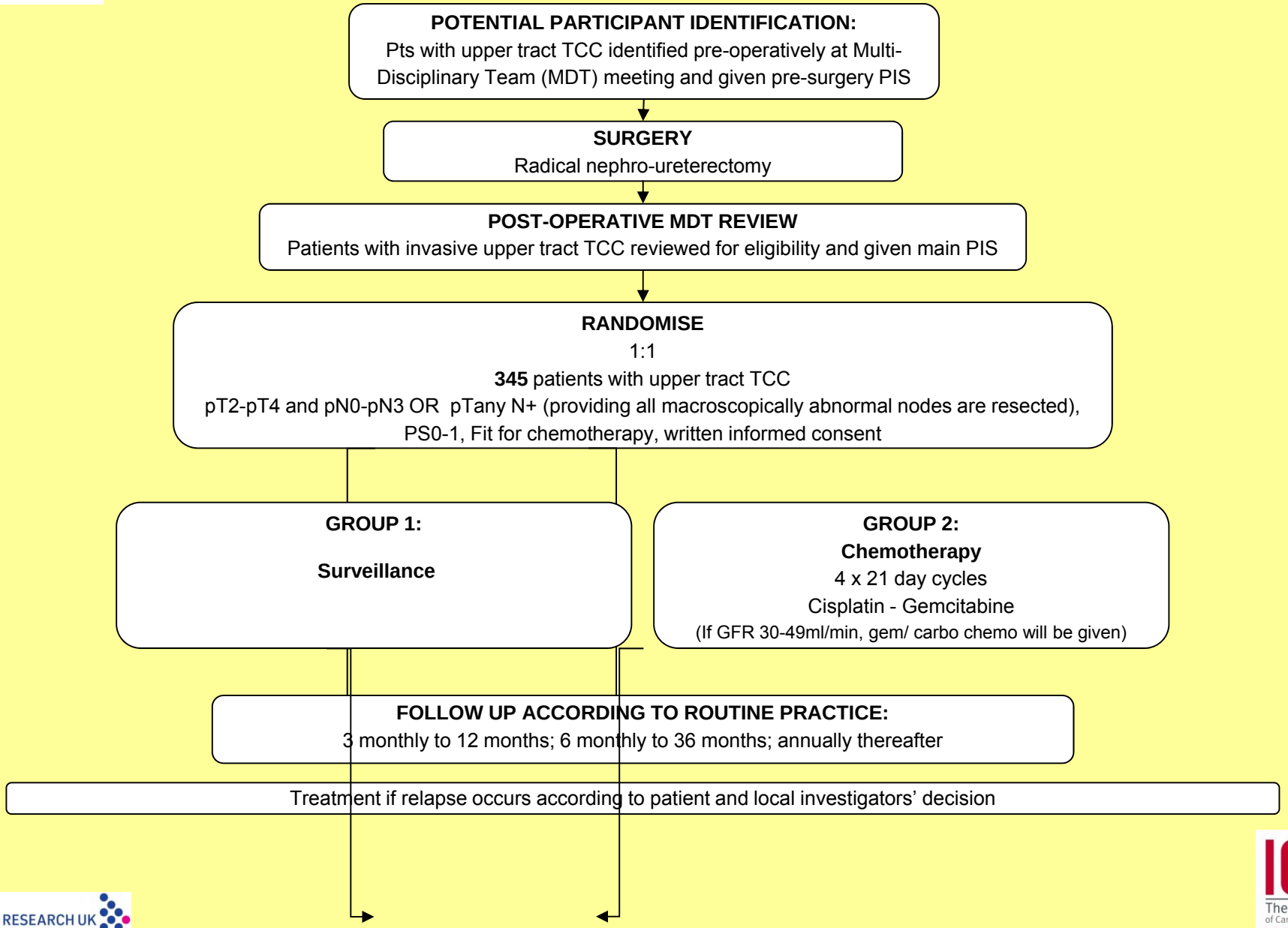
- Survey of 36 centres (BAUS Oncology Annual Meeting, Nov 2011 Birtle et al.):
- 14/36 provide adjuvant chemotherapy on a case by case basis
- 22/36 provide surveillance
- Patient involvement - focus groups

Learning from History…

- EORTC 30994: adjuvant chemotherapy vs chemotherapy on relapse in MIBC
- Start treatment within 90 days of cystectomy- fitness?
- Concurrent prostate cancer
- Data on neo-adjuvant chemotherapy published
- Cisplatin only (GFR)

What do we need to know ?

POUT Trial Schema



funded by CANCER RESEARCH UK

ICR The Institute of Cancer Research ICR-CTSU

Inclusion Criteria

- UUT-TCC pT2-pT4 N0-N3 M0 or pT1 N+ M0
- Fit for chemotherapy
- Willing to receive chemotherapy or surveillance
- Performance status 0-1
- Chemotherapy to start within 90 days of radical nephro-ureterectomy (RNU)

Inclusion Criteria

- Creatinine clearance ≥30 mls/min
  - Gem-cis if > 50, Gem-carbo if 30-49 mls/min
  - Carbo ONLY to be used for sub-optimal renal function not overall fitness.
- Resection of all macroscopic nodes
- NB. repeat negative post-op imaging if N+ on pre-op imaging

Design

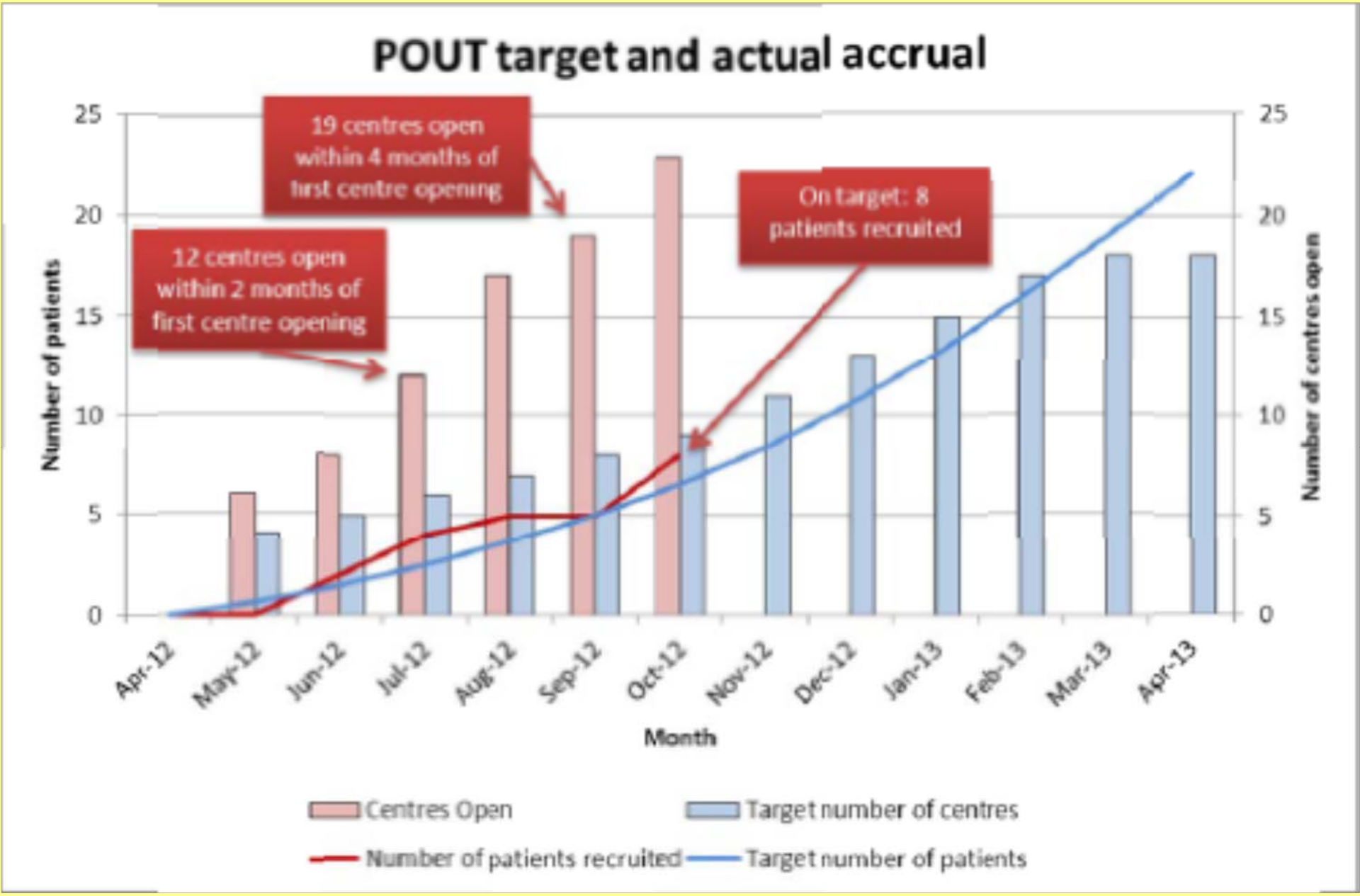
- Standard follow up
- Standard surgical technique
- Sub-studies – translational, quality of life, qualitative and imaging biomarkers (radiological review of pre-operative CT urograms)

Trial Endpoints

- Primary:
  - Disease free survival at 3 years
- Secondary:
  - Overall survival
  - Metastasis free survival
  - Incidence of bladder second primary tumours
  - Incidence of contralateral primary tumours
  - Acute and late toxicity
  - Treatment compliance
  - Quality of life (QoL)

Key Stages

- Identification
- Information-PIC sites
- Patient ownership
- Prompt histology (90 chemo window)
- Follow up
- POUT “Champion”


POUT target and actual accrual
19 centres open within 4 months of first centre opening
12 centres open within 2 months of first centre opening
On target: 8 patients recruited
Number of patients
Number of centres open
0
5
10
15
20
25
Apr-12
May-12
Jun-12
Jul-12
Aug-12
Sep-12
Oct-12
Nov-12
Dec-12
Jan-13
Feb-13
Mar-13
Apr-13
Month
Centres Open
Target number of centres
Number of patients recruited
Target number of patients