**Hypoxia-targeted Intensification of Radiotherapy for Bladder Preservation: A Phase III Randomised Trial of Biomarker Validation (CONCeRT)**

**Background**

Muscle invasive bladder cancer has relatively poor prognosis, with only half of people diagnosed still alive five years later. Radiotherapy is a standard curative treatment, and its efficacy can be improved either by the addition of radiosensitising chemotherapy (5FU/MMC, cisplatin or gemcitabine) or by the use of hypoxia modifying agents nicotinamide and carbogen (CON).

Since these results became available a biomarker 24 gene panel to detect hypoxia has been developed and tested retrospectively using FFPE samples from BC2001 and BCON participants. Subsequent analyses have suggested that hypoxia modifying agents have most effect on survival for people with hypoxic tumours, and that this may have an additive effect when given alongside radiosensitising chemotherapy.

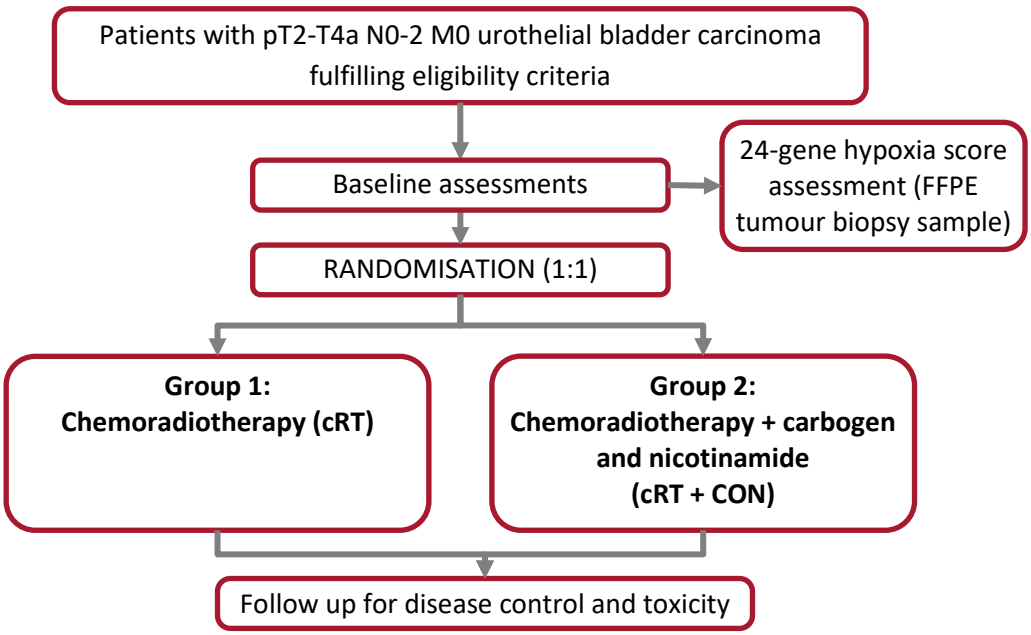
**Aims:**

This trial will test whether giving CON alongside chemotherapy will improve outcomes over chemoradiotherapy alone. It will also investigate validation of a biomarker threshold to identify patients with hypoxic tumours, who would derive maximum benefit by treatment with bladder radiotherapy and CON.

**Study design**

This is a randomised phase III multicentre trial of hypoxia modification during chemo-radiotherapy for bladder cancer, with a biomarker-adaptive threshold design. 550 participants will be included.

**Trial schema**




**Primary endpoint:** 2-year loco-regional recurrence-control (LRC) including invasive recurrence in bladder, pelvic nodes, or need for cystectomy

**Secondary endpoints:** Progression-free survival; overall survival; treatment related toxicity; patient reported outcomes.

**Key inclusion criteria**

1. Histologically confirmed localised muscle invasive urothelial bladder carcinoma, staged T2-T4 N0-2 M0
2. Planned for, and fit to receive, curative chemoradiotherapy
3. FFPE diagnostic tissue blocks available for central analysis
4. Written informed consent

**Key exclusion criteria**

1. Medical contraindication to chemotherapy or CON
2. Simultaneous urothelial carcinoma in upper tract or urethra
3. Pregnancy
4. Active malignancy within 2 years of randomisation
5. Severe renal impairment
6. Co-existing respiratory disease unable to use a closed breathing system (eg, uncontrolled COPD)
7. Known allergy to any component of drugs

**Interventions**

All participants will receive image-guided radiotherapy using a 55Gy/20f regimen treating the whole bladder with the option of whole pelvis for those with nodal disease. Use of adaptive plan of the day radiotherapy is permitted according to local standard practice. Permitted concomitant chemotherapy regimens will be 5-fluorouracil/mitomycin C, gemcitabine according to site's standard regimen, from hospital stock.

Participants allocated to the hypoxia modification group will receive carbogen and nicotinamide (CON) in addition to chemoradiotherapy. Oral nicotinamide (60 mg/kg) 1.5 to 2 hours before each radiotherapy fraction. Carbogen (2% $CO_2$ and 98% $O_2$; 15 L/min 5 minutes before and during radiotherapy). CON should be sourced from hospital stock.

Diagnostic FFPE blocks for all participants should be submitted for central hypoxia gene panel screening at trial entry. Follow up will be in accordance with UK national guidance. Participants may receive neoadjuvant chemotherapy as per standard of care.

**Endpoints**

The primary endpoint is locoregional recurrence control, secondary endpoints include patient reported outcomes, acute and late toxicity and metastasis free, disease free, overall survival.

**Governance**

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