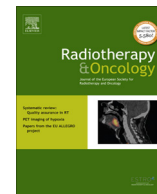


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Original article

Necrosis predicts benefit from hypoxia-modifying therapy in patients with high risk bladder cancer enrolled in a phase III randomised trial [☆]

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ABSTRACT

Background and purpose: Addition of carbogen and nicotinamide (hypoxia-modifying agents) to radiotherapy improves the survival of patients with high risk bladder cancer. The study investigated whether histopathological tumour features and putative hypoxia markers predicted benefit from hypoxia modification.

Materials and methods: Samples were available from 231 patients with high grade and invasive bladder carcinoma from the BCON phase III trial of radiotherapy (RT) alone or with carbogen and nicotinamide (RT + CON). Histopathological tumour features examined were: necrosis, growth pattern, growing margin, and tumour/stroma ratio. Hypoxia markers carbonic anhydrase-IX and glucose transporter-1 were examined using tissue microarrays.

Results: Necrosis was the only independent prognostic indicator ($P = 0.04$). Necrosis also predicted benefit from hypoxia modification. Five-year overall survival was 48% (RT) versus 39% (RT + CON) ($P = 0.32$) in patients without necrosis and 34% (RT) versus 56% (RT + CON) ($P = 0.004$) in patients with necrosis. There was a significant treatment by necrosis strata interaction ($P = 0.001$ adjusted). Necrosis was an independent predictor of benefit from RT + CON versus RT (hazard ratio [HR]: 0.43, 95% CI 0.25–0.73, $P = 0.002$). This trend was not observed when there was no necrosis (HR: 1.64, 95% CI 0.95–2.85, $P = 0.08$). **Conclusions:** Necrosis predicts benefit from hypoxia modification in patients with high risk bladder cancer and should be used to select patients; it is simple to identify and easy to incorporate into routine histopathological examination.

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Muscle invasive bladder cancer has five-year survival rates of 50–60%. Treatment is with radical cystectomy or bladder-sparing protocols involving radiotherapy. Both show similar survival rates [1,2] with the latter preserving a functional bladder in three quarters of patients [3]. The BCON (bladder carbogen and nicotinamide) phase III clinical trial showed the addition of carbogen and nicotinamide (CON) to radiotherapy (RT) improved overall survival (OS) [4]. Not all patients benefit from the additional hypoxia-modifying

therapy and there is a need for biomarkers to improve the individualisation of bladder cancer treatment.

There is evidence in head and neck cancer that hypoxic tumours benefit most from hypoxia-modifying therapy [5–10]. Similar evidence is not available for bladder cancers but, like other solid tumours, they contain hypoxic areas and the expression of high levels of hypoxia-inducible markers is associated with a poor prognosis [11–13].

There is no means to routinely measure tumour hypoxia in the clinic. Once considered the gold standard, the Eppendorf pO_2 histograph is no longer available, endogenous protein markers suffer poor specificity [14] and large intra-tumour variation [15], and exogenous nitroimidazole markers require intravenous/oral administration and the need for prospective assessment has limited the number of studies carried out [16]. As a simple histopathology approach would be an advantage, we hypothesised that tumour features such as necrosis, growth pattern, appearance of

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growing margin, or tumour/stroma ratio (TSR) might reflect tumour hypoxia as well as putative hypoxia markers carbonic anhydrase-IX (CA-IX) and glucose transporter-1 (Glut-1).

Tumour necrosis is believed to represent the endpoint of severe, chronic hypoxia distal to functional blood vessels. In bladder cancer, necrosis has been associated with the expression of hypoxia markers hypoxia inducible factor-1 and CA-IX and a poor outcome following primary cystectomy [13]. Tumour growth pattern [17] and appearance of growing margin [18] are also associated with a poor prognosis in urothelial disease. Solid growing tumours may be more hypoxic; they comprise large tumour islands, which may have less well organised vasculature than papillary tumours. An infiltrative tumour margin may indicate the presence of hypoxia, which can drive invasion and metastasis [19]. TSR may also be indicative of tumour hypoxia. Stromal expression of the hypoxia marker, monocarboxylate transporter 4 predicts poor outcome in breast cancer [20] and high levels of tumour stroma (>50%) have been linked to a worse prognosis in several cancer types [21–24]. Expression of CA-IX and Glut-1 was associated with a poor survival in bladder cancer [11], and so may also predict treatment benefit. Therefore, a retrospective study was performed to investigate the ability of the various histopathological features and putative hypoxia markers to predict benefit from hypoxia modification using samples from patients enrolled in the BCON trial. REMARK

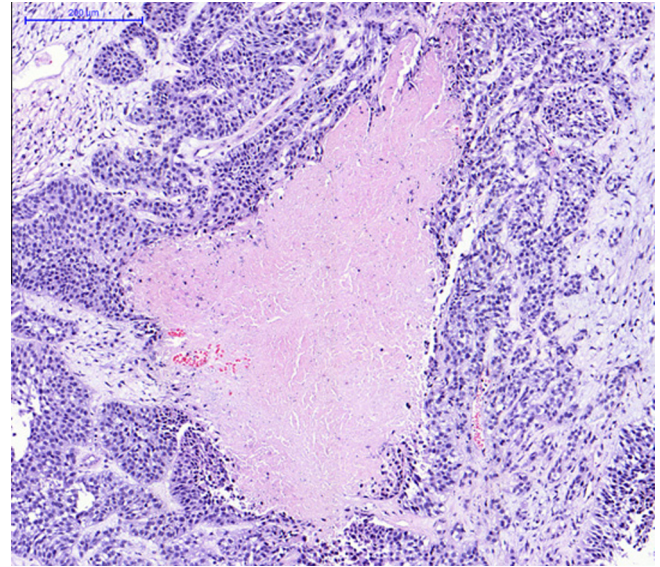


Fig. 2. H&E-stained bladder cancer section with necrosis. Necrosis is identified by the presence of cell ghosts and is eosinophilic and granular. Original magnification 400 $\times$.

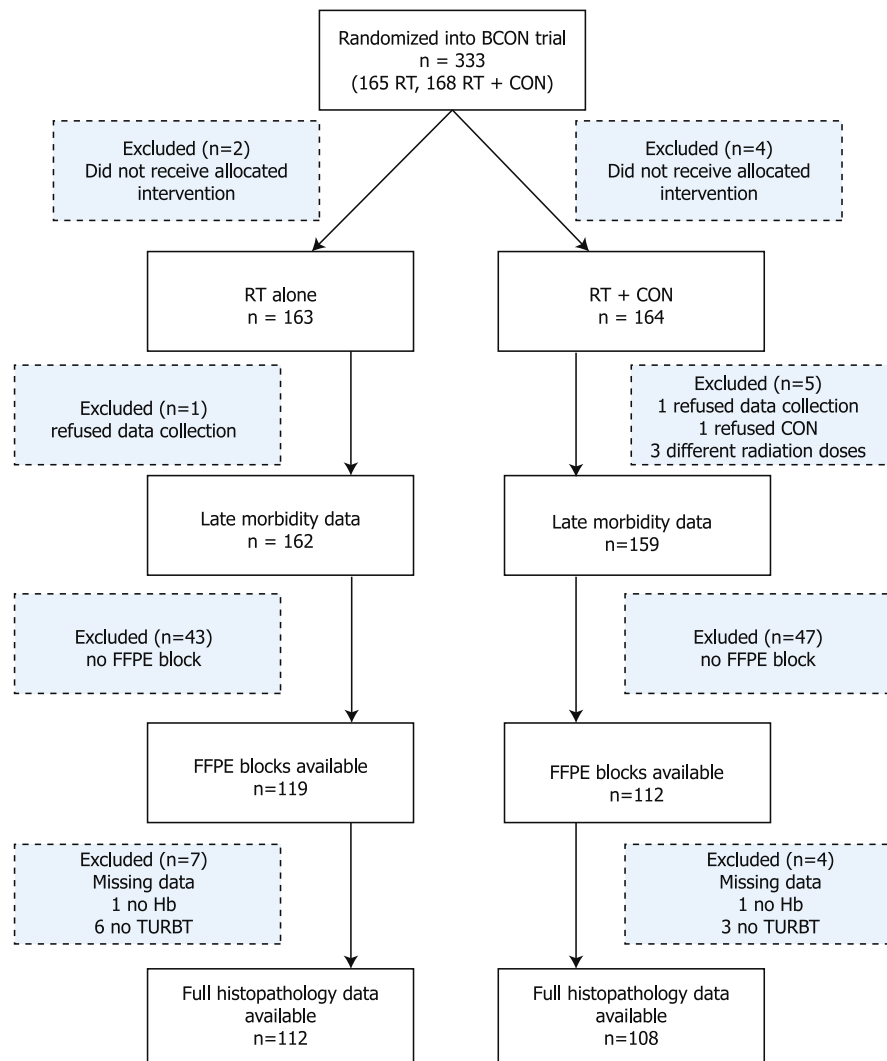


Fig. 1. CONSORT diagram.

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