

# Hypoxia modification with radiotherapy for bladder cancer

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The outcomes in bladder cancer treated with radiotherapy are suboptimal. Recently, Hoskin et al. reported improved survival in patients with bladder cancer treated with radiation therapy with concurrent hypoxia-modification therapy. These results are promising but must be viewed in the context of previous studies and alternative treatment approaches.

The management of muscle-invasive bladder cancer continues to be controversial; there is no solid evidence that overall survival has improved in the past two decades. The most common approach for bladder cancer management is radical cystectomy; bladder-conserving approaches with radiotherapy are far less frequently used. The major challenge in the latter approach are the limitations of radiotherapy due to the proximity of dose-limiting organs including the bladder, rectum and adjacent small bowel. A number of approaches have been developed using radiation-sensitising

chemotherapy to improve local control.<sup>1</sup> In addition, hypoxia is present in most solid human tumours and attempts to overcome its effect have been tried in head and neck cancer and, to a lesser extent, bladder cancer.<sup>2,3</sup>

In a recently published paper, Hoskin et al.<sup>4</sup> report the results of a prospective randomised trial comparing the efficacy of external-beam radiotherapy with and without concurrent carbogen and nicotinamide. This trial was based on previous phase II trials that used a similar approach, that is, hypoxia modification. In the present trial,<sup>4</sup> 333 patients were randomly assigned to either radiotherapy

alone (55 Gy in 20 fractions over 4 weeks or 64 Gy in 32 fractions over 6.5 weeks) or radiotherapy with concurrent carbogen (2% carbon dioxide and 98% oxygen at 15 l/min for 5 min before and during radiotherapy) and oral nicotinamide (60 mg/kg administered 1.5–2 hours before each fraction of radiation). Patients were stratified by centre and their characteristics were well balanced except for a slightly higher proportion of patients with T3 tumours (23.9% vs 18%) in the radiotherapy-alone arm. The primary endpoint of the study was cystoscopic local control at six months. The secondary endpoints included the

overall survival rate and local-relapse-free survival. The results showed improved overall survival at five years in the cohort receiving radiotherapy, carbogen and nicotinamide (50% vs 39%).<sup>4</sup>

The results of this trial are surprising because no previous phase III trial of radiotherapy in bladder cancer has showed improved overall survival, including large randomised trials. The results are difficult to interpret because the primary trial endpoint of improved cystoscopic local control was not achieved. In bladder cancer trials, the use of local tumour control as an endpoint is problematic because many patients do not have follow-up cystoscopies owing to the development of progressive distant disease or comorbidities.<sup>5</sup> Moreover, the higher rate of salvage cystectomy in the radiotherapy-alone group suggests improved local control in the combination arm (13 vs 23 salvage cystectomies). However, in terms of survival, the higher rate of salvage cystectomy should have compensated for the lower local control in radiotherapy-alone patients. The cohort treated with radiotherapy alone had more deaths unrelated to bladder cancer (29 vs 24 patients); therefore, it is difficult to be certain that the treatment intervention caused the overall survival benefit. The trial used CT to define clinical target volumes but no details were provided regarding the verification of treatment delivery.<sup>4</sup>

There are considerable problems with the reproducibility of radiotherapy delivery to bladder cancer that are mostly related to variation caused by bladder filling between fractions and during treatment.<sup>6</sup> Trials of image-guided and adaptive approaches to overcome this problem are ongoing. The difficulties in imaging the actual tumour, rather than

the bladder, pose additional problems that some investigators have tried to overcome by injecting lipiodol around the tumour to facilitate real-time image guidance.<sup>7,8</sup>

The majority of patients with muscle-invasive bladder cancer are managed with radical cystectomy and pelvic lymph-node dissection, while those who are poor surgical candidates are referred for external-beam radiotherapy. A number of investigators have tried to popularise bladder conservation strategies based on combined modality approaches with concurrent chemotherapy and radiotherapy. Unfortunately, little progress has been made in this area in the past two decades. Trials performed in the 1980s and 1990s showed superiority of concurrent cisplatin and radiotherapy when compared with radiotherapy alone.<sup>9,10</sup> However, the single-agent cisplatin had no impact on distant-metastasis rate and, therefore, no survival advantage.<sup>10</sup> Studies of adjuvant multiagent cisplatin-based chemotherapy showed a very modest survival impact.<sup>9</sup> A surgical approach is generally preferred as it defines the microscopic disease extent in the primary tumour and regional lymph nodes. Radical cystectomy offers improved local control for tumours confined to the bladder, and pelvic lymph-node dissection has been shown to cure a proportion of patients with involved pelvic lymph nodes. Unfortunately, the price is the loss of natural bladder function, and although modern continent diversion techniques offer improved quality of life, the long-term effects of surgical management are imperfect.<sup>9</sup>

Bladder preservation strategies are much more complex than the standard surgical approach and require close cooperation between urologists and radi-

ation oncologists with regards to patient selection, response assessment and ongoing management. The best candidates for bladder preservation have small T2 tumours with no coexistent carcinoma *in situ*.<sup>5</sup> Optimal survival has been achieved with immediate salvage cystectomy in patients who do not achieve local control or relapse owing to muscle-invasive disease. The small proportion of bladder cancer patients considered for radiotherapy hinders clinical trials in this area. Most studies are small and require a prolonged accrual phase. The approach in the Hoskin et al.<sup>4</sup> trial merits attention and further study, especially in patients not fit for more aggressive approaches. However, as the Hoskin et al.<sup>4</sup> study shows, distant failures continue to be a major problem in this group of patients. It is important to note that the approach taken does not address the issues of micrometastatic disease and, therefore, is unlikely to have a major impact on overall survival.

Details of the references cited in this article can be accessed at [www.cancerworld.org](http://www.cancerworld.org)

## Practice points

- Bladder cancer management remains a challenge for radiation oncologists; attention to patient selection, optimal treatment planning and delivery is important
- There is a need for studies of adaptive radiotherapy delivery approaches
- The role of hypoxia modification merits further study
- Participation in clinical trials of combined modality approaches is encouraged