

2.

Bladder cancer

Radical treatment

Conventional fractionation (dose per fraction 1.8–2.0 Gray [Gy])

The radiotherapeutic regimens used in studies comparing radiotherapy and surgery for bladder cancer have been delivered using either a conventional regimen of 60–64 Gy in 30–32 fractions over 6–6.5 weeks or hypofractionated radiotherapy of 52.5–55 Gy in 20 fractions (Level 2b).^{1–5}

Hyperfractionation

Two published trials compare hyperfractionation with doses of 1–1.2 Gy per fraction to conventionally fractionated treatment.^{6,7} Pooled analysis suggests a significant benefit from hyperfractionation with a 17% (95% confidence interval, 6–27%) improvement in the rate of local control.⁸ However, the regimens in both arms of these studies used split courses with overall treatment times of eight weeks. This approach would no longer be considered acceptable in a control arm (Level 1b).⁵

Accelerated fractionation

There was no evidence of clinical benefit from 60.8 Gy in 32 fractions given using two fractions per day of 1.9 Gy over a treatment time of 26 days when compared to a standard regime of 64 Gy in 32 fractions over 45 days.⁹ The shorter regimen was associated with a higher rate of intestinal toxicity (Level 1b).⁵

Hypofractionation

The two UK-based randomised controlled trials published in the last five years allowed the use of both conventional (60 Gy in 30 fractions) and hypofractionated radiotherapy (55 Gy in 20 fractions).^{10,11} Although neither study was powered to detect a difference in outcome based on dose and fractionation, there was no difference seen between conventional and hypofractionated radiotherapy (Level 2b).⁵

Partial bladder irradiation

Partial bladder radiotherapy has been studied in two UK-based trials. A trial from Manchester compared whole bladder radiotherapy 52.5 Gy in 20 fractions with partial bladder irradiation of 57.5 Gy in 20 fractions and 55 Gy in 16 fractions.¹² There was no significant difference in local control at five years between the three groups, and late toxicity was similar in all three arms. The BC2001 sub-study compared whole bladder high-dose irradiation with reduced high-dose volume radiation therapy.¹³ There was no difference in locoregional recurrence, late toxicity or overall survival between the two groups (Level 1b).⁵

Radical radiotherapy with radiosensitisation

Two UK-based randomised control trials have demonstrated that radical radiotherapy with a radiosensitiser improves outcomes compared to radiotherapy alone.^{10,11} BC2001 compared radical radiotherapy alone with radical radiotherapy given concurrently with mitomycin C and 5-fluorouracil (5-FU), with the chemoradiotherapy arm showing significantly better two-year locoregional recurrence rates of 67% versus 54% (Level 1b).^{5,10} The Bladder Carbogen Nicotinamide (BCON) investigators compared radical radiotherapy alone to radical radiotherapy given concurrently with carbogen and nicotinamide with a significant improvement in three-year overall survival of 13% in the experimental arm (Level 1b).^{5,11} Some centres within the UK use a weekly gemcitabine chemoradiation protocol based on a multicentre phase II study which has shown acceptable toxicity and comparable outcomes

to those in the literature with a three-year overall survival of 75% and 88% achieving a complete endoscopic response at first check cystoscopy (Level 2b).^{5,14}

Treatment technique

The size of the planning target volume (PTV) is critical to any discussion of dose and fractionation.^{15,16} Some centres use a two-phase (large pelvic volume/small bladder volume) approach, although there is no robust evidence for this approach improving survival outcomes for patients (Level 5).⁵ There is no published evidence using fraction sizes other than 1.8–2 Gy for this approach. All of the dose-fractionation regimens discussed below are based on the assumption that the PTV is <1,000 millilitres (ml) and that three-dimensional (3-D) image-based planning techniques are used. There is also increasing use of adaptive radiotherapy techniques for bladder treatment using a ‘plan of the day’ based on imaging prior to delivery of each fraction. The fractionation evidence has not been tested in this setting, but there is no reason to believe that the recommendations below do not apply to the adaptive setting also.

Recommendations

For radical radiotherapy to the bladder:

52.5–55 Gy in 20 fractions over 4 weeks
60–64 Gy in 30–32 fractions over 6–6.5 weeks (Grade B)

There is robust evidence that radiotherapy with a radiosensitiser using carbogen and nicotinamide or chemotherapy improves outcomes for patients with organ-confined muscle-invasive bladder cancer (Grade A)^{10,11}

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based medicine.⁵

Palliative radiotherapy

The Medical Research Council (MRC) randomised trial BA09 clearly established that 21 Gy in three fractions on alternate weekdays in one week (4–6 elapsed days) is as effective as 35 Gy in ten fractions in two weeks in palliating symptoms in patients with bladder cancer.¹⁷ There was no statistically significant difference in the rate of symptom relief (64% versus 71%; $p=0.192$; 95% confidence interval for the 7% rate difference, –2% to +13%), nor was there any significant difference in the duration of symptomatic relief (Level 1b).⁵ Other palliative regimes which are in use in the UK are 20 Gy in five fractions and 30–36 Gy in 5–6 fractions over 5–6 weeks (Level 2).⁵ These regimes are also used for frail patients not fit for radical radiotherapy treatment.

In the hypofractionated bladder radiotherapy with or without image-guided adaptive planning (HYBRID) trial, a dose of 30–36 Gy in 5–6 fractions given weekly has been used.

For very frail patients, a 6–8 Gy single fraction of pelvic radiotherapy often provides symptomatic relief (Level 4).⁵

Recommendations

For the palliation of local symptoms from bladder cancer:

21 Gy in 3 fractions on alternate days in 1 week is the regimen of choice (Grade A)
30–36 Gy in 5-6 fractions weekly has also been used in this setting (Grade D)

A single fraction of 6–8 Gy may provide useful palliation in patients who are unfit for the recommended regimen (Grade D)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based medicine.⁵

References

1. Shelley MD, Barber J, Mason MD. Surgery versus radiotherapy for muscle invasive bladder cancer. *Cochrane Database Syst Rev* 2001; **2001**(3): CD002079.
2. Booth CM, Siemens DR, Li G *et al*. Curative therapy for bladder cancer in routine clinical practice: a population-based outcomes study. *Clin Oncol (R Coll Radiol)* 2014; **26**(8): 506–514.
3. Gray PJ, Fedewa SA, Shipley WU *et al*. Use of potentially curative therapies for muscle-invasive bladder cancer in the United States: results from the National Cancer Data Base. *Eur Urol* 2013; **63**(5): 823–829.
4. Kotwal S, Choudhury A, Johnston C, Paul AB, Whelan P, Kiltie AE. Similar treatment outcomes for radical cystectomy and radical radiotherapy in invasive bladder cancer treated at a United Kingdom specialist treatment center. *Int J Radiat Oncol Biol Phys* 2008; **70**(2): 456–463.
5. www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009
(last accessed 22/9/16)
6. Edsmyr F, Andersson L, Esposti PL, Littlebrand B, Nilsson B. Irradiation therapy with multiple small fractions per day in urinary bladder cancer. *Radiother Oncol* 1985; **4**(3): 197–203.
7. Näslund I, Nilsson B, Littbrand B. Hyperfractionated radiotherapy of bladder cancer. A ten-year follow-up of a randomized clinical trial. *Acta Oncol* 1994; **33**(4): 397–402.
8. Goldobenko GV, Matveev BP, Shipilov VI, Kilmakov BD, Tkachev S. Radiation treatment of bladder cancer using different fractionation regimens. *Med Radiol (Mosk)* 1991; **36**(5): 14–16.
9. Horwich A, Dearnaley D, Huddart R *et al*. A randomised trial of accelerated radiotherapy for localised invasive bladder cancer. *Radiother Oncol* 2005; **75**(1): 34–43.
10. James ND, Hussain SA, Hall E *et al*. Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer. *N Engl J Med* 2012; **366**(16): 1477–1488.
11. Hoskin PJ, Rojas AM, Bentzen SM, Saunders MI. Radiotherapy with concurrent carbogen and nicotinamide in bladder carcinoma. *J Clin Oncol* 2010; **28**(33): 4912–4918.
12. Cowan RA, McBain CA, Ryder WD *et al*. Radiotherapy for muscle-invasive carcinoma of the bladder: results of a randomized trial comparing conventional whole bladder with dose-escalated partial bladder radiotherapy. *Int J Radiat Oncol Biol Phys* 2004; **59**(1): 197–207.
13. Huddart RA, Hall E, Hussain SA *et al*. Randomized noninferiority trial of reduced high-dose volume versus standard volume radiation therapy for muscle-invasive bladder cancer: results of the BC2001 trial (CRUK/01/004). *Int J Radiat Oncol Biol Phys* 2013; **87**(2): 261–269.
14. Choudhury A, Swindell R, Logue JP *et al*. Phase II study of conformal hypofractionated radiotherapy with concurrent gemcitabine in muscle-invasive bladder cancer. *J Clin Oncol* 2011; **29**(6): 733–738.
15. Muren LP, Ekerold R, Kvinnslund Y, Dahl O. On the use of margins for geometrical uncertainties around the rectum in radiotherapy planning. *Radiother Oncol* 2004; **70**(1): 11–19.
16. Muren LP, Smaaland R, Dahl O. Conformal radiotherapy of urinary bladder cancer. *Radiother Oncol* 2004; **73**(3): 387–398.
17. Duchesne GM, Bolger JJ, Griffiths GO *et al*. A randomized trial of hypofractionated schedules of palliative radiotherapy in the management of bladder carcinoma: results of medical research council trial BA09. *Int J Radiat Oncol Biol Phys* 2000; **47**(2): 379–388.