02 Bladder cancer

Radical treatment

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

The regimens used in studies comparing radiotherapy and surgery for bladder cancer have been 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 with 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 8 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 2 fractions per day of 1.9 Gy over a treatment time of 26 days when compared with 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

Two UK-based randomised controlled trials allowed the use of both conventional (60–64 Gy in 30–32 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. A subsequent individual patient data meta-analysis of these trials demonstrated non-inferiority of hypofractionated radiotherapy in terms of invasive locoregional disease-free survival and toxicity. Superiority for locoregional disease-free survival was confirmed for 55 Gy in 20 fractions (Level 1a).[5,12]

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.[13] There was no significant difference in local control at 5 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.[14] There was no difference in locoregional recurrence, late toxicity or overall survival between the two groups (Level 1b).[5]

02
Bladder cancer

Radical radiotherapy with radiosensitisation

Two UK-based randomised control trials have demonstrated that radical radiotherapy with a radiosensitiser improves outcomes compared with 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 2-year locoregional recurrence rates of 67% versus 54% (Level 1b).[5,10] The Bladder Carbogen Nicotinamide (BCON) investigators compared radical radiotherapy alone with radical radiotherapy given concurrently with carbogen and nicotinamide, with a significant improvement in 3-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 with those in the literature, with a 3-year overall survival of 75% and 88% achieving a complete endoscopic response at first check cystoscopy (Level 2b).[5,15]

Adjuvant radiotherapy

There is currently insufficient evidence to recommend adjuvant radiotherapy following radical cystectomy. A randomised phase II study reported superior outcomes in patients with high-risk disease (T3b+, Grade 3 or positive lymph nodes) who received adjuvant radiotherapy sandwiched between cycles of adjuvant chemotherapy, compared with adjuvant chemotherapy alone.[16] However a systematic review of 28 studies investigating adjuvant radiotherapy for bladder cancer and upper tract urothelial cancer found no clear benefit of adjuvant radiotherapy and noted the quality of the data was limited.[17]

Treatment technique

The size of the planning target volume (PTV) is critical to any discussion of dose and fractionation.[18,19] 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. A phase II trial looking at the use of intensity-modulated radiotherapy (IMRT) to the bladder and pelvic nodes demonstrated low levels of pelvic nodal recurrence rates and toxicity.[20] IMRT or volumetric modulated arc therapy (VMAT) techniques can therefore also be used to deliver bladder radiotherapy (Level 2b).[5]

There is increasing use of adaptive radiotherapy techniques for bladder treatment using a ‘plan of the day’ based on imaging prior to delivery of each fraction, allowing smaller anisotropic margins to be applied. The practical implementation of this technique was shown in the phase II HYBRID trial, looking at plan of the day in weekly ultra-fractionated radiotherapy, which demonstrated improved acute Grade 3 non-genitourinary toxicity rates compared with standard planning.[21] The RAIDER trial, currently recruiting, has developed plan of the day PTV margins and implementation guidance.[22] Whether the adaptive approach leads to improved outcomes is yet to be established. The fractionation evidence has not been tested in this setting, but there is no reason to believe that the recommendations do not apply to the adaptive setting also.

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Bladder cancer

Recommendations

For radical radiotherapy to the bladder:

- 55 Gy in 20 fractions over 4 weeks is the regimen of choice (Grade A)
- 64 Gy in 32 fractions over 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 3 fractions on alternate weekdays in 1 week (4–6 elapsed days) is as effective as 35 Gy in 10 fractions in 2 weeks in palliating symptoms in patients with bladder cancer.[23] 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 that are in use in the UK are 20 Gy in 5 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 with a 1-year invasive, local recurrence-free rate of 86% in patients with localised muscle-invasive bladder cancer unsuitable for radical treatment (Level 2b).[5,21]

Recommendations

For patients unsuitable for radical treatment of bladder cancer:

- 21 Gy in 3 fractions on alternate days in 1 week (Grade A)
- 36 Gy in 6 fractions weekly with or without adaptive planning (Grade B)

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)
- 36 Gy in 6 fractions weekly with or without adaptive planning (Grade B)

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]

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