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Muscle invasive bladder cancer in the elderly patient with a focus on hypofractionated radiotherapy

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Statement of search strategies used and sources of information

PubMed and Google Scholar were searched without limitations on multiple occasions between 12th December 2020 and 4th January 2021 for terms including, but not limited to, 'bladder cancer', 'muscle invasive bladder cancer', 'radiotherapy', 'hypofractionated radiotherapy', 'palliative radiotherapy', 'comprehensive geriatric assessment' and 'elderly'. Further references were identified by manually examining the references lists of relevant publications.

Abstract

Muscle-invasive bladder cancer (MIBC) is most frequently diagnosed in older patients and the presence of multimorbidity and frailty is common. This means that many patients are unsuitable for definitive treatment with radical cystectomy/(chemo)radiotherapy and are at risk of poor survival outcomes and considerable disease-related morbidity. Screening tools for functional status may be

useful to determine the most appropriate treatment for an older person and to identify patients most likely to benefit from comprehensive geriatric assessment and its targeted prehabilitation interventions. For patients unsuitable for definitive treatment, ultra hypofractionated radiotherapy schedules may provide good local control with acceptable toxicity. Short fractionated palliative radiotherapy schedules can provide effective symptom control for patients unsuitable for longer courses of treatment.

Key words
muscle-invasive bladder cancer; elderly; hypofractionated radiotherapy; palliative radiotherapy

Introduction

There are approximately 10,000 new cases of bladder cancer per year in the UK, accounting for 3% of all new cancers. However, bladder cancer is the seventh commonest cause of cancer death with almost 4000 annual deaths [1]. The majority of diagnoses occur in patients aged over 70 and the presence of multimorbidity is common. In line with an ageing population, the numbers of elderly patients with bladder cancer are expected to increase in the future [2-4].

Many elderly patients with muscle-invasive bladder cancer (MIBC) are considered unsuitable for either radical cystectomy (RC) or definitive radiotherapy/chemoradiotherapy (RT/CRT) despite having been diagnosed with potentially curative disease, likely because of the potential toxicity of treatment and estimation of short life expectancy associated with comorbidity and/or advanced age [3-5]. These patients face considerable disease-related morbidity, frequent hospitalisation and risk of death [6]. Hypofractionated RT regimens have often been used in these patients to provide local control and palliate symptoms. This overview will consider the relevant issues for older patients with MIBC and available evidence for its treatment with a focus on hypofractionated RT schedules.

Poor outcomes from MIBC in older patients

MIBC is an aggressive malignancy that has poor survival outcomes in older patients [3, 7]. A number of factors may influence outcomes including disease stage and grade, age, presence of co-morbidity, the treatment offered, its intent and the experience/expertise within the centre that treatment is delivered in [7-9].

The UK audit of non-surgical management of MIBC identifies several findings relevant to the care of the older patient with MIBC as well as deviations from National Institute for Health and Care Excellence (NICE) and Royal College of Radiologists (RCR) guidance [4]. The median age of patients was 78 years. Comorbidity data was not collected, although 36% of patients had a performance status of ≥2. Fifty four per cent of patients were treated with definitive RT despite

64% of patients having stage II/III disease. Older patients were more likely to be treated with palliative RT (median age for patients treated with palliative RT was 80 years versus 75 years for definitive RT). Similar findings were previously observed in population-based studies, which found that older patients were less likely to receive curative intent treatments [5, 7, 8, 10]. Of those treated with definitive RT in the UK national audit, neo-adjuvant chemotherapy (NACT) and CRT were delivered in only 43% and 40% of patients respectively [4]. Age, performance status and comorbidity were reported reasons for omission of chemotherapy but it is known that NACT and CRT are each associated with improved outcomes compared with RC and definitive RT alone respectively [4, 11-13]. Varughese et al also identified considerable delays to commencing treatment following diagnosis of MIBC (median time to starting definitive or palliative RT was >80 days after transurethral resection of bladder tumour (TURBT)) [4]. These delays could potentially impact on patient outcomes given that inferior survival has been observed with delay to RC [4, 14].

In addition to all-cause mortality, rates of cancer specific mortality are highest in the elderly, especially for female patients. It has been suggested that this implies that age/comorbidity alone is not solely responsible for poorer outcomes and that there might be underuse of curative intent treatments in this population [3, 7]. It is important to identify the fitter older patient who would be potentially eligible for curative intent treatments since age in itself does not necessarily equate to poorer outcomes from treatment [8]. The use of RC in older patients might be lower because of concerns regarding perioperative mortality and morbidity, although management within high volume centres and alternative surgical techniques (for example, laparoscopic surgery) might be methods to minimise these risks [2, 9, 15]. CRT may also be reasonably well tolerated as part of a bladder preservation strategy. CRT with mitomycin-C/5-fluorouracil and carbogen/nicotinamide were each evaluated in phase III trials [11, 12]. The median age in both trials was >70 years and CRT did not appear to be associated with significantly greater late toxicity than definitive RT alone. CRT with weekly gemcitabine has been evaluated in a phase II trial and similarly appeared to be associated with acceptable toxicity [16]. A multicentre cohort study of weekly gemcitabine in younger/older patients (≥75 years), and which also re-analysed patients from the carbogen/nicotinamide phase III study by these age categories, found that the efficacy and toxicity of CRT was comparable for the two age categories [11, 17].

In the next section, the use of comorbidity and geriatric assessment tools will be considered.

Comorbidity/geriatric assessment tools in the management of MIBC

The use of performance status scales such as Eastern Cooperative Oncology Group (ECOG) and Karnofsky Performance Scale (KPS) is commonplace in oncology and these are often used as a key determinant of eligibility for treatment. While these basic scoring systems have some advantages including ease of use and general

understanding they have several limitations and their lack of discrimination may fail to accurately describe actual functional status [18, 19].

Multiple different scoring systems for frailty are available in the literature that address various different functional domains including general assessments, multimorbidity, polypharmacy, cognition, mood and functional status. Simcock and Wright recently published an excellent overview of this topic [19]. A step beyond these scales is comprehensive geriatric assessment (CGA), which is a multidisciplinary process to identify the functional limitations of a frail person and to develop a coordinated plan to optimise their potential. Many professional organisations including American Society of Clinical Oncology (ASCO), European Urological Association (EAU), International Society of Geriatric Oncology (SIGO) and NCCN recommend the use of CGA in older patients with cancer including MIBC [20-23]. An excellent overview of CGA in MIBC was recently published [24]. Previous studies in patients with cancer have concluded that CGA may be useful in predicting impaired tolerance of treatment, risk of excess toxicity or a need to modify treatments and this assessment may lead to a change to the planned treatment [21, 25]. However, CGA typically requires geriatrician/multidisciplinary input and there may be practical challenges to the timely implementation of the assessment and its interventions in MIBC [14]. An alternative to routine use of CGA for all older patients might be to augment assessment of performance status by the use of a simple screening tool such as G8 or the Clinical Frailty Score (CFS) to identify those patients who may benefit from CGA and its targeted prehabilitation interventions [19, 26]. This approach is currently being evaluated in a phase III trial including patients with bladder cancer [27]. The current evidence base for the use of CGA in RT is limited with little MIBC specific data and at present there are a lack of predictive tools for radiation toxicity [28, 29].

Hypofractionated radiotherapy for patients unsuitable for definitive treatment

Patients considered too frail or otherwise unsuitable for definitive treatment of MIBC are at high risk of considerable disease-related morbidity especially haematuria (with associated risk of clot retention requiring hospitalisation) and irritative bladder symptoms which require relief for the duration of survival [6, 30]. Hypofractionated palliative RT may provide effective symptom/disease control and a number of schedules are recommended by RCR including 21 Gy in 3 fractions on alternate days in 1 week, 30-36 Gy in 5-6 fractions weekly, 20 Gy in 5 fractions in 1 week and a single fraction of 6-8 Gy [31]. In this section, the evidence for hypofractionated radiotherapy schedules will be considered with a focus on the phase III Medical Research Council (MRC) BA09 and phase II HYpofractionated Bladder Radiotherapy with or without Image guided aDaptive planning (HYBRID) clinical trials [32, 33].

i) Short fractionated/single fraction schedules

The UK national audit and a multicentre observation series confirm that a number of different palliative RT dose fractionation schedules are used in routine UK practice, some of which are not included in RCR recommendations [4, 31, 34]. This may reflect individual clinician decision making, local protocols and patient preference but could be an indicator of the use of less appropriate schedules in frail/elderly patients with limited life expectancy. There is limited evidence as to the optimum dose fractionation schedule in the palliative treatment of MIBC and the best evidence comes from the MRC BA09 phase III trial [32]. In this study patients unsuitable for definitive treatment for MIBC were randomised to either 21 Gy in 3 fractions or 35 Gy in 10 fractions using unplanned RT or 3 dimensional conformal radiotherapy (3dCRT). The primary endpoints were clinician-assessed symptomatic improvement in bladder symptoms at 3 months and changes in bladder/bowel symptoms between baseline and 3 months. Secondary endpoints included survival endpoints and quality of life (QoL) assessments. Published twenty year ago, the overall findings of the trial were that there was no significant difference between the two schedules in terms of effectiveness or toxicity. Symptomatic data at 3 months was evaluable in just over half of patients, which reduced the planned power of the study and reflects the challenges of performing trials in a population at high risk of deteriorating health/death. However, early symptomatic improvement was reported in just over half of the evaluable patients in each arm and the primary endpoint of symptomatic improvement at 3 months occurred in 71% and 64% of evaluable patients in the 35 Gy in 10 fraction and 21 Gy in 3 fraction arms respectively (p=0.192). In a pooled analysis, symptomatic improvement in haematuria, frequency, dysuria and nocturia at 3 months was observed in 88%, 82%, 72% and 64% of evaluable patients respectively. Interestingly, urinary symptoms appeared to improve in the majority of patients. This is in contrast to the findings of previous studies, which have observed that urinary symptoms were more difficult to effectively control than haematuria (which typically responds well to RT) [33, 35]. It is possible this is related to bladder irritation from residual disease or as a consequence of RT toxicity [30]. The median time to deterioration of symptoms in BA09 was 9 months, with a median overall survival of 7.5 months for the whole cohort [32]. This suggests that prolonged symptom control might be possible in some patients for the duration of survival.

A key concern regarding palliative RT in this population is the impact of treatment-related toxicity on QoL, and careful selection of patients who are likely to benefit is important especially when a proportion of patients may fail to complete treatment or die shortly after [34, 36]. In BA09, although approximately a third of patients reported an acute worsening of bowel and urinary symptoms (excluding haematuria) at the end of RT, only a minority had symptoms that were worse at 3 months than at baseline [32]. Furthermore, for most patients palliative RT did not appear to significantly impact QoL. Approximately two thirds of patients reported no deterioration or an improvement in QoL at the end of treatment and at 3 months (although QoL was only evaluable in 3 months in 33% of patients). Similarly poor survival outcomes to those in BA09 have been reported in observational series [34, 35]. For those patients with the poorest prognosis but who are still considered likely to benefit from RT, use of single fraction schedules such as 6-8 Gy may be preferable

to even short fractionated courses [31]. The presence of stage III/IV disease and ECOG performance status III/IV predict for particularly limited prognosis [34].

ii) Ultra hypofractionated schedules

There may be a dose response relationship in MIBC and a higher total RT dose might improve outcomes [37-39]. Several retrospective series and a number of phase II trials have investigated the use of ultra hypofractionated RT schedules of 30-36 Gy in 5-6 fractions weekly, which have a higher equivalent dose in 2 Gy fractions (EQD2) to the tumour than 21 Gy in 3 fractions. For example, assuming an alpha beta ratio for the tumour of 10 Gy, the EQD2 for 36 Gy in 6 fractions is 48 Gy_{10} compared with 29.75 Gy_{10} for 21 Gy in 3 fractions [33, 35, 37, 40-45]. A summary of the outcomes/toxicity data from ultra hypofractionated radiotherapy studies can be seen in **Table 1**. This higher effective dose might translate into improved disease control compared with short palliative RT schedules. Rates of cystoscopy assessed local control at 3 months were 80-90% in recent phase II studies of 36 Gy in 6 fractions weekly compared with 38% with 21 Gy in 3 fractions in the BA09 trial, although only 14% of patients in BA09 had cystoscopic follow up at 3 months [32, 33, 37].

There are challenges in comparing the outcomes of ultra hypofractionated weekly schedules given that many of the studies are retrospective, contained heterogenous populations and were published several years ago. The best evidence comes from the recent HYBRID phase II trial, which incorporated an adaptive radiotherapy (ART) strategy [33]. HYBRID randomised 65 patients with T2-4 N0 M0 MIBC to 36 Gy in 6 fractions weekly delivered using a standard treatment plan or 36 Gy in 6 fractions weekly delivered using an online adaptive 'plan of the day' strategy. The median age and Charlston comorbidity score was 85 years and 7 respectively, which is representative of real-world patients treated with ultra hypofractionated and short palliative RT schedules [4]. The median overall survival was 18.9 months with 1 and 2 year estimates of 61.5% and 46.2% respectively. These findings are in keeping with a recent phase II study of ultra hypofractionated RT and appear to compare favourably with survival outcomes for those patients who received palliative treatments (1 year OS 55%) or no treatment (1 year OS 32%) identified in a recent UK national study of outcomes for non-metastatic MIBC [5].

The higher total dose delivered with 30-36 Gy in 5-6 fractions weekly than with shorter schedules and the longer overall treatment time mean ultra hypofractionated treatments are more appropriate for patients estimated to otherwise have a life expectancy of at least 6 months. Having said that, the weekly fractionation schedule may offer greater convenience to patients, allow some recovery from acute toxicity and provide the opportunity for weekly clinical review giving the option to stop treatment early if it is not tolerated [40]. Rates of acute genitourinary (GU) grade 3 toxicity were more frequent than non-GU (including gastrointestinal (GI)) toxicity and affected 17% and 9% of patients in the standard and ART arms respectively. Acute non-GU grade 3 toxicity affected 13% and 6% of patients in the standard and ART arms respectively. Late toxicity was rare at a

median of 38.8 months follow up, with 4% of patients in the ART arm experiencing grade 3 late GU toxicity. These toxicity findings appear comparable with observational series/non-randomised phase II trials of ultra hypofractionated RT, where acute ≥grade 3 GU and GI toxicities were up to 18% and 17% respectively and late ≥grade 3 GU and GI toxicities were up to 44% and 7% respectively [33, 35, 37, 40-45]. HYBRID was not powered to directly compare its two arms and while the benefits in terms of patient outcomes/toxicity remain to be determined, HYBRID has demonstrated that implementation of plan of the day ART is feasible for a frail/elderly population [33].

Finally, it should be noted that intensity modulated radiotherapy (IMRT), and especially volumetric modulated arc therapy (VMAT), might have several advantages compared with 3dCRT for patients with MIBC [37]. These include greater target conformality/normal tissue sparing and, for VMAT, faster treatment delivery which could minimise the impact of intra-fraction motion and be more tolerable for a frail/elderly population [46].

Conclusions including future directions

A number of challenges exist in the management of MIBC in the elderly bladder cancer patient. There may be underuse of definitive treatments in older patients and it is of crucial importance to identify those who would be potentially eligible for RC or definitive RT/CRT including improving access to NACT and/or CRT [4, 5]. With an aging population and increasing multimorbidity, it is essential that greater consideration be given to the design of oncology services. Closer working with geriatricians and greater use of simple frailty screening tools by oncologists is needed to identify patients who might benefit from multidisciplinary comprehensive geriatric assessment and pre-habilitation [19, 24]. Clinical trials are needed to evaluate the impact of these assessments/interventions on outcomes. In the NHS, there appear to be unacceptable delays to commencement of definitive as well as palliative RT as a consequence of the design of diagnostic pathways and improving these processes has the potential to significantly improve survival [4, 14]. For patients not eligible for definitive treatment, the BA09 and HYBRID clinical trials demonstrate that short fractionated and ultra hypofractionated RT schedules can provide effective palliation of symptoms and disease control with acceptable toxicity [32, 33]. These trials also show that it is possible to undertake clinical trials in a frail/elderly population, which is important to ensure that the evidence base reflects the population of patients with MIBC. In summary, the management of MIBC is complex and requires multidisciplinary decision making, access to specialist treatment services and a holistic approach to patient assessment in order that patients receive the optimal treatment for their individual circumstances [5, 47].

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Table 1: A summary of studies of ultra hypofractionated radiotherapy for muscle invasive bladder cancer in patients not suitable for definitive treatment. The randomised phase III trial BA09 is included for comparison.

Author	*Year*	*Study type*	*Number of patients*	*Dose fractionation*	*RT technique*	*Survival*	*Local control/symptom improvement*	*Acute toxicity*	*Late toxicity*
Duchesne	2000	Randomised phase III trial	500 (symptomatic improvement data available for 272)	35 Gy in 10 fractions over 2 weeks versus 21 Gy in 3 fractions on alternate days	3dCRT/conventional	Median OS 7.5 months	3 month symptomatic improvement: 71% 35 Gy in 10 fractions 64% 21 Gy in 3 fractions	Per cent of patients with worse symptoms at end of treatment: 35 Gy in 10 fractions GU* up to 34% GI up to 41% 21 Gy in 3 fractions GU* up to 31% GI up to 37%	Per cent of patients with worse symptoms at 3 months post treatment: 35 Gy in 10 fractions GU* up to 18% GI up to 22% 21 Gy in 3 fractions GU* up to 24% GI up to 21%
Huddart	2021	Randomised phase II trial of adaptive plan of the day (AP) versus standard plan (SP)	65	36 Gy in 6 fractions weekly	3dCRT/IMRT	1 year OS 61.5%	3 month LC 81%	AP grade 3 GU 9% SP grade 3 GU 17% AP grade 3 non-GU 6% SP grade 3 non-GU 13%	AP grade 3 GU 4%
Hafeez	2017	Phase II trial	55	36 Gy in 6 fractions weekly	3dCRT	1 year OS 62%	3 month LC 92%	≥grade 3 GU 18% ≥grade 3 GI 4%	1 year ≥grade 3 GU 4% No ≥grade 3 GI
Dirix	2015	Retrospective cohort	44	34.5 Gy in 6 fractions weekly	3dCRT	Mean OS 10.5 months	Mean haematuria free survival 13 months	≥grade 3 GU 9% No ≥grade 3 GI	≥grade 3 GU 19% No ≥grade 3 GI

Kouloulias	2013	Retrospective cohort	58	36 Gy in 6 fractions weekly	3dCRT	Median PFS 14 months	95% improvement in haematuria 67% improvement in urinary symptoms	No ≥grade 3 GU/GI	No ≥grade 3 GU/GI
Jose	1999	Phase II trial	65	30-36 Gy in 5-6 fractions weekly	3dCRT/conventional	2 year OS 21%	3 month LC 62%	≥grade 3 GU 12% ≥grade 3 GI 2%	≥grade 3 GU 44% ≥grade 3 GI 2%
McLaren	1997	Retrospective cohort	55	30-36 Gy in 5-6 fractions weekly	3dCRT	Median OS 9 months	92% improvement in haematuria 24% improvement in urinary symptoms	≥grade 3 GU 18% ≥grade 3 GI 9%	No ≥grade 3 GU/GI
Scholten	1997	Retrospective cohort	123	36 Gy in 6 fractions weekly	Conventional	5 year OS 36%	5 year LC 31%	No ≥grade 3 GU/GI	No ≥grade 3 GU 5 year ≥grade 3 GI 9%
Rostom	1996	Retrospective cohort	70	36-39 Gy in 6 fractions weekly 34.5 Gy in 6 fractions weekly	3dCRT/conventional	5 year OS 28%	74% improvement in urinary symptoms	No ≥grade 3 GU/GI	≥grade 3 GU 1% ≥grade 3 GI 7%
Salimen	1992	Retrospective cohort	94	30 Gy in 6 fractions over 3 weeks	Conventional	Median OS 9.6 months	3 month LC 40%	Acute GU toxicity not graded ≥grade 3 GI 17%	Late toxicity not graded

3dCRT, 3 dimensional conformal radiotherapy; IMRT, intensity modulated radiotherapy; LC, local control; GI, gastrointestinal; GU, genitourinary; OS, overall survival; RT, radiotherapy

*Genitourinary symptoms excluding haematuria