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Hypofractionationation in Carcinoma of Urinary Bladder: An Approach for Elderly Patients

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ABSTRACT

Hypofractionated radiotherapy in Carcinoma of urinary bladder delivers higher doses of radiation per session over a shorter overall treatment period compared to conventional radiotherapy. This condensed treatment schedule has been shown to be as effective as standard fractionation in many cancer types, achieving similar rates of tumor control and overall survival. Furthermore, hypofractionation may offer advantages in terms of improved tumor control in certain cancers, potentially due to the biological impact of the higher doses per fraction. This approach also offers increased convenience for patients, reducing the number of hospital visits required for treatment. The shorter treatment duration can also translate to reduced healthcare costs and improved resource allocation.

INTRODUCTION

Urinary bladder cancer represents a significant health concern, particularly among the elderly population, posing a notable challenge due to its prevalence and associated morbidities. Hypofractionated radiation therapy, a treatment modality that delivers higher radiation doses per fraction over a condensed treatment period compared to conventional fractionation, has gained increasing prominence in the management of bladder cancer within this demographic. This approach offers potential advantages for elderly patients, often presenting with comorbidities that may complicate or preclude tolerance of longer, more conventional radiation therapy regimens.

Many bladder cancer patients over 75 are unfit for surgery or standard radiotherapy (1-3).This older group has unmet needs; a UK audit showed nearly 50% of curable patients receive no or only palliative radiotherapy.5-7 Untreated, they face years of symptoms like hematuria and pain (3). Ultrahypofractionated radiotherapy, like the MRC BA09 trial's 21 Gy in 3 fractions, offers an option, but control rates are modest.8 Higher doses (30-36 Gy in 6 Gy weekly fractions) show promise.(4) Large radiotherapy margins increase toxicity. Image-guided adaptive therapy, using a plan-of-the-day, improves targeting, especially beneficial in ultrahypofractionation where each fraction is a large part of the total dose. Single-center studies show feasibility(5-7).

TRIALS-

Hypofractionation aims to maintain treatment efficacy while minimizing the burden of prolonged treatment schedules, improving patient convenience and potentially reducing overall treatment time and associated healthcare costs.

The HYBRID trial (8) assessed adaptive plan-of-the-day (POD) image-guided radiation therapy for bladder cancer. Patients with muscle-invasive bladder cancer unsuitable for radical therapy received 36 Gy in 6 weekly fractions. Patients were randomized to standard planning (SP) or adaptive planning (AP).

The primary endpoint was nongenitourinary Common Terminology Criteria for Adverse Events (CTCAE) grade ≥3 toxicity. CTCAE ≥G3 nongenitourinary toxicity rates were 6% for AP and 13% for SP. Local control at 3 months was 81.3% (combined groups). POD adaptive radiation therapy was successfully implemented across multiple centers. Weekly ultrahypofractionated 36 Gy/6 fraction radiation therapy is safe and effective. The study included patients with a median age of 85 and significant comorbidity. A 3-month local control rate of over 80% and a median survival time of 18.9 months were observed.

A Phase II study(5) assessed weekly 6 Gy radiotherapy fractions (30–36 Gy total) in 65 patients with T2–T4 bladder cancer. Complete response was seen in 62% of assessable patients at cystoscopy. Local control was achieved in 25% of patients. Median survival was 35 weeks; 2-year actuarial survival was 21%. Main acute toxicity was urinary frequency (grade 3 in seven patients, grade 4 in one). Late bladder toxicity included persisting frequency, severe hematuria, and reduced bladder capacity. The regimen is a satisfactory palliative option for patients unable to tolerate standard radiotherapy, but significant late morbidity may occur.

Radical treatments employing hypofractionated radiotherapy have emerged as a viable approach in managing carcinoma of the urinary bladder, offering potentially significant benefits to patients. Hypofractionation involves delivering higher doses of radiation per fraction over a shorter overall treatment period compared to conventional fractionation. This approach has demonstrated comparable efficacy to standard treatments while reducing the burden of prolonged treatment schedules. The benefits observed include improved patient convenience, reduced treatment time, and potentially lower healthcare costs. Furthermore, hypofractionation may offer radiobiological advantages, such as enhanced tumor control by exploiting the differential repair capacities of tumor cells and normal tissues. Ongoing research continues to refine hypofractionation protocols and optimize patient selection criteria to maximize therapeutic outcomes and minimize potential side effects in bladder cancer management.

In a Study(9) Two radiotherapy schedules for locally advanced bladder cancer were compared: 64 Gy in 32 fractions and 55 Gy in 20 fractions. A meta-analysis of individual patient data from BC2001 and BCON trials was conducted. 782 patients were included, with median follow-up of 120 months.The 55 Gy in 20 fractions schedule showed a lower risk of invasive locoregional recurrence. Both schedules had similar toxicity profiles. Hypofractionated radiotherapy (55 Gy in 20 fractions) is non-inferior and superior to 64 Gy in 32 fractions regarding invasive locoregional control. The study concluded 55 Gy in 20 fractions should be considered the standard of care for bladder preservation. This study acknowledged limitations due to non-randomized fractionation and differences in data collection between trials.Shorter treatment protocols offer socioeconomic advantages.

A phase II trial [10] assessed the response of muscle-invasive bladder cancer (MIBC) to concurrent chemoradiotherapy. Fifty patients with T2-3 N0 M0 transitional cell carcinoma received weekly gemcitabine and 52.5 Gy radiotherapy in 20 fractions. Ninety-two percent of patients completed all four gemcitabine cycles; four stopped early due to bowel toxicity. Eighty-eight percent achieved a complete endoscopic response at 3 months post-treatment. At a median 36-month follow-up, 3-year cancer-specific survival was 82%, and overall survival was 75%. Sixty-four percent of patients remained disease-free with an intact bladder.The treatment showed a high response rate, durable local control, and acceptable toxicity. The study suggests this chemoradiotherapy warrants further investigation in a phase III trial. The gemcitabine dose was lower than typical systemic doses, suggesting radiosensitization as

the primary mechanism. The results compare favorably to previous studies using radiotherapy alone or other chemoradiotherapy regimens[10].

Radical cystectomy is the standard treatment for non-metastatic muscle invasive bladder cancer. Trimodal therapy (TMT), including maximal transurethral resection, concurrent chemotherapy, and radiotherapy, is an alternative. Hypo-fractionated radiotherapy in TMT shows 2-year recurrence-free survival rates of 43–83% and 5-year overall survival rates of 36–58%. Late toxicities are generally acceptable, with less than 12% experiencing grade ≥3 gastrointestinal issues and 4–46% with grade ≥3 genitourinary issues. This approach needs further evaluation in prospective trials, incorporating quality-of-life assessments. Shorter treatment duration improves patient quality of life and cost-effectiveness. The study reviewed 5 phase III and 13 phase II trials involving 2016 patients with transitional cell carcinoma[11].

A randomized trial compared accelerated (AF) and conventional fractionation (CF) radiotherapy for bladder cancer. 229 patients were randomized; 129 to AF and 100 to CF. AF used two fractions daily, totaling 60.8 Gy over 26 days; CF used one fraction daily, totaling 64 Gy over 45 days. AF showed increased acute bowel toxicity (44% vs 26% in CF), but similar bladder toxicity. No significant difference was found in local control, disease-free survival, or overall survival between AF and CF. Three-year overall survival was 54% for AF and 47% for CF; five-year survival was 37% for AF and 40% for CF.The study concluded that AF did not improve efficacy over CF and was associated with increased acute bowel toxicity [12].

Table 1 summarise major studies in hypofractionation in Ca urinary bladder

The rationale behind hypofractionated radiation therapy lies in the biological characteristics of bladder cancer cells and their response to radiation. By delivering higher doses per fraction, hypofractionation may enhance tumor cell kill while potentially sparing surrounding healthy tissues due to their different repair mechanisms. This approach is particularly relevant for elderly patients who may experience age-related decline in physiological reserve and thus benefit from shorter treatment durations. Ongoing research continues to investigate the optimal fractionation schedules and patient selection criteria for hypofractionated radiation therapy in bladder cancer to maximize its therapeutic benefits and minimize potential side effects.

CONCLUSION

Hypofractionated radiotherapy presents a potentially advantageous treatment modality for bladder cancer in elderly patients. The administration of higher radiation doses per fraction over a reduced treatment duration may lessen the treatment burden on this susceptible demographic. Further investigation is warranted to validate these findings. Hypofractionation may offer substantial improvements in the quality of life for senior adults receiving bladder cancer treatment.

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Table 1 - Summary of major studies in hypofractionation in Ca urinary bladder

S.no	Study	Design	Material and methods	Conclusion
1.	Huddart R et al.	Prospective	Patients with muscle-invasive bladder cancer unsuitable for radical therapy received 36 Gy in 6 weekly fractions	Weekly ultrahypofractionated 36 Gy/6 fraction radiation therapy is safe and effective.
2.	Jose C.C et al.	Prospective	weekly 6 Gy radiotherapy fractions (30–36 Gy total) in 65 patients with T2–T4 bladder cancer	The regimen is a satisfactory palliative option for patients unable to tolerate standard

				radiotherapy
3.	Choudhury A et al .	Prospective	Two radiotherapy schedules for locally advanced bladder cancer were compared: 64 Gy in 32 fractions and 55 Gy in 20 fractions	The study concluded 55 Gy in 20 fractions should be considered the standard of care for bladder preservation
4.	Choudhury A et al .	Prospective	Fifty patients with T2-3 N0 M0 transitional cell carcinoma received weekly gemcitabine and 52.5 Gy radiotherapy in 20 fractions	.The treatment showed a high response rate, durable local control, and acceptable toxicity.
5.	Alan Horwich et al.	Randomised controlled trial	Accelerated Fractionation used two fractions daily, totaling 60.8 Gy over 26 days; Conventional Fractionation used one fraction daily, totaling 64 Gy over 45 days.	The study concluded that AF did not improve efficacy over CF and was associated with increased acute bowel toxicity