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Original article

Trimodalities for bladder cancer in elderly: Transurethral resection, hypofractionated radiotherapy and gemcitabine

Trimodalités pour le cancer de la vessie chez les personnes âgées : résection transurétrale, radiothérapie hypofractionée et gemcitabine

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ABSTRACT

Purpose. – A prospective phase II study carried out to evaluate hypofractionated radiotherapy with concurrent gemcitabine for bladder preservation in the elderly patient with bladder cancer.
Patients and methods. – Thirty-one patients were enrolled, age ≥ 65 years, diagnosed with transitional cell carcinoma of the urinary bladder, after a maximum safe transurethral resection of a bladder tumour. They received 52.5 Gy in 20 fractions using 3D conformal radiotherapy with concurrent 100 mg/m^2 gemcitabine weekly as a radiosensitizer.
Results. – All patients completed their radiation therapy course, while seven patients received their chemotherapy irregularly due to grade 3 toxicities. Twenty-five patients (80.6%) achieved a complete response. At 2-years, overall survival was 94.4% and disease-free survival was 72.6%. T3 and residual after transurethral resection are factors that adversely affect disease-free survival.
Conclusion. – Hypofractionated radiotherapy and gemcitabine as a radiosensitizer in elderly as organ preservation for transitional cell carcinoma bladder cancer have acceptable toxicity profile with good response rate and disease-free survival, keeping salvage cystectomy for persistence or recurrence of invasive cancer.

Mots clés :
Cancer de la vessie
Radiothérapie hypofractionée
Cystectomie de récupération

RÉSUMÉ

Objectifs de l'étude. – Il s'agit d'une étude prospective de phase II pour évaluer la radiothérapie hypofractionée avec gemcitabine concomitante pour la préservation de la vessie chez les personnes âgées atteintes de cancer de la vessie.
Patients et méthodes. – Trente-et un-patients âgés de 65 ans et plus, atteints d'un carcinome transitionnel de la vessie de stade clinique T2 ou T3, N0, M0, après une résection transurétrale maximale, ont été inclus. Ils ont reçu une radiothérapie conformationnelle tridimensionnelle de 52,5 Gy en 20 fractions et 100 mg/m^2 de gemcitabine par semaine en tant que radiosensibilisateur.
Résultats. – Tous les patients ont terminé leur radiothérapie, tandis que sept patients ont reçu leur chimiothérapie irrégulièrement en raison d'une toxicité de grade 3. Vingt-cinq patients (80,6 %) ont obtenu une réponse complète. À 2 ans, la probabilité de survie globale était de 94,4 % et celle de survie sans maladie de 72,6 %. Le stade T3 et un résidu après la résection transurétrale étaient des facteurs affectant négativement la survie sans maladie.

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Conclusion. – La radiothérapie hypofractionnée pour le cancer de la vessie transtionnel chez les personnes âgées et la gemcitabine comme radiosensibilisateur, avec pour objectif la préservation de l'organe, a un profil de toxicité acceptable, avec des bons taux de réponse et de survie sans maladie, en gardant la cystectomie de sauvetage pour la persistance ou la récidive du cancer invasif.

1. Introduction

Bladder cancer is the second common cancer in Egyptian men (10.7%), in particularly in upper Egypt (12.60%), and it represents 21.1% age-adjusted rate in men [1]. The incidence of bladder cancer is increasing with age; patients' ages 60 to 70 years represented 35.73%, while patients at least 70 years represents about 21.26% among Egyptian population with bladder cancer [2].

Only half of elderly patients with bladder cancer receive a radical treatment [3]. Radical cystectomy is not feasible for all elderly patients either because a patient is unfit for major surgery or refuses it; radiotherapy used for such patients. Chemotherapy, as a radiosensitizer, and radiotherapy achieved comparable to survival to cystectomy [4].

Hypofractionation is an attractive and convenient choice for elderly as it limits their travelling frequency and waiting time. Multiple studies used hypofractionated radiotherapy in elderly for palliation [5]; however, during the last decade hypofractionated schedules were used for radical treatment [6].

Hypofractionation with weekly radiosensitizer is effective and tolerated [5–8]. In elderly, the addition of chemotherapy to radiotherapy has been shown to improve 5-years locoregional control rates from 54% to 67% and 5-years survival from 35% to 48% [9].

Gemcitabine as a radiosensitizer in bladder cancer has been studied and found to be well tolerated and effective [10,11]. However, there is no prospective study evaluating gemcitabine concurrently with hypofractionated radiotherapy in elderly who are less likely to complete trimodalities treatment compared with younger patients [12]. Due to the lack of evidence, we conducted this work to study the toxicity and efficacy of hypofractionated radiotherapy and gemcitabine for bladder cancer, as a bladder conservative strategy.

2. Patients and methods

This study recruited 31 patients between January 2011 to December 2016 and approved by our institutional ethics committee and informed consent. Our patients were unfit or refusing cystectomy. Patients were eligible if their age was at least 65 years, diagnosed with clinical stage T2 or T3, N0, M0 transitional cell carcinoma of the urinary bladder (pelvis MRI, pelvis–abdomen CT and chest x-ray) after maximum safe transurethral resection of a bladder tumour. Patient must have Eastern Cooperative Oncology Group (ECOG) performance score 2 or less, normal complete blood count, serum concentrations of creatinine 2.0 mg/dl or less, bilirubin 2 mg/dl or less, AST, and ALT 3 or less, upper limits of normal. Patients who had squamous cell carcinoma, earlier pelvic radiation therapy, systemic chemotherapy, intravesical chemotherapy or BCG were ineligible.

2.1. Treatment protocol

Radiation started within 45 days after transurethral resection. Patient were planned to receive 52.5 Gy as total dose delivered in 20 fractions, five fractions per week, using 3D conformal radiotherapy. Patients received gemcitabine as a radiosensitizer at a dose 100 mg/m^2 weekly on Saturdays as a 30-minute infusion for 4 weeks, 2 to 4 h before radiation session.

Simulation was done with the empty bladder in supine position. The clinical target volume included the bladder with additional 1.5 cm, the prostate and prostatic urethra (in men].

2.2. Revaluation

Acute toxicity was assessed during treatment and 6 weeks later according to Radiotherapy Oncology Group (RTOG) recommendations for genitourinary symptoms, while late toxicity was assessed and recorded every 3 months [13].

Quality of life assessements by NCCN-FACT FBlSI-18 questionnaire for bladder cancer patients were done as a baseline before treatment and 3 months after treatment.

Patients underwent assessment of response 3 months after chemoradiation, radiologically by pelvis CT and/or MRI and cystoscopy at 3 months and 6 monthly thereafter. The radiological complete response was confirmed by biopsy and cytology. The presence of superficial recurrence were treated by intravesical chemotherapy. However, salvage cystectomy was indicated in cases of persistent invasive cancer, intractable urinary symptoms or incontinence.

2.3. Statistical methods

Kaplan-Meier actuarial method from the time of diagnosis to the last follow-up was used to estimate disease-free survival and overall survival [14]. Log-rank test was used to compare survival rates.

3. Results

This is prospective phase II; included 31 eligible patients with bladder cancer attending South Egypt Cancer Institute, Assiut University. Patients signed a consent from and the study was approved by the institute's ethical committee. Patient's characteristic are presented in Table 1.

All patients completed their radiation therapy with supportive care, including painkillers (tramadol hydrochloride in eight patients) for cystitis during most of the course.

Twenty-four patients received their chemotherapy regularly while three patients received three doses of gemcitabine, three patients two doses and a patient received chemotherapy only once, all of them due to grade 3 toxicity (Table 2).

All patients were followed regularly according to schedule. Follow-up was considered from the onset of treatment.

Patients tolerated the treatment protocol with a good quality of life (Table 3). A patient developed grade 3 late bladder toxicity and another patient rectal stenosis.

Twenty-five patients (80.6%) achieved complete radiological and pathological response during first transurethral resection assessment after treatment. Five patients still had muscle invasive carcinoma and underwent cystectomy, however, the fourth patient had non-muscle invasive tumour subjected to repeated transurethral resection.

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