

Original article

A prospective randomized trial for postoperative vs. preoperative adjuvant radiotherapy for muscle-invasive bladder cancer

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Abstract

Purpose: Although radical cystectomy is considered to be the primary treatment for muscle-invasive bladder cancer, it is associated with unfavorable outcome. Local recurrence is still a major problem. Survival rates as well as quality of life are far from being satisfactory. Postoperative radiotherapy is considered the standard adjuvant treatment in the NCI-Egypt. This is a prospective randomized study conducted to compare preoperative with postoperative radiotherapy as regard the survival and complication rates.

Patients and methods: In the period from May, 2004 to June 2007, 100 eligible patients were included into the study, 50 patients in each treatment arm. Pelvic irradiation was identical in both groups aiming at 50 Gy/25 Fs/5 wk. Radical cystectomy was the standard surgery. Locoregional control, survival rates, and complications rates were compared in both arms.

Results: Patients had a median follow-up period of 32 months (range 0–69 months). Patients had an average age of 54.8 ± 9.5 years with a male/female ratio 3:1. In the present study, transitional cell carcinoma constitutes (51%), while squamous cell carcinoma was reported in 46% of cases. Grades II and III pathology were 81% and 17%, respectively. Pathological stage P_{2b} was encountered in 39.5% of the patients followed by P_{3b} (33.3%) and P_{3a} (14.6%). For the preoperative group, the 3-year overall survival, disease-free survival, locoregional control, and metastases-free survival rates were 53.4%, 47.4%, 89.3%, and 61.5%, respectively. The corresponding figures for the postoperative group were 51.8%, 34.1%, 80.6%, and 55.7% for the postoperative group. None of the patients had serious radiation reactions.

Conclusion: In our study, preoperative radiotherapy was almost equivalent to postoperative radiation therapy as regard OS, DFS, as well as complication rates. Given the recent physical developments in radiation therapy techniques and the biological rationale for treating the pelvis after cystectomy, adjuvant radiotherapy should be re-evaluated world wide. Preoperative radiotherapy may re-emerge as a useful tool for adjuvant treatment. © 2013 Elsevier Inc. All rights reserved.

Keywords: Postoperative; Preoperative; Adjuvant radiotherapy; Muscle-invasive bladder cancer

1. Introduction

Radical cystectomy remains to be the primary treatment for muscle-invasive bladder cancer. For resectable lesions, the reported 5-year overall survival rates ranged from 48%–66% in the literatures [1–6]. However, the results were significantly worse (20%–35%) when reporting upon locally advanced tumors (pT3N0, pT4aN0, or with pelvic

nodal involvement). Local recurrence either alone or combined with systemic relapse has been reported in 23%–50% of locally advanced patients [7]. Time to development of local recurrence is relatively short, with a median time of typically less than 12 months [4,8–11]. In 30% of relapsed patients, local recurrence was the first site of relapse. Interestingly, only one-third of the local recurrences were symptomatic, which suggests that local recurrence might precede distant metastasis. Moreover, 30% of those who had distant metastasis when undergoing local evaluation proved to have local recurrence as well [12]. The patients who developed local recurrence have a median survival of only 5 months

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from the time of diagnosis of the recurrence [13]. These high-incidence rates and the location of the local recurrence within the vicinity of pelvic irradiation have emphasized the need for adjunctive local therapy.

A prospective randomized trial proved the beneficial effect of postoperative radiotherapy (PORT) in locally advanced bladder cancer patients with significant improvement of disease-free survival (DFS) of 49% and 44% for PORT and cystectomy alone, respectively [3,4]. These trials, as well as an RTOG and other Egyptian nonrandomized series suggested postoperative radiotherapy as a standard adjuvant treatment of locally advanced bladder cancer in the NCI-Cairo, Egypt [5,6,14–18]. Randomized trials as well as many retrospective studies of preoperative radiotherapy have suggested improved survival rates [1,2,19–24]. However, only 1 out of the 6 randomized preoperative trials in the published English literatures has proven to be significant [1].

As far as we know, there is no randomized study comparing preoperative and postoperative radiotherapy in bladder cancer. In this work, we designed a randomized trial aiming at comparing the relative merits and drawbacks of both regimens and their impact on the local control and survival of the patients.

2. Patients and methods

In the period from May 2004 to June 2007, a controlled randomized, open (with allocation concealment), parallel-group study was held in the Radiotherapy Department, National Cancer Institute, Cairo University. The study aimed to compare preoperative (test arm) to postoperative radiotherapy (control standard arm) as an adjuvant treatment for nonmetastatic muscle-invasive bladder carcinoma. Patients with age \leq 60 years, WHO performance 1 or 2, medically fit for radical cystectomy and socioeconomic status compatible with adequate follow-up were considered eligible for the study. Consecutive eligible patients who met the inclusion criteria were registered. Written informed consent was obtained from the patients before assignment to treatment. Thereafter, patients were randomly allocated into the two groups using sealed-envelope method.

The initial evaluation included chest radiograph, computed tomographic scan, bone scan, full blood picture, kidney and liver function tests, cystoscopy with examination under anesthesia and biopsy.

2.1. Radiotherapy

In both treatment groups, all patients were planned to receive 50 Gy/25 F/5 wk, 2 Gy/F. In the preoperative arm, surgery was to be performed 2–4 weeks after radiotherapy. In the postoperative group, pelvic irradiation was to be delivered after a period not more than 4 weeks. All patients were treated on 6 MV-linear accelerator. The upper border

of the target volume was at L₅-S₁ and the lower border at the lower margin of obturator foramen. The lateral border was 1–2 cm lateral to the pelvic brim. The anterior border was at the anterior border of symphysis pubis while the posterior border included the anterior one-third of the rectum (anterior junction of S2-S3). The 2D CT-based treatment planning using 3 fields (1 anterior and 2 lateral) or 4 fields (box technique).

2.2. Surgery

Radical cystectomy had the same procedure in both arms; namely cystectomy and pelvic lymphadenectomy with prostatectomy in males and total hysterectomy and salpingo-oophorectomy (anterior pelvic exenteration) in females. In addition, operation included removal of the distal common iliac, hypogastric, obturator, and external iliac lymph nodes.

2.3. Outcome

Primary end-points are locoregional control (LRC) rates and early and late surgical and radiation reactions. Secondary end-points are overall survival (OS), and metastasis-free survival (MFS) and disease-free survival (DFS). Toxicity is reported according to the RTOG scoring scheme for upper GIT, rectal, and skin reactions [25].

2.4. Comparisons

Survival rates are analyzed on intention-to-treat basis while for complication, the data is analyzed on treatment-received bases. The survival estimates were calculated using the Kaplan-Meier method. The comparison between the survival curves of the 2 groups was done using the log-rank tests. All reported *P* values are two sided; *P* value \leq 0.05 was considered significant. The relapse-free survival rate was calculated from the date of cystectomy to the date of relapse whether locoregional or distant metastasis. The overall survival rate was calculated from the date of diagnosis to the date of last follow-up or death.

3. Results

3.1. Patients' characteristics

In the study period, 100 patients were recruited, 50 patients in each arm. Table 1 shows patients and tumor characteristics. Apart from creatinine and tumor grade, both treatment groups were comparable in terms of baseline characteristics (Table 1).

3.2. Deviation from the designed protocol

Preoperative group: 7 Patients did not undergo radical cystectomy due to:

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