Neoadjuvant Hormonal Therapy Versus Radiotherapy Alone in Treatment of Locally Advanced Prostate Cancer

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Abstract

Introduction: Despite adequate local therapy for carcinoma of the prostate, significant proportion of patients developed a progressive or metastatic disease. Neoadjuvant hormonal therapy not only provides possible early systemic treatment for a subclinical disease, but may also help in improving local disease control by increasing the number of patients eligible for definitive local therapy (via down staging).

Objective: To compare neoadjuvant hormonal therapy before definitive radiotherapy and radiotherapy alone in treatment of locally advanced prostate cancer.

Patients and Methods: We retrospectively compared the oncologic outcome of neoadjuvant hormonal therapy before radical radiotherapy versus radical radiotherapy alone in patients with locally advanced prostatic cancer (T3-T4, Nx, M0) treated between June 2004 and September 2007. Thirty seven patients were included in the study as two groups; group I included 19 patients treated with neoadjuvant hormonal therapy before and during radical radiotherapy (LHRH analogue for four months with added flutamide in the 1st month), and group II included 18 patients treated by radical radiotherapy alone. The dose of radiation therapy was 70G (44G to the whole pelvis and 26 G to the prostate and seminal vesicle). Patients were followed for a minimum of 5 years. Follow-up included serum PSA, and TRUS performed three months after therapy. Five-year survival and biochemical-disease-free survival were calculated for both treatment groups.

Results: The mean patient age was (71.3 y) and (69.7 y) for group I and II respectively. Mean pretreatment PSA was 37.1 ng/ml in group, I and 39.5 ng/ml in group II. Twenty six patients (70.2%) were T3 [group, I (12 patients) and group II (14 patients)] while 11 patients (29.8%) were T4 [group, I (6 patients) and group II (5 patients)]. The Mean follow-up was 61.5 months in group, I and 68 months in group II. There was significant reduction in prostate volume in group, I with a reduction ratio of 25.5% while in group II volume reduction was insignificant. Eleven patients (29.73%) died due to tumor progression, four (10.81%) in group I and seven (18.91%) in group II. Five-year survival rate was 80% in group, I compared to 52.5% in group II. Additionally 5-years biochemical disease-free survival was 79% in group, I compared to 57% in group II. The time to PSA nadir was earlier in group, I compared to group II (11.2Vs 19.2 months).

Conclusion: Neoadjuvant hormonal therapy combined with radiotherapy showed benefits in terms of 5-year overall survival, biochemical disease-free survival and time to PSA nadir compared to radiotherapy alone. Prospective randomized trial is needed to recommend optimal course, dose and patient selection criteria.

Key Words: Radiotherapy – Cancer prostate – Neoadjuvant – Hormonal therapy.

Introduction

PROSTATIC carcinoma is the most common cancer among men in the United States, and it is potentially a curable disease in patients with localized disease, radical prostatectomy or radiotherapy may definitively eradicate all disease, resulting in overall survival of approximately 75% [1]. According to the national cancer institute (Cairo University, Egypt) cancer pathology registry during years 2003 and 2004 showed an incidence of 49-95.7% of prostatic carcinoma and prostatic tumors respectively among male genital tract tumors [2]. The reported prevalence of prostate cancer in Egypt is 8.5% [3].

In developed countries the increasing use of PSA as screening tool, diagnosis of prostate cancer has progressed toward early stage detection [4], but in Egypt locally advanced and even metastatic disease are still the first ongoing clinical presentation. Despite adequate local therapy as radical prostatectomy or radiotherapy, significant proportion of patients develops progressive or metastatic disease 15-40% [8].

Hormonal therapy plays a major role in the treatment of advanced prostatic cancer, and it has been studied extensively in the neoadjuvant setting.
Based on these results, phase III trials have been conducted for evaluation of the androgen blockade of various types before radiation therapy \[6,7,9,10\].

Although consistent improvement was seen in disease survival, the Radiation Therapy Oncology Group (RTOG) study 86-10 \[7\] and European organization for research of treatment of cancer (EORTC) \[8\] were powered to detect differences in overall survival.

So the advent of hormonal therapy helped to maximize cure rates for patients who received definitive therapy in organ confined disease, theoretically by eliminating micro-metastatic disease. On the other hand, the role of hormonal therapy in locally advanced prostate cancer is to provide early control for asymptomatic metastatic disease and to improve local disease control as well as allowing measurement of the tumor response to the applied therapy that may help in identifying of such regimen as a standard treatment modality \[4\].

**Aim of the study:**

To compare between the neoadjuvant hormonal combined with definitive radiotherapy and radiotherapy alone in the treatment of locally advanced prostate cancer.

**Patients and Methods**

This study was done in collaboration with Urology and Clinical Oncology and Nuclear Medicine Department at Faculty of Medicine Zagazig University. In the period from June 2004 till June 2012.

We retrospectively studied the effect of neoadjuvant hormonal therapy followed by radiotherapy with curative intent in patients with locally advanced prostate cancer compared with those treated with radical radiotherapy alone.

The study included 37 patients; all these patients had locally advanced (T3-T4 Nx M0) prostatic adenocarcinoma.

The work-up of these patients included complete history taking, physical examination including digital rectal examination, serum PSA, CBC, Liver and kidney function tests, pelviabdominal CT with or without pelviabdominal MRI and finally radioisotope bone scan.

TRUS prostatic biopsy was done for all patients with histopathological assessment and identification of the Gleason score.

19 patients received neoadjuvant hormonal therapy in the form of LHRH analogues (leuprolide acetate 7.5mg s.c. monthly) plus flutamide 250mg tablets TDS (during the first month of LHRH therapy to control transient increase in testosterone level), for four months before and during the radiotherapy regimen, while 18 patients received radiotherapy alone. The radiotherapy course for both groups was given as a total dose of 70Gy, the first 44Gy in 22 fractions were given to the whole pelvis while the remaining 26Gy in 13 fractions were given to the prostate and seminal vesicles.

Three dimension conformal radiotherapy (3D-CRT) on linear accelerator 6-12Mv photon, the prescribed dose was recorded at the center of the target volume, 1.8-2Gy/fraction.

Follow-up of all patients included physical examination, complete laboratory investigations, serum PSA, and TRUS three month after completion of the therapy and semiannually after that. CT or MRI, bone scan were done annually.

Acute and late toxicity were reported for all patients according to RTOG/EORTC scoring system \[11\].

At the end of the follow-up period the 5-year survival and biochemical-disease free survival were calculated using the Kaplan-Meier curve for survival analysis.

**Results**

The study included 37 patients with locally advanced prostatic adenocarcinoma.

The first group had 19 patients with a mean age of (71.3 y) while the mean age in group two was (69.7 y). Regarding the pre-treatment PSA in both study groups, we had median PSA of 37.1ng/ml in group 1 and 39.5ng/ml in group 2. And there were no statistical difference in both groups. Regarding tumor stage and grade in both groups it is summarized in Table (1).

<table>
<thead>
<tr>
<th>Tumor stage (T)</th>
<th>T4</th>
<th>T3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>Group II</td>
<td>4</td>
<td>14</td>
</tr>
</tbody>
</table>

The follow-up period ended at June 2012 with a median follow-up time of 68 month in group I and 61.5 month in group II.

**Table (1):** Tumor characteristics in both groups.

<table>
<thead>
<tr>
<th>Median follow-up time (months)</th>
<th>Gleason score</th>
<th>Tumor Stage (T)</th>
<th>Tumor characteristic</th>
</tr>
</thead>
<tbody>
<tr>
<td>8-10</td>
<td>6</td>
<td>7</td>
<td>32.6% 10.5% 57.9% 36.9% 63.1%</td>
</tr>
<tr>
<td>61.5</td>
<td>5</td>
<td>3</td>
<td>27.8% 16.7% 55.6% 22.3% 77.7%</td>
</tr>
</tbody>
</table>

The follow-up period ended at June 2012 with a median follow-up time of 68 month in group I and 61.5 month in group II.
At the end of the follow-up time we had 12 (32.43%) died patient. Eleven patients (29.73%) died due to tumour progression, 4 (10.81%) in group I and 7 (18.91%) in group II, while one patient (in group II) died due to other cause.

Regarding the prostate volume in both study groups, in group one the mean prostate volume was 74.5 (SD 19.17) and there was significant reduction in prostate volume to a mean of 55.3 (SD 18.475) \( (p=0.003) \) and the reduction ratio was 25.7\% while in group 2 the mean prostate volume was 73.3 (SD 16.467) which showed insignificant reduction in prostate volume to a mean of 68.6 (SD 16.165) \( (p=0.523) \) and reduction ratio was 6.5\%.

Regarding the 5-year survival it is shown in Fig. (1).

![Kaplan Meier Curve for the 5 year survival in both groups.](image)

In group I the 5 year survival was 80\% and that was higher than group II that had 5-year survival of 52.5\%.

On the other hand the 5-years biochemical disease free survival was 79\% in group I which was higher than that for group II 57.1\% (Fig. 2).

![Kaplan Meier curve for Biochemical relapse.](image)

Also it was noticed that in group I that the time to PSA nadir was earlier in group I than in group II (11.15 month and 19.2 months respectively) Table (2).

<table>
<thead>
<tr>
<th>Prostate volume</th>
<th>Prostate volume</th>
<th>Time to PSA nadir</th>
</tr>
</thead>
<tbody>
<tr>
<td>after treatment</td>
<td>before treatment</td>
<td>Group II</td>
</tr>
<tr>
<td>55.3 (SD 18.475)</td>
<td>74.5 (SD 19.17)</td>
<td>11.1 months Group I</td>
</tr>
<tr>
<td>68.6 (SD 16.165)</td>
<td>73.3 (SD 16.467)</td>
<td>19.2 months Group II</td>
</tr>
</tbody>
</table>

Regarding the adverse effects of radiotherapy, there were 6 patients (31.5\%) in group I that had acute G3 rectal symptoms (one patient with rectal bleeding and was treated conservatively), versus 8 patients (44.4\%) in group II that had acute G3 rectal symptoms. At 5 years, there was one patient in both groups, had G3 rectal toxicity.

As regard the adverse effects of hormonal therapy in group I, 7 patients (36.8\%) suffered from hot flushes & hepatic toxicity and 5 (26.3\%) patients developed fatigue and gastrointestinal toxicities.

**Discussion**

Management of locally advanced prostate cancer (T3-4 NxM0) is a therapeutic challenge due to the importance of both local disease control as well as treatment of undetectable microscopic metastasis [12].

The biological rationale for using hormonal treatment with EBRT include a reduction in tumor volume and enhanced biological effects [13]. This combination is relatively inexpensive, well tolerated and readily available.

The use of neoadjuvant hormonal therapy in the treatment of locally advanced prostate cancer was discussed in many studies, yet radiotherapy is still the corner stone in the treatment protocol.

In this study we retrospectively analyzed the efficacy of radiotherapy alone or in combination with neoadjuvant hormonal therapy in patients with locally advanced disease.

Radiotherapy induced late toxicities in our study showed similar incidence as RTOG 92-02 study Hanks et al. [14].

The calculated 5 years overall survival (80\%) for patients in group I receiving neo-adjuvant
hormonal therapy and radiotherapy was comparable to the published data by Hanks et al., 2003 in which 78.5% 5 years overall survival was achieved in STAD-RT arm [14].

Similar results were obtained from RTOG 86-10 study [13] in which the addition of combined androgen blockade as neoadjuvant to radiotherapy reduced the 5y incidence of local progression from 71% to 46%.

Also these results were comparable to the results obtained by Jiri et al., 2012 in spite of the absence of two arms in this study [18].

Our results regarding the 5-year biochemical disease free survival (79%) also compares to the results obtained from the same study by Jiri et al. [18] that showed biochemical disease free survival was 62% in patients receiving neoadjuvant hormonal therapy for 2 months only.

We noticed a significant reduction in the prostate volume in group 1 by 25.5% and this emphasis the results obtained from Zelefsky et al., 1994 [16]. Of course this is important in reducing the tumor bearing prostate volume and the surface area of radiotherapy exposure and eventually the local radiotherapy side effects.

Also in our study neoadjuvant hormonal treatment seemed to achieve earlier PSA nadir than in patients receiving radiotherapy alone where it was 11.1 moth and 19.2 month in group I and II respectively.

Conclusion:
Radiotherapy is an important line in the treatment of locally advanced prostatic adenocarcinoma. Hormonal treatment (androgen deprivation therapy) in combination with radiotherapy shows benefits in terms of 5 years survival, biochemical disease free survival and time to PSA nadir. Prospective randomized trial is needed to recommend optimal course, dose and patients selection criteria.

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