

Impact of comorbidity in elderly prostate cancer patients treated with brachytherapy

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Objective: To analyze the correlations among comorbidity and overall survival (OS), biochemical progression-free survival (b-PFS) and toxicity in elderly patients with localized prostate cancer treated with ^{125}I brachytherapy.

Methods: Elderly men, aged ≥ 65 years, with low-intermediate risk prostate cancer, were treated with permanent ^{125}I brachytherapy as monotherapy. Comorbidity data were obtained from medical reports using age-adjusted Charlson comorbidity index (a-CCI). The patients were categorized into two age groups (<75 and ≥ 75 years old), and two comorbidity score groups (a-CCI ≤ 3 and >3). Toxicity was scored with Radiation Therapy Oncology Group (RTOG) scale.

Results: From June 2003 to October 2009, a total of 92 elderly patients underwent prostate brachytherapy, including 57 men (62%) with low-risk prostate cancer, and 35 men (38%) with intermediate-risk prostate cancer. The median age of patients was 75 years (range, 65-87 years). Forty-seven patients (51%) had a-CCI ≤ 3 and 45 patients (49%) a-CCI >3 . With a median follow-up period of 56 months (range, 24-103 months), the 5-year actuarial OS and b-PFS were 91.3% and 92.4% respectively, without statistical significance between two Charlson score groups. Toxicity was mild. None of the patients experienced gastrointestinal (GI) toxicity, and only 4 patients (4%) experienced late genitourinary (GU) grade-3 (G3) toxicity. No correlation between acute GU and GI toxicity and comorbidity was showed (P=0.50 and P=0.70, respectively).

Conclusions: Our data suggest that elderly men with low-intermediate risk prostate cancer and comorbidity can be considered for a radical treatment as ^{125}I low-dose rate brachytherapy.

Key Words: Prostate cancer; brachytherapy; elderly; comorbidity; toxicity; overall survival; biochemical control



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Introduction

Comorbidity is an important consideration in oncology practice, particularly among older patients. One of the most extensively studied instruments for measuring comorbidity was Charlson comorbidity index (CCI) (1).

In a variety of common cancers, including prostate cancer, increasing comorbidity was associated with a lower likelihood of receiving potentially curative therapy, a shorter overall survival (OS), and a greater likelihood of dying from other causes (2-6). However, elderly patients

are an extremely heterogeneous population as regards comorbidity: subjects can vary from very fit to not being able to live independently due to comorbidities. Thus, unlike advanced age, clinicians may be offering a radical treatment, as brachytherapy, in a selected series of patients with low-intermediate risk disease. Despite the lack of randomized studies and only elderly population-based studies, some institutional case series showed brachytherapy to produce excellent biochemical control (b-DFS) in elderly patients with localized prostate cancer compared

with alternative curative treatments (7-10). Similar survival outcomes were showed comparing patients aged >60 years than younger with clinically localized prostate cancer and treated with brachytherapy (11,12).

The aim of our study was to evaluate the impact of comorbidity on toxicity profiles and outcomes in a series of elderly patients who underwent low-dose rate brachytherapy (LDR-BT) with ^{125}I seeds implant.

Patients and methods

Patients characteristics

Patients aged more than 65 years and treated with LDR-BT as monotherapy, were selected for this analysis. LDR-BT was offered to patients with clinically localized prostate cancer: low-risk [T1-T2a; Gleason score (GS) ≤ 6 ; prostate specific antigen (PSA) < 10 ng/mL] and intermediate-risk (T2b-T2c or GS=7; PSA=10-20 ng/mL). Risk groups were defined according to National Comprehensive Cancer Network (NCCN). Clinical stage was based on the 2002 International Union Against Cancer (UICC)(13,14).

A PSA relapse was defined according to the Phoenix definition (PSA nadir+2 ng/mL) (15). Karnofsky performance status (KPS) ≥ 70 and life expectancy longer than 5 years were eligible criteria for our study.

All patients underwent blood tests, including PSA level, digital rectal examination, computed tomography (CT) scan of the pelvis, bone scan, transrectal ultrasonography with multiple (≥ 12) needle biopsy cores of the prostate to stage disease.

Follow-up was performed every 3 months in the first year, and every 6 months in the following years. At each follow-up, PSA level was assessed and acute and late toxicity was scored using Radiotherapy Oncology Group (RTOG) toxicity scale (16).

Brachytherapy technique

The brachytherapy procedure was performed using a transrectal ultrasound-guided (TRUS) approach, with planned total dose of 145 Gy, according to the protocol of the American Association of Physicist in Medicine (AAPM-TG 43)(17).

For each patients, a transrectal ultrasound was performed 2 weeks before the implantation date to estimate the number of radioactive sources to order and implant into prostate.

After spinal anaesthesia, the seeds implant was run with intraoperative transrectal guidance (images at 5-mm were

acquired). The treatment planning was performed using the planning system (TPS) Vari Seed 8.0 (Varian Medical System, Palo Alto, CA, USA). The prostate and the organs at risk were contoured according to ESTRO guidelines (urethra, rectum and penile bulb); the dose constraints used for treatment plan evaluation were 217 Gy to 0.1 cc of the urethra and 145 Gy to 0.3 cc of the anterior rectal wall (18). A mean of 78 seeds (range, 46-135 seeds) were implanted, with the activity of 0.400 mCi (19). Seven weeks after the implantation, a CT scan was performed for each patient to compare the planned dose distribution and the effective dose received by prostate and other organs at risk.

Charlson comorbidity index (CCI)

Comorbidity data were obtained from medical reports using age-adjusted Charlson comorbidity index (a-CCI). The Charlson score takes into account the presence of 19 diseases weighted on the basis of their association with mortality. A Charlson sum is calculated according to the number of morbidities affecting an individual. For each morbidity, a number of points are allocated and the sum of these points gives an overall score. This sum can be used in conjunction with the patient's age as the Charlson score to calculate a probability of survival.

A malignant solid tumor is one of clinical condition associated to CCI score, in example for patient without other comorbidities, malignancy was scored with a point of 2 or 6 for metastatic disease, thus we arbitrarily decided to not considered prostate cancer as a morbidity in a-CCI calculating, firstly because all patients of our series were affected by prostate cancer and second to obtain a more homogeneous evaluation of other comorbidities in the final calculation of overall score.

For each patients, CCI-aged adjusted score was computed, defining two comorbidity levels: ≤ 3 (low-moderate) and > 3 (high).

Statistical analysis

The follow-up period was calculated from the end of brachytherapy. Analysis was performed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). Survival curves were obtained with Kaplan-Meier method. Log-rank test was used to evaluate influence of comorbidity on OS. We used a cut-off point of 75 years, whereby the patients were subdivided into age ≤ 75 years and age ≥ 75 years. $P < 0.05$ was considered statistically significant. Fisher exact test was used

Table 1 Clinical characteristics of all patients (N=92)

Characteristics	No. of patients	%
Age (year)		
≤75	51	55
>75	41	45
AJCC tumor classification		
T1a	4	4
T1b	3	3
T1c	24	26
T2a	31	35
T2b	17	18
T2c	13	14
Gleason score		
≤6	85	92
7	7	8
Pretreatment PSA (ng/mL)		
≤10	84	91
>10	8	9
NCCN risk group		
Low risk	57	62
Intermediate risk	35	38

to determine association between age-adjusted comorbidity and acute toxicity.

Results

Patients

From June 2003 to October 2009, a total of 92 elderly patients with localized prostate underwent low-dose rate ¹²⁵I brachytherapy implant at the Department of Radiation Oncology, IRCCS-CROB. The median age of patients was 75 years (range, 65-87 years). Low-risk disease occurred in 57 patients (62%) and intermediate-risk disease in 35 patients (38%). The clinical characteristics of patients are reported in *Table 1*. The median follow-up time was 56 months (range, 24-103 months).

At the time of statistical analysis, 80 patients (87%) were alive without disease, and only 4 patients (4%) were alive with disease (half of these patients had an age of greater than 75 years). There were 8 deaths (9%) over the period of follow-up, including 5 deaths from other causes and only 1 patient (age: 85 years) died for prostate cancer 72 months after brachytherapy implantation. Among this group, 6 patients were ≥75 years old and 2 patients were <75 years old.

Table 2 Age and comorbidity (N=92)

Variables	No. of patients	%
Age (years)		
65-75	43	47
75-85	42	46
85-95	7	7
Co-morbidity		
None	50	54
MI	14	15
DM (without end-organ damage)	11	12
COPD	4	4
Ulcers	3	3
Cerebrovascular disease	6	6
Mild liver disease	6	6
CRF	3	3
Malignance solid tumour	3	3
Lymphoma	2	2
a-CCI score		
2	10	11
3	37	40
4	22	25
5	10	11
6	9	8
7	3	3
8	2	2

MI, myocardial infarction; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; CRF, chronic renal failure

a-CCI

The a-CCI score was calculate to be ≤3 in 47 patients (51%) and >3 in 45 patients (49%). In our series, all died patients had a-CCI ≥3. Descriptive characteristics of a-CCI score are shown in *Table 2*.

OS and biochemical disease-free survival

Biochemical recurrence occurred in 7 patients (8%) while 85 patients (92%) were free from biochemical failure. The median time to PSA failure was 27 months (range, 8-40 months). The actuarial 5-year b-DFS and OS were 92.4% and 91.3% respectively (*Figure 1A,B*).

Survival analyses of non-prostate cancer mortality across Charlson groups revealed no statistical significance between

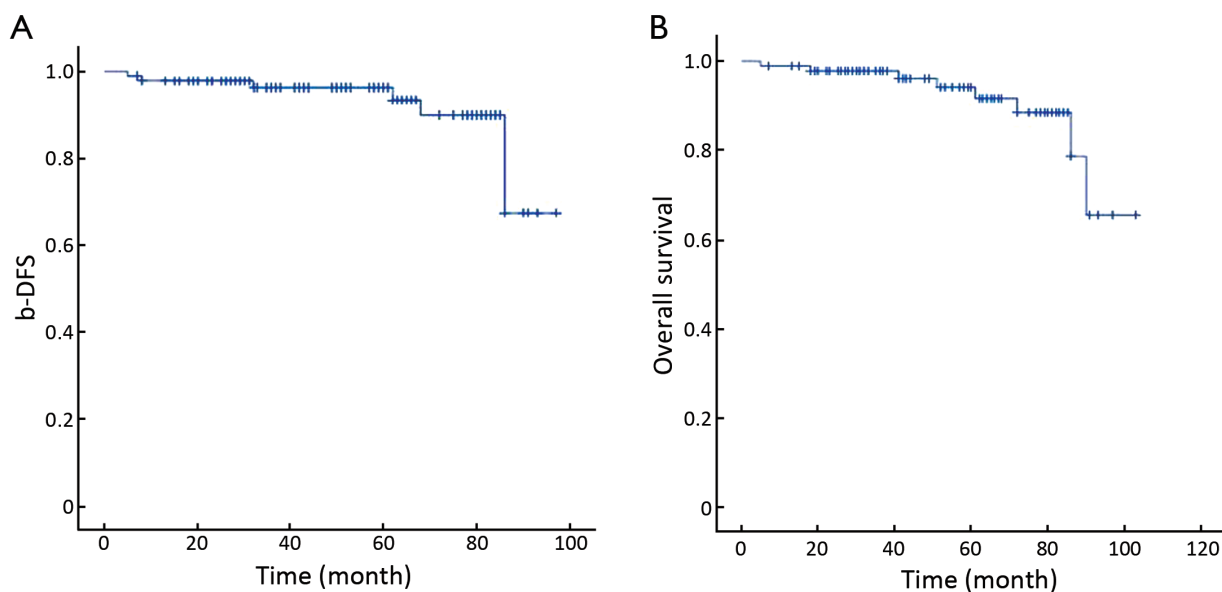


Figure 1 Survival curves. A. b-DFS; B. OS

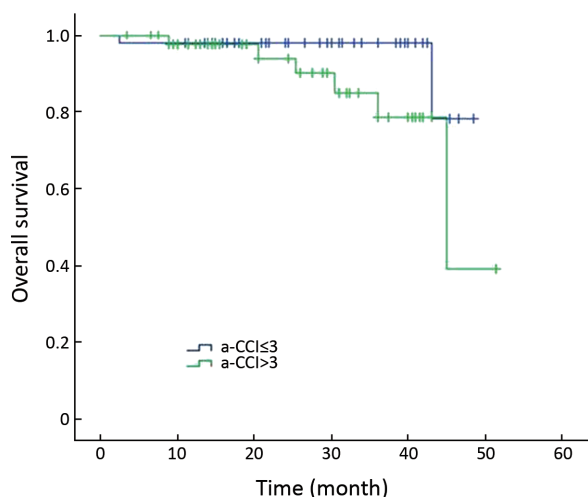


Figure 2 Overall survival and a-CCI

two groups of patients, showing an actuarial 5-year OS of 95.7% for patients with lower-moderate comorbidity (a-Charlson score ≤ 3) and 5-year OS of 86.7% for those with most significant comorbidity (a-Charlson score > 3) ($P=0.08$) (Figure 2).

Toxicity

About toxicity profile: 24 patients (26%) experienced

grade-2 (G2) acute genitourinary (GU) toxicity consisting in a frequency of urination less than one hour and dysuria requiring local anesthetic drugs. Only 4 patients (4%) experienced late grade-3 (G3) GU toxicity, because of obstructive symptoms requiring transurethral resection of prostate (TURP) in 3 patients (3%) and catheterization for longer than 2 weeks in 1 patient (1%). There was no acute G3 gastrointestinal (GI) toxicity.

A pure nonparametric correlation analysis between acute toxicity and a-CCI was also performed using Fisher exact test, which was tailed on two groups of patients adjusted for a-CCI (≤ 3 ; > 3). About acute toxicity (GU and GI), the difference between two groups was not statistically significant ($P=0.50$ and $P=0.70$ respectively) (Table 3).

Discussion

The optimal treatment choice for clinically localized prostate cancer is controversial particularly in elderly men with presumed multiple concomitant medical morbidities. In a treatment decision making, age at diagnosis is an important determinant of therapy as remaining life expectancy, tumor grade, and comorbidity. Generally active surveillance is appropriate for men with very low risk prostate cancer when life expectancy < 20 years or men with low risk disease with life expectancy < 10 years (20). Literature data showed equivalent outcome, comparing

Table 3 Acute toxicity and comorbidity

	No. of patients (%)		P
	Age <75 years (N=42)	Age ≥75 years (N=50)	
GU toxicity			
G0	4 (4%)	5 (5%)	0.50
G1	28 (30%)	22 (24%)	
G2	18 (20%)	15 (17%)	
GI toxicity			
G0	28 (30%)	26 (28%)	0.70
G1	16 (17%)	10 (11%)	
G2	5 (5%)	7 (9%)	

radical prostatectomy, external beam radiotherapy and brachytherapy as monotherapy in clinically localized prostate cancer patients (8-21,22). However, excellent outcomes were reported in some institutional case series about elderly patients with localized prostate cancer treated with LDR-BT (23,24). In literature, there were limited data on prognostic value of comorbidity. The impact of comorbidity on survival outcomes (using Charlson score) was reported both with conservative management and with active treatment for patients with prostate cancer (25,26).

Several studies reported a clear association between comorbidity and mortality in men with prostate cancer, but others didn't find any association (27,28). In a retrospective analysis on 107 patients aged ≥75 years, received radical external beam radiotherapy for prostate cancer, Fiorica *et al.* reported an acceptable rate of toxicity and a better survival for patients with mild comorbidities or good performance status (29). Neider *et al.* in a largely unselected cancer prostate population, including also high-risk patients, treated with radical prostatectomy or external beam radiotherapy or with endocrine treatment alone, showed a statistically significant correlation between high comorbidity and early death (30). The aim of our study was to evaluate the impact of comorbidity on survival outcomes and toxicity profiles in a series of elderly patients who underwent LDR-BT with ¹²⁵I seeds implant.

However, it's difficult to compare existing studies due to: different study design (samples, treatments), the lack of wide use of a standard comorbidity assessment and various comorbidity tools used. It's not clear whether comorbidities

can influence the acute and late toxicities due to an active treatment.

We found only one study reported urinary, bowel and erectile morbidity in unselected population-based sample of older men affected by prostate cancer who underwent brachytherapy alone, with none survival outcomes evaluation. With respect to explanatory variables (demographic variables, treatment variables, tumor related variables, risk factor for complications), age and higher CCI were associated to major urinary and bowel complications (31).

We examined 92 patients to evaluate the role of comorbidity in treatment outcomes: survival and toxicity. None correlation between toxicity and comorbidity was found in our study, perhaps because our sample was "fit" to treatment with a KPS ≥70 and not had major comorbidities; furthermore in the a-CCI score calculation, each decade of age over 40, contributes 1 point to the risk index score, which is added to the score from CCI. Thus, since over half of our patients (54%) had an age ≥75 years, probably, age had more impact on the a-CCI score than the medical comorbidity conditions.

About OS, we found no significant difference between two comorbidity groups, although the 5-year OS was shorter in patients with a-CCI >3 with respect to those with a-CCI ≤3. These data, probably, depend on the small sample size and the follow-up period.

Many different tools are available for the assessment of comorbidity but only few studies examined the performance of different comorbidity measures in prostate cancer setting, thus the optimal comorbidity index for clinical use remains unclear (32,33).

A radical approach is a safe and effective strategy, in elderly cancer patients (34,35). Our data suggest that comorbidity does not affect compliance to treatment and even results in terms of OS and b-DFS. As reported in a previous work, we believe that LDR-BRT could have a great role in elderly men treatment choice because it is a safety and efficacy treatment (36).

Although several studies have investigated the value of CCI to predict outcomes after radical prostatectomy, further studies are needed to investigate about ideal comorbidity assessment tool in elderly prostate cancer patients treated with brachytherapy (37-39).

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