



Radical radiotherapy for localized prostate cancer in elderly

S. Stojanovic¹, Lj. Radosvic-Jelic¹, C. Tulic², I. Popov¹,
D. Babic¹, M. Acimovic¹, D. Masulovic³

¹Institute of radiology and oncology, Belgrade

²Institute of urology and nephrology, Clinical Center of
Serbia, Belgrade

³Institute of radiology, Clinical Center of Serbia, Belgrade

rezime **Background:** Prostate cancer is an age related neoplasm, with high incidence in the group of elderly man. The correct management must to be balanced between the benefits of the treatment and its disadvantages. Radiotherapy as definitive treatment is commonly reserved for older patients and patients with high surgical risk and is widely used as a treatment of choice.

Aim: The aim of this study was to determine the role of radical radiotherapy for localized prostate carcinoma in patients 70 years age or older concerning treatment morbidity, local control, disease free and overall survival.

Material and methods: A clinical prospective non-randomized study was performed including 103 elderly patients with an age 70 or above, between January 1991 and April 2005, at the Institute for Oncology and Radiology of Serbia. Median age of patients was 74,89 years (range 70- 80 years). Stage distribution was as follows: stage A - 3 patients (2.9 %), stage B - 69 patients (67%) and stage C - 31 patients (30.1%). Out of 103 patients, initial PSA value was noted in 87 patients. The mean value of initial PSA was 18,06 ng/ml. Radical radiotherapy was conducted on megavoltage linear accelerators with high energy photons (10, 18 MeV) and total tumor dose of 65 Gy.

Results: Low grade acute complications were registered in 70 patients (65%). Mean follow up time was 40, 13 months. The disease outcome at the last follow up show that 79 patients (76.7%) had no evidence of disease and 24 patients (23.3%) relapsed. Overall survival rates were 65, 29% and 44, 52% and disease free survival 66, 59% and 63, 26% at 5 and 10 years. Disease specific survival was at 5 and 10 years 73,32% and 65, 42% respectively. Late sequelae (gradus I and II) are registered in 22 patients (21.36%), out of 103.

Conclusion: Radical radiotherapy for localized carcinoma of the prostate is effective treatment option in elderly patients with good local control, present treat-

ment tolerance providing good quality of life and long term cure.

Key words: prostate cancer, radiotherapy, elderly

INTRODUCTION

Prostate adenocarcinoma is one of the most common tumors, which is predominantly found in elderly men and becoming increasingly important as life expectancy rises. Careful examination of autopsy specimens demonstrates that approximately 40- 50% of men over the age of 70 harbor a prostatic malignancy. However, only a third of diagnosed patients died of the condition, and mortality is usually for other causes in the elderly¹.

In the elderly, a number of factors may cause a different approach to prostate cancer treatment as: life expectancy, risk of significant morbidity, intolerance to some forms of treatment and social problems². Although an age of 70 is frequently quoted as a cut- off point between different management strategies a life expectation of 10 years is usually considered more important than a chronological age².

The correct management must to be balanced between the benefits of the treatment and its disadvantages. These patients will be offered a choice of treatment, or combinations thereof, ranging from observation or watchful waiting, early versus delayed hormonal therapy to control disease progression, or treatment modalities with curative intent such as full dose of radiotherapy or radical prostatectomy. As patients grow older, palliation and improvement of quality of life replace cure and prolongation of life as objectives. Radiotherapy as definitive treatment is commonly reserved for older patients and patients with high surgical risk and is widely used as a treatment of choice. An analysis on a large series of prostate cancer in elderly men, conducted by the SEER Program of the National Cancer Institute, clearly showed how, beside hormonal therapy, radiotherapy is the local treatment most frequently administered³. Radical prostatectomy is indicated

in appropriately selected older patients in generally good health, but despite a careful clinical evaluation a high percentage of tumors are under-staged, having spread beyond the gland at the surgery⁴.

The aim of this study was to determine the role of radical radiotherapy for localized prostate carcinoma in patients 70 years age or older concerning treatment morbidity, local control, disease free and overall survival.

MATERIAL AND METHODS

In the Institute for Oncology and Radiology of Serbia, from January 1991 to April 2005, a clinical prospective non- randomized study was performed including 103 elderly patients with an age 70 or above.

Median age of patients was 74,89 years (range 70-80 years). Stage distribution (according to AJCC) was as follows: stage A- 3 patients (2.9%), stage B-69 patients (67 %) and stage C - 31 patients (30.1%). All patients had histologically confirmed adenocarcinoma of the prostate. Regarding tumor grade, 38 patients (36.9%) had grade I, 43 (39.9%) grade II, 18 patients (17.5%) grade III and 4 patients (3.8%) had unknown grade. Biopsy by transurethral resection (TUR) was performed in 82 patients (79.6) and transperineal biopsy was done in 21 patients (20.4%). All patients were in good condition with high Karnofsky index (between 80- 100%). Out of 103 patients, initial PSA value was noted in 87 patients. The mean value of initial PSA was 18,06 ng/ml (range 3,38- 60 ng/ml).

Patient's characteristics are presented in Table 1.

External beam radiotherapy was delivered with megavoltage linear accelerators and high- energy photons (10, 18 MeV). Local and locoregional technique included anterior and posterior two parallel opposed fields with tumor dose of 45-50 Gy in 22-24 fractions, 2.08 Gy per fraction, 5 day per week, followed by a boost of 15-20 Gy in 6-8 fractions to the prostate with two lateral parallel fields (four-field technique). The total tumor dose within the prostatic volume was 65 Gy. Dose was specified at mid-plane.

Tumor response rate was evaluated six months after radiotherapy by digital rectal examination (DRE), abdominal and pelvic ultrasound, PSA, chest X ray, peripheral blood count and serum biochemistry and liver function tests.

Acute complications occurred during and immediately after radiotherapy and late post irradiation complications, diagnosed 6 months and later after radiotherapy are scored to RTOG/ EORTC recommendations^{5,6}.

For statistical analysis of the results the descriptive method, Kaplan-Meier table and long- rank test were applied⁷.

RESULTS

Low grade (mild and moderate) acute complications were registered in 70 patients (65%). The most frequent complications were perineal dermatitis in 25 patients (24.3 %), cystitis in 20 patients (19.4%), diarrhea in 19 patients (18.4%) and proctitis in 10 patients (9.7%). More than one complications are registered in 9 patients (Table 2).

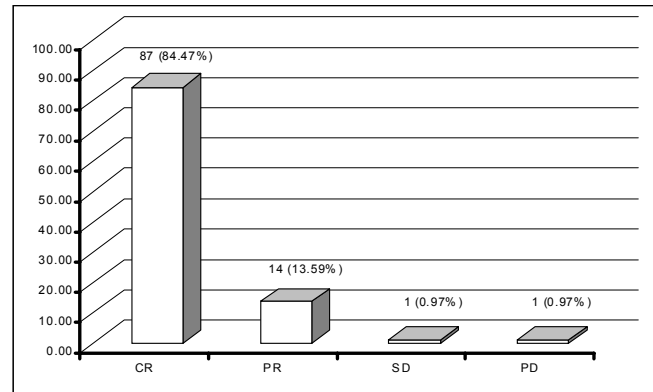


FIGURE 1.
RESPONSE RATE 6 MONTHS AFTER RADIOTHERAPY

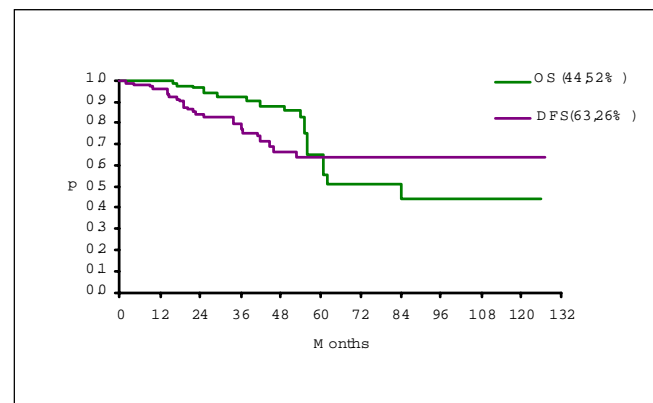


FIGURE 2
10 YEARS OS AND DFS

Radiotherapy was administered continuously without breaks in all patients, due to the low- grade complications, which were treated with adequate symptomatic therapy.

Six months after finished radiotherapy complete response (CR) with PSA level = 4 ng/ml were registered in 87 patients (84.5%) and partial response (PR) in 14 patients (13.6%). Stable disease and progression of disease (bone metastases) are registered in one patient each.

Mean follow up time was 40, 13 months (range 6- 127 months).

The disease outcome at the last follow up show that 79 patients (76.7%) had no evidence of disease and 24 patients (23.3%) relapsed. The most frequent site of relapse were bones in 15 patients (14. 6%) and biochemical relapse only was noted in 8 patients (7.8%). One patient had metastases in regional lymph nodes.

Overall survival rates were 65, 29% and 44, 52% and disease free survival 66, 59% and 63, 26% at 5 and 10 years. Disease specific survival at 5 and 10 years 73,32% and 65, 42% respectively. Eight patients died due to cancer and 6 died from intercurrent disease. (Figure 2)

Late sequelae (gradus I and II) are registered in 22 patients (21.36%), out of 103. Twelve patients had mild skin fibrosis, 4 patients (3.9%) urethral stricture which not re-

TABLE 1
CHARACTERISTICS OF PATIENTS

Total	103	
Median age (year range)	74,89 (70-80)	
Stage (by AJCC)	A	3(2,9%)
	B	69(67%)
	C	31(30.1%)
Pathology	Adenocarcinoma	
Grade	I	38(36.9%)
	II	43(39.9%)
	III	18(17.5%)
	Unknown	4(3.8%)
Initial PSA value (ng/ml)	Mean range	87/103
	18.06(3.38-60-)	84.47%
	≤10	31(35.6%)
	> 10	56(64.4%)

quired urological intervention and 6 patients (5.4%) proctitis. (Table 2)

In our study we tried to tested some prognostic parameters as initial value of PSA (PSA =10 ng/ml and PSA10) and tumor stage (A+B vs. C) and find some correlation to disease outcome.

We compared initial value of PSA, PSA =10 ng/ml and PSA10 ng/ml with tumor stage A+ B and C. There was not statistical significant difference ($p=0,536$) and correlations between this two parameters. We didn't find relationship between initial value of PSA and grade distribution ($p=0,454$) and also grade to stage distribution ($p=0,342$).

Than we tested initial values of PSA and compared to overall survival and disease free survival in a mean follow-up time of 40, 13 months. Patients with PSA =10 had no statistically superior overall survival compared with patients with PSA10 ng/ml ($p=0,383$). In disease free survival there was no statistically significant difference too ($p=0,077$).

The similar results we got when we tested disease stage A+B vs. C in relation to overall and disease free survival. Overall survival and disease free survival rates showed no significant difference according to stage ($p=0,199$) ($p=0,213$).

DISCUSSION

Even if radical radiotherapy is use more than fifty years, the number of studies which were published results of treatment in prostate cancer in elderly is very rare.

The definition of "elderly" is not clear exactly. Some authors analyzed men 65 years age or older and some patients with 70 years or above. Putative screening programmes for prostate cancer usually exclude those over 70 years and there is a consensus that PSA should only be measured in elderly if there is clinical evidence for prostate cancer. Kirk D in his study reported that in man over 75 years without urinary symptoms, measuring PSA is misguided act all too frequently committed in the quest against cancer².

In our study the majority of patients (67%) were in stage B with initial PSA value 10 ng/ml in 56/87 patients (64, 36%). Similar results reported other authors. Villa et al treated with radical radiotherapy 105 patients (65.5%) between 70-79 years and 15 patients (65.2%) 80 years age or older in T2 stage. Initial PSA value more than 10 ng/ml was diagnosed in 60 % and 56.5% patients in both groups respectively⁸. In study of Johnstone et al . T2 stage was diagnosed in 450 / 516 patients between 71 to 80 years and 33/44 patients older than 80 years. Initial PSA 10 ng/ml was detected in 131 patients between 71 to 80 years and 18 patients in group older than 80 years⁹.

We registered acute complications in our paper in 65% of patients and they were low grade and didn't have a significant impact of quality of life. Reversible acute effects in Stanford study, proctitis registered in 8% of patients and cystitis in 14% make no difference to the same acute complications in our study¹⁰. In Italian study 68.8% men showed acute toxicity and among them 9.3% had acute complications grade II-III⁸. Our results relating disease outcome and treatment are in accordance with literature data . We reported 5- years overall survival and disease specific survival of 66,59% and 73, 32%. Huguenin et al. reported 5-year overall and disease specific survival of 66% and 78% in their study treated elderly men with definitive radiotherapy⁸. But, Villa et al reported much better results: 5-years overall survival 90,2% and disease specific survival 93,7% (8). The Pattern of Care study and the series of the Fox Chase center in Philadelphia show that treatment results of patients aged 70 years or above are similar to those registered in younger patients¹¹. Also, Arcangelli et al. found at 5 and 10 years overall survival of 70% and 50% in 199 younger patients with mean age of 59 years¹².

Villa et all noted late complications in 19.7% of patients and 5.5% showed grade II-III sequelae⁸. Late sequelae reported in RTOG study, urethral stricture in 4.6% of patients and rectal complications in 1.7% are very similar to our results¹³. We reported almost equal number and type of complications.

The impact of total tumor dose and selection of adequate irradiation techniques are very important to achieve optimal tumor response rate and minimize toxicity. We used four field- box local or locoregional technique with total tumor dose of 65 Gy. Besides this technique which is widely used, many authors were irradiated the patients using a rotational technique based of two opposing lateral arcs of 120° with or without the partial shield of a half field (blocked-arc techniques)¹⁴ or in last few years with three-dimensional conformal radiotherapy (3D-CRT)¹⁵. 3D CRT is based on the ability to define anatomically

TABLE 2

ACUTE AND LATE COMPLICATIONS

Acute toxicity (grade I and II)	No of pts	%	Late complications (grade I and II)	No of pts	%
dematitis	25	24.3	skin fibrosis	12	11.7
cystitis	20	19.4	urethral stricture	4	3.9
proctitis	10	9.7	proctitis	6	5.4
diarrhea	19	18.4			

each structure in the pelvis, to precisely calculate dose delivery to them, and for possibility to apply a higher dose to prostatic volume with exclusion of normal critical organs from irradiation volume with the aim to improve treatment outcome and minimize toxicity. In study of Geinitz et al. elderly patients were treated with 3D-CRT and total tumor doses ranging between 66 to 70.2 Gy. Acute and late complications were lower¹⁵. But some authors don't believe that a strategy of dose escalation with 3D-CRT could have a positive impact on the treatment results of patients aged more than 70 years due to probability of high grade complications⁸.

CONCLUSION

External beam radiotherapy is generally well tolerated by the elderly patients. The treatment results, incidence and grade of complications are acceptable. Radiation therapy in curative intent should be offered to the elderly patients as safe and effective treatment options taking into account concomitant disease and life expectancy. We need some more studies to evaluate the role of 3D-CRT on the clinical outcome in elderly patients.

*SUMMARY**RADIKALNA RADIOTERAPIJA LOKALIZOVANOG KARCINOMA PROSTATE KOD STARIH PACIJENATA*

Uvod: Karcinom prostate je neoplazma koja se javlja sa godinama pacijenata, zbog čega je incidenca visoka kod starijih muškaraca. Pravilan izbor terapije zavisi od potencijalnih koristi i nedostataka određenih terapijskih modaliteta. Radikalna radioterapija se najčešće primenjuje i široko je prihvaćena u lečenju starijih pacijenata i pacijenata kod kojih postoji rizik od hirurškog lečenja.

Cilj: Cilj studije je bio da prikaže ulogu radikalne radioterapije u lečenju lokalizovanog karcinoma prostate pacijenata sa 70 godina i starijih, a u odnosu na komplikacije lečenja, lokalnu kontrolu, preživljavanje bez znakova bolesti i sveukupno preživljavanje.

Material i metod: Na Institutu za onkologiju i radiologiju Srbije u periodu od januara 1991. do aprila 2005. godine sprovedena je prospektivna nerandomizovana studija na 103 pacijenata obolelih od karcinoma prostate sa

70 godina i starijih. Srednja starost pacijenata bila je 74, 89 godina (rang 70- 80 godina). Pacijenti su bili sledećih stadijuma bolesti: stadijum A - 3 pacijenta (2,9%), stadijum B - 69% (67%) i stadijum C - 31 pacijent (30,1%). Od 103 pacijenta, inicijani PSA je imalo 87 pacijenata. Srednja vrednost inicijalnog PSA bila je 18,06% ng/ml. Radikalna radioterapija je sprovedena na megavoltanim linernim akceleratorima visokih energija (10,18 MeV) i ukupnom tumorskom dozom od 65 Gy.

Rezultati: Akutne komplikacije niskih gradusa zabeležene su u 70 pacijenata (65%). Srednje vreme praćenja iznosilo je 40,13 meseci. Na poslednjoj kontroli 79 pacijenata (76,7%) je bilo bez znakova bolesti, a u 24 pacijenata (23,3%) dijagnostikovano je relaps. Sveukupno preživljavanje je bilo 65,29% i 44,52%, a preživljavanje bez znakova bolesti 66,59% i 63,26% na 5 i 10 godina. Preživljavanje specifično za bolest iznosilo je 73,32% i 65,42% na 5 i 10 godina. Kasne komplikacije (gradusa I i II) registrovane su u 22 pacijenta (21,36%), od ukupno 103 pacijenta.

Zaključak: Radikalna radioterapija lokalizovanog karcinoma prostate predstavlja efikasnu terapijsku opciju u lečenju starijih pacijenata, kojom se postižu dobri rezultati lokalne kontrole i preživljavanja, uz nisku toksičnost i očuvanje kvaliteta života.

Ključne reči: karcinom prostate, radioterapija, stariji

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