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NONRANDOMIZED COMPARISON OF RADICAL PROSTATECTOMY VERSUS EXTERNAL RADIATION IN PATIENTS WITH PROSTATE CANCER: A 14-YEAR FOLLOW-UP IN KARLOVAC GENERAL HOSPITAL

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Summary

Radical prostatectomy (RP) and radical external radiotherapy (RT) are standard curative options for patients with localized prostate cancer (CaP). There are no conclusive randomized studies comparing these two methods in terms of oncological outcome. The aim of our nonrandomized study was to compare oncological outcome of our patients with localized CaP treated surgically with those underwent RT.

We analyzed 115 consecutive patients with newly diagnosed localized CaP in Karlovac General Hospital from January 1994 to January 2008. Sixty four (55.7%) underwent RP and 51 (44.3%) external RT. The patients in RP group were significantly younger and with lower serum prostate-specific antigen (PSA) value, while there was no significant difference between the patients in RP and RT group in term of pathologic stage, pathologic grade (Gleason score) and risk group distribution. The median follow-up was 44 months (range 5-168). There was no difference in PSA recurrence rate between the patients in RP and RT group. Time to PSA recurrence was significantly shorter after RP (median 16 months, range 2-86) than after RT (median 36, range 10-73). The overall 5-year PSA recurrence-free survival rate, estimated by Kaplan-Meier method was 57.2%. There was no difference in PSA recurrence-free survival between the patients in RP and RT group.

Although nonrandomized and with a limited follow-up, our study supports a general consensus that there is no significant difference in oncological outcome between the patients with localized CaP treated with RP and those submitted to RT.

KEY WORDS: *prostate cancer, radiotherapy, radical prostatectomy, survival*

NERANDOMIZIRANA USPOREDBA REZULTATA RADIKALNE PROSTATEKTOMIJE I RADIKALNOG ZRAČENJA U LIJEČENJU BOLESNIKA S KARCINOMOM PROSTATE 14-GODIŠNJE PRAĆENJE U OPĆOJ BOLNICI KARLOVAC

Sažetak

Radikalna prostatektomija i radikalno perkutano zračenje standardne su metode liječenja bolesnika s lokaliziranim karcinomom prostate. Ne postoje zaključna randomizirana istraživanja koja uspoređuju onkološki ishod bolesnika liječenih ovim dvjema metodama. Cilj našeg nerandomiziranog ispitivanja bio je usporediti onkološke rezultate liječenja bolesnika s lokaliziranim karcinomom prostate liječenih kirurški s onima podvrgnutim radikalnom zračenju prostate.

Analizirali smo 115 susljednih bolesnika s novodijagnosticiranim lokaliziranim karcinomom prostate u Općoj bolnici Karlovac u razdoblju od siječnja 1994. do siječnja 2008. Šezdeset jedan pacijent (55,7%) podvrgnut je radikalnoj prostatektomiji, a 51 (44.7%) radioterapiji. Pacijenti podvrgnuti radikalnoj prostatektomiji bili su značajno mlađi i imali značajno nižu vrijednost serumskog PSA, dok nije bilo značajne razlike između terapijskih skupina po pitanju patološkog stadija, patološkog gradusa (Gleason score) i distribucije po skupinama prema stupnju rizika. Medijan praćenja bolesnika iznosio je 44 mjeseca (raspon 5-168). Nije utvrđena značajna razlika u incidenciji PSA recidiva među terapijskim skupinama bolesnika. Vrijeme do pojave PSA recidiva bilo je značajno kraće kod bolesnika nakon radikalne prostatektomije (medijan 16 mjeseci,

raspon 2-86), nego kod bolesnika nakon radikalne radioterapije (medijan 36 mjeseci, raspon 10-73). Ukupno stopa 5-godišnjeg preživljenja bez porasta PSA, procijenjena Kaplan-Meierovom metodom, iznosila je 57,2%. Nije utvrđena razlika u preživljenu bez biokemijskog recidiva između bolesnika nakon radikalne prostatektomije i onih podvrgnutih radikalnoj radioterapiji.

Iako nerandomizirano i s praćenjem bolesnika ograničenog trajanja, naše ispitivanje podupire opće prihvaćeni stav da nema značajnih razlika po pitanju onkološkog ishoda između bolesnika s lokaliziranim karcinomom prostate liječenih radikalnom prostatektomijom i onih podvrgnutih radikalnom zračenju prostate.

KLJUČNE RIJEČI: *karcinom prostate, radioterapija, radikalna prostatektomija, preživljenje*

INTRODUCTION

A wide use of prostate-specific antigen (PSA) testing in the last two decades resulted in increasing incidence of CaP in developed countries. Recently 65-91% of the patients with CaP in western countries are diagnosed with localized disease and underwent curative treatment (1, 2). There are two standard modalities of radical treatment for CaP: radical prostatectomy (RP) and radical radiotherapy (RT) which can be performed as external beam therapy or transperineal brachytherapy. There are no randomized studies comparing RP with either external beam therapy or brachytherapy for localized CaP, but there is a general consensus that external irradiation offers the same long-term survival results as surgery, and that external irradiation provides a quality of life at least as good as by surgery (3, 4).

In Croatia, PSA-testing has been widely used during last 15 years. There is no organized screening for CaP but early detection procedures inaugurated in routine activities of urologists and even general practitioners resulted in an increased number of localized CaP diagnosed over last years. Radical surgery and external beam therapy are standard options for curative treatment for localized CaP in our country, while brachytherapy has not yet been used on regular basis. Radical prostatectomy is routinely performed in many centers. External beam therapy is available in some clinical institutions while three-dimensional conformal therapy was introduced in only one in 2006. There is no published data about treatment of patients with CaP in Croatia. There are no studies that compare results of surgically treated patients with those who underwent RT.

The aim of our study was to answer the following questions: How did we treat patients with localized CaP diagnosed in the Karlovac General Hospital in last 14 years period? How many patients underwent RP and how many RT? What were the patients' characteristics in these two groups? At the end, we tried to compare the oncological outcome of patients treated surgically with those who underwent RT.

PATIENTS AND METHODS

From January 1994 to January 2008, 115 consecutive patients underwent curative treatment for CaP. In 113 patients, cancer was confirmed pathologically after transrectal ultrasound-guided biopsy and in 2 patients, cancer was assessed cytologically after fine-needle biopsy. The standard pretreatment work-up consisted of routine laboratory tests, chest X-ray, bone scintigraphy, pelvic CT scan and cystoscopy.

The patients were not randomized, but an indication for definite treatment in each case was made by one of the four urologists.

RP was performed retropubically in 62 patients and using laparoscopic approach in 2 patients. In all surgically treated patients, limited or extended pelvic lymph node dissection was done.

RT was performed in two different centers. Twenty-eight patients underwent conventional external irradiation of the prostate and 23 patients three-dimensional RT for CaP. Six patients with high-risk tumors started with adjuvant hormonal therapy before irradiation and maintained the treatment for 2 years.

Follow-up was provided through 3- or 6-month visits. The standard post-treatment check-ups consisted of a physical examination and PSA testing in all patients, and pelvic CT scans, bone scintigraphy in selected cases. The PSA recurrence following RP was defined as two consecutive values of 0.4 ng/mL or greater. Following RT, the definition of biochemical relapse was three consecutive increases of PSA value.

Statistics

Yates' chi-square test and T-test were used for testing of qualitative and quantitative parameters, respectively. Survival rates were estimated using the Kaplan-Meier product-limit method. Differences between the groups were calculated using the log-rank test.

RESULTS

From January 1994 to January 2008, CaP was diagnosed in 603 patients in Karlovac General Hospital, Dept. of Urology. Tumors were classified as localized ($T_{1-2}N_0M_0$) in 238 (39.5%), locally advanced ($T_{3-4}N_{0-1}M_0$) in 244 (40.5%) or metastatic ($T_{1-4}N_1M_1$) in 121 (20.0%) patients. Hundred and fifteen patients (19.1%) underwent radical treatment, 445 (73.8%) hormonal and 43 (7.1%) patients accepted recommendation for watchful waiting. Of 115 radically treated patients, 64 (55.7%) underwent RP and 51 (44.3%) external beam irradiation with curative intent.

Mean age of the patients in the surgically treated group was 65.0 years (range 51-75) and 69.2 (range 59-77) in the group of radically irradiated patients (p<0.001). T-stage was lower, but not significantly in the surgical group (p=0.07), with 53 (82.8%) and 11 (17.2%) classified as pT_{1-2} and pT_{3-4}, respectively. Among irradiated patients, 34 (66.7%) were classiffied as cT_{1-2} and 17 (33.3%) as cT_{3-4}. Positive lymph nodes were found in 4 (6.2%) surgically treated patients during pelvic lymph node dissection. In surgically treated patients, Gleason score 2-7 was found in 49 (76.5%) and Gleason score 8-10 in 10 (15.7%) patients. Between the patients submitted to RT, 35 (68.6%) were classified as Gleason 2-7 and 10 (19.6%) as Gleason score 8-10 (p=0.49). The preoperative PSA value was significantly lower (p<0.001) in the surgically treated group (mean 9.9 ng/mL, range 0.71-33.7) compared to the PSA value in patients undergoing RT (mean 20.0, range 1.8-92.0). Thirty (46.9%) patients in the RP group were classified as low risk, 18 (28.1%) as intermediate risk, 16 (25.0%) as intermediate risk, while these figures for the RT group were 18 (35.2%), 14 (27.5%) and 19 (32.3%), respectively (p=0.31) (Table 1).

Median follow-up of 115 study patients was 44 months (range 5-168) i.e., 45 months (range 5-168) in the RP group and 43 months (range 6-160)

Table 1.
PATIENT CHARACTERISTICS AND DESCRIPTIVE STATISTICS

	All patients No.,%	Patients with radical prostatectomy No.,%	Patients with radiotherapy No.,%	p
No. of patients	115	64 (55.7)	51 (44.3)	
Age, yr Mean (median) Range	 66.4 (67.0) 51-77	 65.0 (66.0) 51-75	 69.2 (69.0) 59-77	 <0.001
Stage T_{1-2} T_{3-4}	 87 (75.7) 28 (24.3)	 53 (82.8) 11 (17.2)	 34 (66.7) 17 (33.3)	 0.07
Pathologic grade Gleason score 2-7 Gleason score 8-10 Gleason score x	 84 (73.0) 20 (17.4) 11 (9.6)	 49 (76.5) 10 (15.7) 5 (7.8)	 35 (68.6) 10 (19.6) 6 (11.8)	 0.49
PSA, ng/ml Mean (median) Range	 14,3 (9,01) 0.71-92.0	 9.9 (8.4) 0.71- 33.7	 20.0 (12.1) 1.8-92.0	 <0.001
Risk groups Low Intermediate High	 48 (41.8) 32 (27.8) 35 (30.4)	 30 (46.9) 18 (28.1) 16 (25.0)	 18 (35.2) 14 (27.5) 19 (32.2)	 0.31
PSA recurrence	35 (30.4)	20 (31.2)	15 (29.4)	0.99
Time to recurrence Median, months Range	 30 2-86	 16 2-86	 36 10-73	 <0.01

for the patients in RT group. During the follow-up PSA recurrence was noticed in 35 (30.4%) of all radically treated patients. After RP PSA recurrence occurred in 20 (31.2%) patients, and after RT in 15 (29.4%) patients (p=0.99). Time to PSA recurrence was significantly shorter (p<0.01) after RP (median 16 months, range 2-86) than after RT (median 36 months, range 10-73).

Clinical recurrence was reported in 6 patients after RP and in 5 patients after RT. Biochemical relapse preceded clinical recurrence in all patients. Nine patients with PSA recurrence after RP underwent adjuvant RT and four adjuvant hormonal therapy (HT). Five patients with PSA recurrence after RT underwent HT.

During the follow-up, a tumor-specific death was not observed in the surgically treated patients, while 2 patients died of CaP in the RT group. The 5-year PSA recurrence-free survival rate, estimated by the Kaplan-Meier method was 57.2% for all radically treated patients (Figure1). There was no

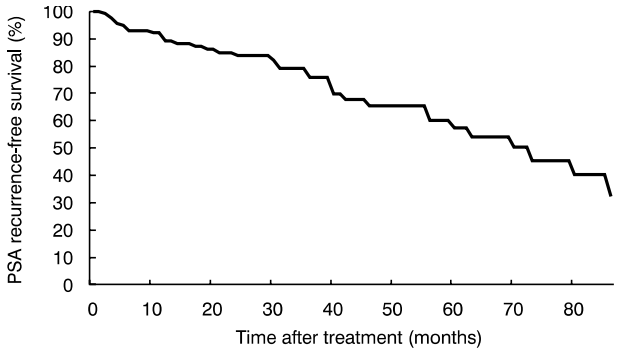

Figure 1. Overall PSA recurrence-free survival

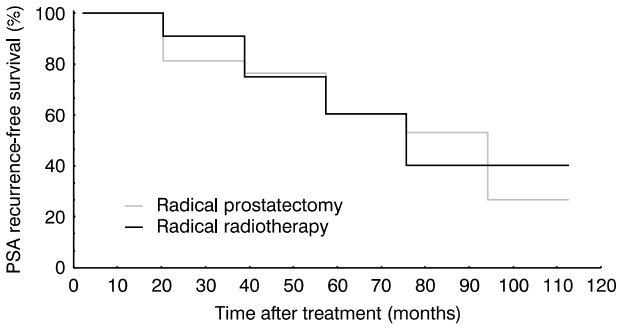

Figure 2. PSA recurrence-free survival in patients after RP (—) and RT (—)(p=0.34)

statistically significant difference in PSA recurrence-free survival between patients in RP (53.3%) and RT (60.2%) group (p=0.34) (Figure 2). There was no difference in PSA recurrence-free survival between the groups comparing patients stage for stage. No statistically significant difference was noticed in PSA recurrence-free survival between the groups comparing patients within the same risk groups.

DISCUSSION

CaP is now recognized as one of the principal medical problems facing the male population in Europe with estimated 2.6 million new cases diagnosed each year (5). In developed countries, 15% of all malignancies are CaP, while this percentage is four times smaller in developing countries (6). In Croatia, the incidence rate of CaP increased from 7% of all malignancies in 1993 to 13% of all malignancies in 2005, with a recent incidence rate of 70.6/100000 males (7). The rate of patients with localized CaP is increasing, too.

The rate of patients with localized CaP (40.5%) in our study is lower than in some screening method-based studies (91%), but comparable with studies based on early detection (47%) (2,8).

The increasing number of the patients with localized CaP faces urologists, oncologists and radio-oncologists with dilemma: is it better to treat these patients surgically or with RT? There are no conclusive randomized studies on this issue, but there are some unfinished studies with interim results available (9).

In that situation, we analyzed our radically treated patients with CaP in the last fourteen years. The study suffers from some limitations: the number of our patients was relatively small, the patients were not randomized, procedure for RT was not uniform for all patients, median follow-up was too short for definitive conclusions, but some observations and conclusions are still possible analyzing our results.

Our study was conducted by urologists. One of the two treatment options for our patients with localized CaP was chosen by one of four urologists in the study. This fact can explain predomination of surgically treated patients (55.7%) in our study in comparison with patients undergoin RT (44.3%). Jung et al., in their study of 85,088 men with localized CaP, showed a strong association between the different specialist consulted and primary therapy received (10). According to our observation, it seems that urologists tend to choose RP for younger patients with a lower PSA value and RT for older patients with a higher PSA value.

The rate of our patients with biochemical disease progression (30.4%) was very close to data from the Di Stazi´s study (32.8%) (9). Like our observation, Di Stazi found no difference in the PSA recurrence rate between the patients in RT and RP group (9). Median time to biochemical progression was significantly shorter in our patients than in the Di Stazi´s study (9). Di Stazi observed no difference in time to progression between the RT group and the RP group, while, in our study, biochemical progression occurred significantly faster in patients undergoing RP than in patients after radiation therapy. It must be emphasised that criteria for progression were not defined equally in both studies.

Five-year PSA recurrence-free survival rate of the surgically treated patients in our study (53.3%) was comparable with data in studies from the 90-ties (11,12), but it is significantly lower in comparison with recently published data (13). The

lower PSA recurrence-free survival rate in our study could be explained by the fact that the patients with introperatively confirmed extracapsular extension or nodal involvment were not excluded from the study, but the survival was assesed for all surgically treated patients togeather.

Five-year PSA recurrence-free survival rate for the irradiated patients in our study was similar to results in other studies comparing PSA-free survival rate for the patients in the same risk groups (14,15). It was not possible to compare oncological results between the groups of our patients receiving different radiation doses.

CONCLUSION

In conclusion, although nonrandomized and with a limited follow-up, our study supports a general consensus that there is no significant difference in oncological outcome between the patients with localised CaP treated with RP and those submitted to RT. Further investigations and completion of some unfinished studies will be necessary for definitive conclusions. Because of the specific prolongued natural history of CaP and requirement for long-lasting investigations with 10- or 15-year follow-up, definitive evidence-based conclusions on this issue mignt not be available in the near future.

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