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ORIGINAL ARTICLE

Combination of adjuvant radiotherapy and androgen deprivation therapy after radical prostatectomy in high risk prostate cancer patients – results from retrospective analysis

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Summary

Purpose: *We retrospectively evaluated the outcome in prostate cancer (PCa) patients receiving combination of adjuvant radiotherapy (ART) and androgen deprivation therapy (ADT) after radical prostatectomy (RP).*

Methods: *Between 2004 and 2012, 132 patients were referred for ART to the Department of Oncology, University Hospital, Split.*

Fifty-six consecutive patients with at least one proven or possible adverse prognostic factor such as pelvic lymph nodes invasion (LNI), lymphovascular invasion (LVI), high tumor grade and high preoperative prostatic specific antigen (PSA) level received combination of ART and ADT, while 76 patients received ART alone.

The ADT consisted of a luteinizing hormone releasing hormone (LHRH) agonist or bicalutamide at a dose of 150 mg per day. The duration of ADT was left at the discretion of the treating physician and it lasted 6 to 36 months (median 24). The effect of combination of ART and ADT on biochemical relapse-free survival (bRFS), metastases-free survival (mFS), disease-specific survival (DSS) and overall survival (OS) was estimated using the Kaplan-Meier method.

Results: *After a median follow-up time of 61 months (range 13.6-113), the 5- and 7-year bRFS were 90.5 and 77.2%, respectively. Distant relapse occurred in 5 patients, resulting in 5- and 7-year mFS of 95.9 and 81.7%, respectively. During follow-up, 7 patients died (2 PCa deaths), resulting in 5- and 7-year DSS and OS of 100% and 94.7% and 90.6 and 81.5%, respectively.*

Conclusions: *This retrospective study shows high bRFS, mFS, DSS and OS rates with the combination of ART and ADT in high-risk PCa patients.*

Key words: *adjuvant, androgen deprivation, prostate cancer, radiotherapy*

Introduction

A large proportion of men in western countries are diagnosed with clinically localized PCa and the majority of them are treated with RP [1-4]. RP provides long-term disease control in 75% of the patients with clinically localized PCa [5,6]. After RP, PSA levels, as a surrogate for disease control, should fall to undetectable levels (i.e., <0.2 ng/ml) 6 weeks after surgery [5,6]. The factors connected with increased risk of recurrence, both local and distant, after RP are extracapsular extension (ECE), seminal vesicle invasion (SVI), positive margins (PM) and LNI [7-9]. The three most important trials of ART after RP (i.e., EORTC 22911, SWOG 8794 and ARO 96-02 trials) in patients with such pathologic features have shown improved bRFS [7-9]. However, the results regarding mFS and OS were not consistent. Only the SWOG trial, after 10 years of follow up, showed benefits in OS and mFS when ART was applied [8]. This controversy might be attributed to the differences in tumor characteristics among the examined cohorts.

Modern, good clinical practice guidelines do not uniformly suggest the best approach to pa-

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tients with increased risk of PCa recurrence after RP [10,11]. The question is whether ART is required for all patients with pathologic T3 stage (pT3) of disease. Another question is whether ART, as only postoperative therapeutic modality in patients with pT3 PCa, is sufficient to control the disease. Moreover, optimal treatment of patients after RP with LNI is not well defined: should these patients be treated with ADT alone or combination of ADT and ART? Similarly, treatment of patients after RP with other proven risk factors for recurrence, such as high preoperative PSA level (i.e. >10 ng/ml) or poorly differentiated tumors (Gleason score >7), or possible risk factors for recurrence such as LVI in the definitive pathologic findings is not optimally defined as well. Here, the important clinical and scientific question is: are these negative prognostic factors indicative for ADT administration ? The question is also whether, when, how long and in what form ADT should be administered.

Despite the biologic advantage of adding ADT to RT, i.e. cytoreductive and synergistic effects, examining studies that focused on the use of ADT in patients who underwent RP and then ART, it is not possible to provide guidance regarding the use of ADT in conjunction with RT [12-15]. The weaknesses of these studies include non-randomized study designs, small sample sizes, lack of statistical power, lack of group equivalence on pathologic risk factors, large differences in ADT protocols, primary focus on biochemical recurrence, differences in RT techniques and total dose administered [12-15]. Of course, randomized, well-designed and controlled trials are needed to provide definitive evidence.

In our institution, starting in 2004, we have considered that patients with ECE, SVI, PM and LNI with at least one of pathologic features such as high preoperative level of PSA, high grade tumors and LVI should postoperatively receive combination of ART and ADT. Therefore, we retrospectively evaluated the results of combined therapy in a group of patients with high risk of PCa recurrence.

Methods

Between 2004 and 2012, 132 patients were referred to the Department of Oncology and Radiotherapy at the University Hospital Split, Croatia for ART, and they all had indications for ART (i.e. SVI, ECE, PM). Concomitantly with ART, 56 consecutive patients with at least one proven or possible adverse prognostic factor such as LNI, LVI, high tumor grade and high preoperative PSA level, received also ADT.

Besides negative pathologic features for local PCa relapse, all 56 patients were considered as high risk for PCa dissemination due to negative prognostic pathologic features. Consecutively, all of them, besides ART, received ADT as well.

Androgen deprivation therapy

The median time between RP and ADT was 2.2 months (range 0.4-12.3). ADT concomitantly with ART was given to 44 patients (79%) and sequentially to ART was given to 12 patients (21%) with median duration of 24 months (range 6-36). Fifty-four patients (96%) were treated with LHRH agonist (goserelin or leuprolide) and 2 (4%) were treated with bicalutamide at a dose of 150 mg per day. In order to prevent initial "flare" phenomenon, patients treated with LHRH agonists received non-steroidal antiandrogens (flutamide at a dose of 250 mg, 3 times daily or bicalutamide at a dose of 50 mg, once daily), starting 1-2 weeks before the first injection of LHRH agonist, lasting for 4 weeks. LHRH agonists were administered every 12 weeks. The decision about the type and the duration of ADT was left at the discretion of the clinical oncologist.

Adjuvant radiotherapy

The median time between RP and ART was 3.8 months (range 1.1-10.1). Forty-six patients (82%) were treated with two-dimensional RT (2D) and 10 (18%) with three-dimensional conformal RT (3D-CRT) to the pelvis, seminal vesicle bed and prostate bed. All patients, regardless of pathologic stage, were treated with ART to the postoperative prostate bed, with median dose of 66 Gy (range 66-70). Twenty-eight patients (50%) with pT3b and 2 patients (4%) with pT4 received 54 Gy to seminal vesicle bed. Twenty-seven patients (48%), i.e., 19 patients with pathologically proven LNI and 8 patients without lymph node dissection (LNI not proven pathologically) but with high risk (>15%) of pelvic nodal involvement according to the Roach formula (they were clinically node-negative on preoperative computed tomography (CT) and/or magnetic resonance imaging (MRI)) received a median dose of 46 Gy to the pelvis (range 40-50) [16]. In all patients RT was delivered with conventional fractionation of 2 Gy per fraction.

Statistics

bRFS, mFS, DSS and OS rate at 5 and 7 years were estimated using the Kaplan-Meier method with log-rank test [17]. Elapsed time was measured from the date of induction of adjuvant therapy. Descriptive statistics were used to analyse patient characteristics and safety profile.

Commercial software (IBM SPSS 19.0) was used for statistical analyses. A patient was considered biochemical relapse-free when there was no evidence of PSA relapse. PSA relapse was defined as a rise above

0.2 ng/mL plus two additional consecutive PSA rises measured at least 3 months apart. The first date with PSA level above 0.2 ng/mL was regarded as the date of PSA relapse. A patient was considered metastasis-free when there was no evidence of distant metastases. Confirmation of distant metastases was performed using bone scintigraphy or radiological methods such as CT or MRI. DSS rate was defined as the percentage of patients who had not died of PCa in a defined period of time (time from the start of treatment until the time of death). OS rate was defined as the percentage of patients who were still alive after they started adjuvant treatment for PCa.

Results

Patient characteristics

The median follow-up time was 61 months (range 13.6-113). Nineteen patients (34%) had LNI. Of these patients, 2 (4%) had pT4 stage, 11 (20%) pT3b stage, 4 (7%) pT3a stage and 2 (4%) pT2c stage. Thirty-seven patients (66%) had high grade tumors (Gleason score 4+3 or 8-10), 33 (59%) had high preoperative PSA level (>10 ng/ml) and 27 (48%) had LVI. Median preoperative PSA level was 13.2 ng/ml (range 4.4-64.0) and median postoperative PSA level was 0.2 ng/ml (range 0.00-8.1). Twenty patients (36%) had undetectable level of postoperative PSA (PSA <0.2 ng/mL). PM was found in the pathologic specimens of 36 (64%) patients. The patient characteristics are shown in Table 1. The database for this analysis was closed on December 31, 2013.

Clinical results

The 5- and 7-year bRFS were 90.5 and 77.2%, respectively (Figure 1). Out of 7 patients with biochemical relapse, 6 had high-grade tumors, 5 had LVI and 5 had preoperative PSA level >10 ng/ml. Six of them had PM.

Distant relapse occurred in 5 patients (bone metastases in 3 patients, lymph node metastases in 1 and brain metastases in 1), resulting in 5- and 7-year mFS of 95.9 and 81.7%, respectively (Figure 2). All patients with distant relapse had high-grade tumors, LVI and preoperative PSA level >10 ng/ml. Three of them had PM.

Four patients progressed both biochemically and with distant metastasis. The patient with brain metastases progressed only with distant metastases.

During follow-up, 7 patients died (2 PCa deaths), resulting in 5- and 7-year DSS and OS of 100% and 94.7% and 90.6 and 81.5%, respectively (Figures 3 and 4).

Table 1. Patient characteristics

Characteristics	*Number of patients (%)*
Median age, years (range)	65 (40-74)
Tumor stage	
pT2	5 (9)
pT3a	20 (36)
pT3b	28 (50)
pT4	3 (5)
Nodal status	
pN0	25 (45)
pN1	19 (34)
pNx	12 (21)
Gleason score	
7 (4+3)	16 (29)
8-10	21 (38)
Median of preoperative PSA level (ng/ml) (range)	13.2 (4.4-64.0)
Preoperative PSA level (ng/ml)	
< 10	18 (32)
>10	33 (59)
Unknown	5 (9)
Lymphovascular invasion	
Yes	27 (48)
No	29 (52)
Positive margin	
Yes	36 (64)
No	8 (14)
Unknown	12 (21)
Median time between RP and ART (months, range)	3.8 (1.1-10.1)
Radiotherapy technique	
2D	46 (82)
3D-CRT	10 (18)
Median RT dose (Gy, range)	
To prostate bed	66 (66-70)
To seminal vesicle bed*	54
To pelvis	46 (40-50)
Median time between RP and ADT (months, range)	2.2 (0.4-12.3)
ADT	
LHRH agonist	54 (96)
bicalutamide 150 mg	2 (4)
Duration of ADT (months)	
6-12	7 (13)
13-24	27 (48)
>24	22 (39)

*this dose was fixed to 54 Gy. For abbreviations see text

Toxicity

Late genitourinary (GU) and gastrointestinal (GI) toxicity during follow-up were registered and the maximal score for each symptom was

Table 2. Late gastrointestinal and genitourinary toxicity using the Common Toxicity Criteria for Adverse Events v4.0

Symptom	*Grade*	*N (%)*
Proctitis	2	7 (13)
	3	2 (4)
Cystitis	2	6 (11)
	3	1 (2)
Incontinence	2	6 (11)
Urethral stricture	2	7 (13)

graded using the CTCAE v 4.0 scoring system [18]. The 10-year incidence of late grade 2 or 3 GU toxicity was 35%. The 10-year incidence of late grade 2 or 3 GI toxicity was 17%. Table 2 provides an overview of crude late GU and GI toxicity incidence.

Discussion

There is a number of issues related to the treatment of patients with PCa in almost all stages of disease. The specific biology of PCa is different in various patients, and depends on many prognostic factors. Strategies for optimal treatment of PCa can be controversial, and different opinions and approaches exist between physicians. Patients with RP, pathologic findings of ECE, SVI, and/or PM and negative prognostic factors such as LNI, high preoperative PSA level, and high tumor grade contribute to increased risk for both local and distant recurrence and require special attention [7-9,19]. Treatment results of such patients have not changed since the introduction of ART [7-9]. Unfortunately, since then we have not witnessed any significant improvement, neither

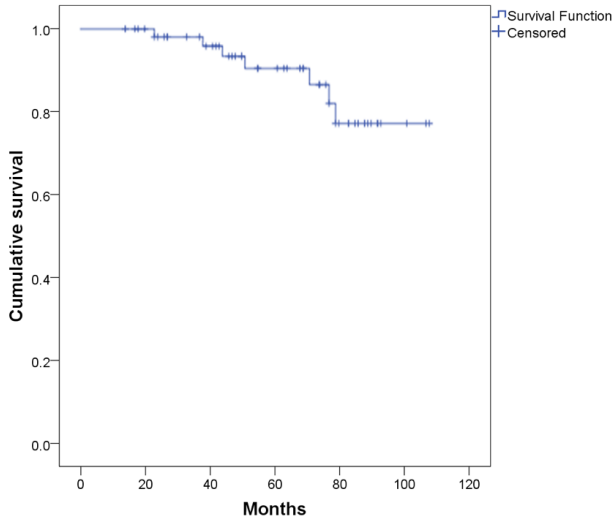

Figure 1. Biochemical relapse-free survival.

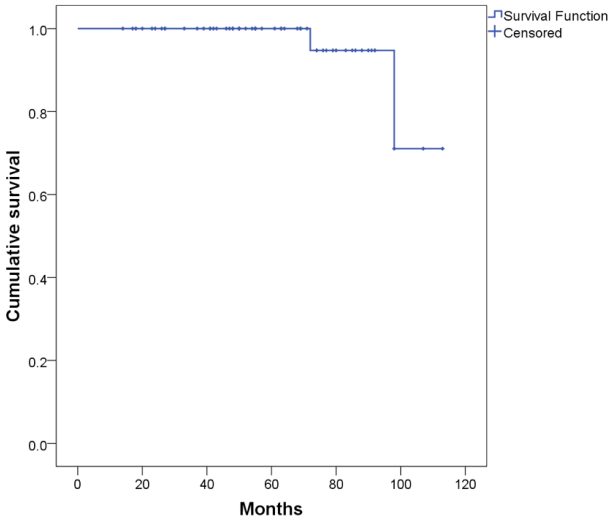

Figure 2. Metastasis-free survival..

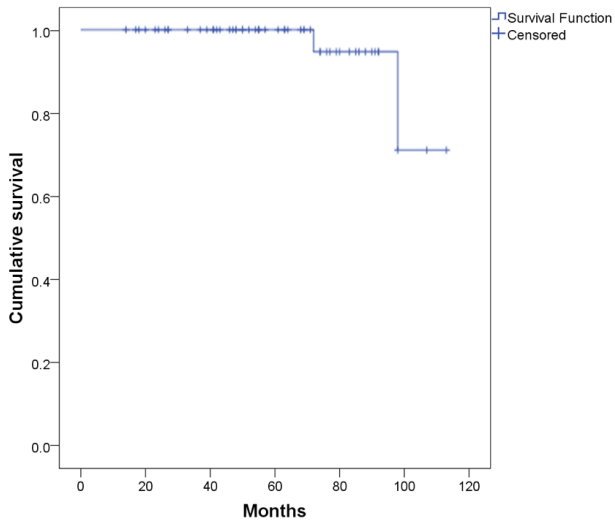

Figure 3. Disease-specific survival.

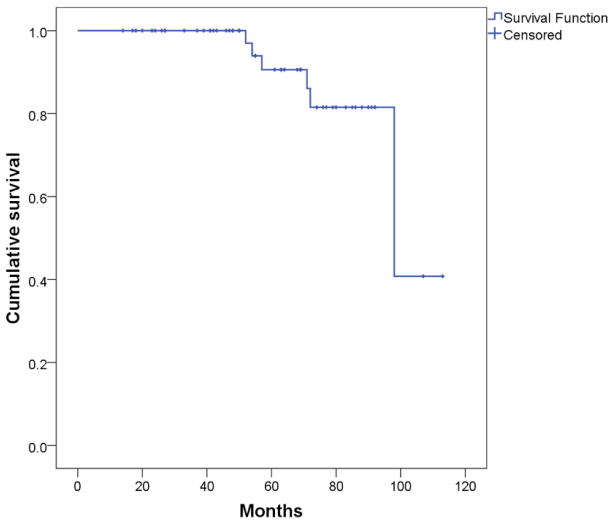

Figure 4. Overall survival.

in the treatment nor in the selection of patients for optimal therapy. Clearly, there is unmet need for better, more active therapies in the future and better selection of patients for therapy.

Namely, 3 prospective randomized trials of adjuvant treatment have shown that there is a gain in bRFS in the group of patients with ECE, SVI, and/or PM who received ART compared to control groups [7-9]. However, the results are not consistent regarding OS and mRFS. Only the SWOG 8794 trial has shown statistically significant gain in OS and mFS in the group of patients who received ART [8]. But, in the same SWOG study the bPFS rates at 5 and 10 years were 61% and 47%, respectively, for the postoperative RT arm, defining the need for better disease control [8]. Similarly, in the EORTC 22911 study with a median follow-up of 5 years, the bPFS rate was 74% in the postoperative RT arm [7]. It is obvious that tumors in a rather significant number of patients have radioresistant clones or initially disseminated tumor cells with high potential for relapse, both local and distant. Therefore, there is a significant clinical problem with such patients with the mere question of how to improve the outcome of patients after RP in the adjuvant setting. One of the potentially important questions is whether the addition of ADT to ART could further improve the therapeutic results in such patients. Further important questions include the definition of patients that should be candidates for combination of ART and ADT and also the prognostic factors that suggest the need for administration of ADT with ART. These questions are addressed by an ongoing phase III clinical trial which will recruit approximately 3000 PCa patients to help answer two important questions for men who have undergone RP: what is the best way to use RT after RP and what is the best way to use ADT with any RT given after RP [20].

In our retrospective study we have analysed the efficiency of the combination of ADT and ART in rather pathologically and clinically defined high risk PCa patients (besides ECE, SVI, PM as known factors indicating ART after RP, factors like LNI, high preoperative PSA level [>10 ng/ml], high grade tumors [Gleason score >7] and presence of LVI in pathological findings were considered as indication for ADT as well). After a median follow-up time of 61 months, the 5- and 7 -year bRFS were 90.5 and 77.2%, mFS were 95.9 and 81.7%, DSS were 100 and 94.7% and OS were 90.6 and 81.5%, respectively. Moreover, we demonstrated that the combination treatment was associated with a good safety profile, with a relatively low incidence of serious GI or GU late morbidity (the incidence of late grade 3 GI and GU toxicity was 4 and 2%, respectively) (Table 2). These results are in accordance with previously published results of bRFS, mFS, OS and safety profile in clinical trials, in which patients were treated with combination of ART and ADT [13,14]. In the study by Choo et al., with 78 patients with pT3 and/or PM after RP, relapse-free rates at 5 and 7 years were 94.4 and 86.3%, respectively. Survival rates were 96% at 5 years and 93.1% at 7 years.

The cumulative incidence of grade 3 late GI and GU toxicity at 36 months were 0 and 2.7%, respectively [13]. In another retrospective study by Ost et al., 43% of 225 patients after RP received combination of high-dose ART and ADT. After a median follow-up time of 5 years, the 7-year bRFS and mFS were 84 and 88%, respectively. The 7-year probability of late grade 3 GU and GI toxicity was 10 and <1%, respectively [14]. But, in contrast to these two trials, our study points out the group of patients with indications for ART and an increased risk of distant recurrence. Namely, well-defined prognostic factors classify PCa into 3 prognostic groups, before radical treatment. These factors are: clinical disease stage, pretherapeutic PSA level and tumor Gleason score [21-23]. Based on these factors the risk of recurrence and the treatment modality are defined. Pathological findings after RP such as ECE, SVI and PM predict risk of local recurrence and define the need for ART [24-26]. High preoperative PSA level (>10 ng/mL), preoperative PSA velocity (preoperative annual PSA velocity of more than 2.0 ng/ml and PSA doubling time ≤3 months), high grade tumors (Gleason score >7) and LNI predict risk of distant recurrence [24-26]. However, there are no clear recommendations based on these prognostic factors, even for patients with LNI, for adjuvant ADT or ADT and ART combined [27]. Currently, adjuvant ADT has only been shown to be effective in patients with significant nodal disease, giving rise to better DSS and OS, but the place of ART after RP in patients who have proven LNI remains unclear [27,28]. There are 2 small Italian retrospective studies on patients with pathologically proven LNI, which have studied the role of ART in combination with ADT in such patients. Both of them have shown that ART applied concurrently with ADT improved bRFS, DSS and OS of node-positive patients and that ART was an independent predictor of bRFS and DSS [29,30]. On the other hand, besides LNI, there are other potential prognostic factors such as high preoperative PSA

level, high tumor grade and LVI which can indicate the need for adjuvant ADT, in combination with ART. LVI is found in approximately 5-53% of specimens after RP and has been associated with aggressive clinical features [31]. The existing literature is conflicting and of insufficient homogeneity to definitively establish LVI as an important independent prognostic factor of biochemical recurrence in PCa prostatectomy specimens. After comprehensive systematic literature review of 19 studies examining the association between LVI in prostatectomy specimens and PCa recurrence, a group of authors failed to perform metaanalysis due to significant heterogeneity in the study population, disease characteristics and the quality of the studies [31]. They concluded that additional, adequately powered studies are required to determine the clinical value of reports of LVI involvement. In the meantime, the use of LVI status as an independent prognostic factor for medical decision-making is not recommended [31].

This retrospective study shows excellent bRFS, mFS, DSS and OS rates with the combination of ART and ADT in patients with proven and possible risk factors, both for local and distant recurrence of PCa after RP. We are aware of evident shortcomings of our study (retrospective nature, small sample size, different duration of ADT, different doses of ART). Nevertheless, we believe that our results will contribute to further defining the best treatment approaches in this field.

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