Oncological Outcome of Cytoreductive Radical Prostatectomy in Prostate Cancer Patients With Bone Oligometastases

Tian Lan, Ye Chen, QinJun Su, and JianJun Ye

OBJECTIVE To explore the role of cytoreductive radical prostatectomy (CRP) for locally resectable and distant oligometastatic prostate cancer (CaP).

PATIENTS AND METHODS Oligometastases were defined as the presence of 5 or fewer metastatic lesions detected on 99mTc bone scan and no suspicious visceral involvement at pretreatment imaging. Clinical data on 111 consecutive patients who were diagnosed as oligometastatic CaP in our center from 2005 to 2016 was retrospectively collected. In this retrospective cohort study, 35 patients underwent CRP and androgen deprivation therapy, and 76 patients underwent androgen deprivation therapy alone. Oncological outcomes were analyzed by employing Kaplan-Meier method.

RESULTS The median follow-up of both groups was 35 months. In whole cohort analyses, prostate-specific antigen (PSA) decrease velocity (P = .167), PSA half-time (P = .263), and PSA nadir (P = .196) were not significantly different between 2 groups. Meanwhile, the differences in oncological outcomes between 2 groups did not reach statistical significance with regard to PSA relapse-free survival (P = .184), clinical progression-free survival (P = .118), and cancer-specific survival (P = .773). In addition, similar results were also observed in prespecified subgroup analyses (lower PSA group [0-100 ng/mL, P = .543], lower Gleason score group [6-7, P = .266], lower clinical T stage group [2-3 stage, P = .962], lower radiological N stage group [0 stage, P = .364]).

CONCLUSION In our study, significant benefit from CRP has not been detected in patients with oligometastatic CaP. Facing current trend, it demands deliberate consideration to select candidates for cytoreductive surgery, and the selection criteria should be further refined by incorporating additional prognostic factors. UROLOGY 131: 166–175, 2019. © 2019 Elsevier Inc.

Androgen deprivation therapy (ADT) is the standard treatment for men with prostate cancer (CaP) and skeletal metastases,[1] and cytoreductive radical prostatectomy (CRP) is not historically advocated for metastatic CaP due to the view that biological nature of metastasis could not be reversed by local treatment. However, recent data showed local treatment for primary tumor could reduce cancer-specific mortality in several malignancies[2-4] despite established metastatic spread. Hypothetically, metastatic CaP represents a heterogeneous disease in which selected patients with a low number of nonvisceral metastases might have a favorable oncological profile and thus might benefit from removal of primary tumor. Several studies began to explore the clinical benefits of CRP for metastatic CaP with similar considerations.[5-10]

Although biological mechanism involved in cytoreductive treatment could not be elucidated, some investigations began to advise that CRP should be considered as a therapeutic option for oligometastatic CaP.[11] Meanwhile, current studies also suggested that CRP was feasible in well selected patients who responded well to neoadjuvant ADT.[5] Nevertheless, resection of primary tumor in patients with metastatic CaP is still controversially debated[8,12,13] as the absence of high quality evidence limited the generalizability of their findings. In this study, using detailed clinical data and predefined inclusion criteria we conducted a retrospective cohort study aiming to explore the role of cytoreductive surgery for oligometastatic CaP basing on the current definition of oligometastatic disease.

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PATIENTS AND METHODS

Study Design and Conduct

Oligometastatic CaP was defined as the presence of 5 or fewer metastatic lesions on Tc-99m MDP bone scan, as well as the absence of visceral metastases with or without suspicious pelvic or retroperitoneal nodal involvement at pretreatment imaging. With the approval of ethics committee we collected the clinical information on consecutive patients who had been diagnosed as oligometastatic CaP in our center from November 2005 to September 2016. Inclusion criteria included: (1) newly diagnosed oligometastatic CaP; (2) The Eastern Cooperative Oncology Group performance status score of 0-1 and without severely clinical presentation including urinary retention, hydronephrosis, and hematuria; (3) histologically confirmed adenocarcinoma; (4) not received radiotherapy, chemotherapy, abiraterone acetate, or ketoconazole in hormone-sensitive phage; (5) bone MRI/CT had been performed in case of equivocal bone metastases detected by bone scintigraphy; and (6) written informed consent. Finally, a total of 111 patients were included in this retrospective study. Seventy-six patients received ADT alone and 35 patients with locally resectable tumors underwent CRP plus ADT. As previously described, surgical procedures were performed by a single surgeon using a standard technique of retropubic radical prostatectomy with extended pelvic lymph node dissection comprising 9 selective fields, namely the external iliac, internal iliac, obturator and common iliac lymph nodes bilaterally, and the presacral lymph nodes.[14]

Clinical outcomes

The nadir of prostate-specific antigen (PSA) was defined as the lowest level that PSA drops after initial treatment. Variables associated with PSA decay kinetics included PSA declined velocity and half time. PSA relapse-free survival (PRFS) was defined as the time from treatment initiation to PSA biochemical relapse (BCR). BCR was defined as serum PSA increase to 0.2 ng/mL validated by 2 consecutive rises at 2-week intervals if PSA dropped to undetectable levels after treatment. If PSA nadir was still detectable, BCR was defined by 2 consecutive increases above PSA nadir, 1 week apart, resulting in 2 50% increases over the nadir. Clinical progression-free survival (CPFS) was defined as the time from treatment initiation to the first evidence of castration resistance prostate cancer (CRPC). CRPC was diagnosed while biochemical progression or radiologic progression was confirmed in the presence of castrate serum testosterone levels defined by <1.7 nmol/L. Biochemical progression was defined as 3 consecutive rises in PSA 1 week apart resulting in 2 50% increases over the nadir, as well as PSA level was more than 2.0 ng/mL. Radiological progression was defined as appearance of either 2 or more new bone lesions on bone scan or a soft tissue lesion using Response Evaluation Criteria in Solid Tumors (v1.1). Cancer-specific survival (CSS) was defined as the time from treatment initiation to death from CaP. CSS rate was defined as the percentage of patients who have not died from CaP.

Statistical analysis

Continuously variables were summarized with descriptive statistical measures (mean with standard deviation and median with interquartile range [IQR]), and categorical data were described using contingency tables. Fisher's exact test was used to assess the association between categorical variables, and *t* test was used to assess mean between-group differences for continuous measures. Survival curves were estimated by means of the Kaplan-Meier methods. Multivariate time-to-event analysis was performed with the use of a Cox proportional-hazards model. All *P* value determinations were 2 sided, at a significance level of .05. All analyses were performed with the SPSS software (version 22.0).

RESULTS

Characteristics of study cohorts

The median follow-up was 35 (QR, 22−51) months in combined group (CRP plus ADT) and 35 (IQR, 25−45) months in control group (ADT alone) (P = .135). The demographic and clinical characteristics of included patients were shown in Table 1. To evaluate the validity and reliability of extracted data in our study, survival analyses were performed for whole cohort using recognized risk-factors (Gleason score, PSA, clinical T stage, radiological N stage, alkaline phosphatase [ALK], and risk stratification of Japan Cancer of the Prostate Risk Assessment [J-CAPRA]). Result suggested most of risk factors had significant prognostic features for CPFS (Fig. 1). In addition, comparing to control group, patients in combined group had lower PSA level (P = .003), lower cT stage (P = .000), lower N stage (P = .015), lower Gleason score (P = .001), and fewer number of bone metastases (P = .019). Meanwhile, there was a significant difference in J-CAPRA score between 2 groups implying the lower progression-risk of combined group (P = .000).

Androgen deprivation therapy

ADT was achieved through bilateral orchiectomy (surgical castration), luteinizing hormone-releasing hormone analogues, or through complete androgen blockade (luteinizing hormone-releasing hormone analogues combined with androgen antagonists). Twenty-three (65.7%) patients in combined group and 45 (59.2%) patients in control group received combined androgen block with bicalutamide (P = .513). The mean time from diagnosis to ADT initiation was 6.8 ± 4.8 days in combined group and 6.1 ± 2.4 days in control group (P = .403). Continuous ADT was adopted in 27 patients (77.1%) of combined group and 68 patients (89.5%) of control group (P = .086). Meanwhile, the mean duration of ADT was 34.0 ± 15.6 months in combined group and 38.2 ± 20.6 months in control group (P = .285) during follow-up. These data suggested that the modality of hormone therapy was not different between 2 groups (Supplementary Table 1). In addition, in combined group, 10 patients (28.6%) received neoadjuvant ADT before CRP, 30 (85.7%) received immediate ADT after surgery, and ADT was delayed in 5 patients (14.3%) with 3-8 weeks interval after CRP.

Subsequent therapy for clinical progression

ADT were continued to maintain castration level of testosterone in all patients after clinical progression. The percentage of patients who received Zoledronic acid was 20.0% in combined group and 34.2% in control group (P = .128). In combined group, additional therapies for progression were as follows: 8 (44.4%) patients did not received subsequent treatment for CRPC, 5 (27.8%) patients received flutamide or estramustine, 2 (11.1%) received abiraterone acetate, and 3 (16.7%) received docetaxel. In control group, 36 (67.9%) patients without secondary therapy, 5 (9.4%) patients received chemotherapy with docetaxel, 4 (7.5%) received Abiraterone acetate, and 8 (15.0%) received flutamide or estramustine. These data suggested the modality of subsequent therapies for CRPC in 2 groups were well balanced (P = .500) (Supplementary Table 1).

Table 1. Descriptive characteristics of 111 consecutive patients diagnosed with oligometastatic prostate cancer between 2005 and 2016

	Combined Group N (%)	Control Group N (%)	*P* Value
Baseline Characteristics			
N	35 (100%)	76 (100%)	
Follow-up (mean, month)	36.86 ± 16.55	39.21 ± 20.62	.555
Age (mean, y)	67.83 ± 7.19	71.17 ± 7.73	.030
≤59	5 (14.3%)	6 (7.9%)	.284
60-69	14 (40.0%)	26 (34.2%)	
70-79	15 (42.9%)	34 (44.7%)	
≥80	1 (2.9%)	10 (13.2%)	
ECOG performance status score*			
0	33 (94.3%)	64 (84.2%)	.137
1	2 (5.7%)	12 (15.8%)	
Charlson comorbidity score			
<5	32 (91.4%)	60 (78.9%)	.105
6-10	3 (8.6%)	16 (21.1%)	
Serum HGB (Mean, g/L)	144.0 ± 14.5	133.9 ± 18.8	.006
≤12	2 (5.7%)	10 (13.2%)	.233
>12	33 (94.3%)	65 (85.5%)	
Missed	0	1 (1.3%)	
Serum ALB (Mean, g/L)	41.1 ± 4.6	38.4 ± 4.2	.004
≤35	2 (5.7%)	15 (19.7%)	.054
>35	33 (94.3%)	60 (78.9%)	
Missed	0	1 (1.3%)	
Serum ALK (Mean, IU/L)	90.9 ± 70.6	165.0 ± 274.6	.121
≤125	31 (88.6%)	52 (68.4%)	.029
>125	4 (11.4%)	23 (30.3%)	
Missed	0	1 (1.3%)	
Serum LDH (Mean, IU/L)	186.0 ± 39.2	184.0 ± 60.6	.878
≤250	25 (71.4%)	59 (77.6%)	.641
>250	1 (2.9%)	4 (5.3%)	
Missed	9 (25.7)	13 (17.1)	
Diagnostic characteristics			
Serum PSA value (ng/mL)	90.4 ± 152.8	502.9 ± 806.0	.003
≤20	13 (37.1%)	13 (17.1%)	.000
20-100	16 (45.7%)	15 (19.7%)	
100-500	5 (14.3%)	26 (34.2%)	
≥500	1 (2.9%)	22 (28.9%)	
Volume of Prostate (cc)	54.45 ± 27.68	50.55 ± 26.58	.480
PSA density (ng/mL/cc)	1.68 ± 2.92	11.10 ± 22.49	.015
Positive cores of biopsy			
≤50 %	5 (14.3%)	5 (6.6%)	.016
>50 %	29 (82.9%)	53 (69.7%)	
Missed	1 (2.9%)	18 (23.7%)	
Biopsy Gleason grade group†			
1	8 (22.9%)	10 (13.2%)	.001
2	14 (40.0%)	9 (11.8%)	
3	5 (14.3%)	8 (10.5%)	
4	6 (17.1%)	27 (35.5%)	
5	2 (5.7%)	21 (27.6%)	
Missed	0	1 (1.3%)	
Clinical TNM stage			
Clinical T stage			
cT1	1 (2.9%)	2 (2.6%)	.000
cT2	23 (65.7%)	12 (15.8%)	
cT3	6 (17.1%)	11 (14.5%)	
cT4	2 (5.7%)	21 (27.6%)	
Missed	3 (8.6%)	30 (39.5%)	
Radiological N stage			
cN0	25 (71.4%)	24 (31.6%)	.015
cN1	7 (20.0%)	23 (30.3%)	
Missed	3 (8.6%)	30 (39.5%)	
Number of bone metastases (mean)	2.37 ± 1.22	2.93 ± 1.12	.019
1	9 (25.7%)	6 (7.9%)	.068
2	13 (37.1%)	24 (31.6%)	

Continued

Table 1. Continued

	Combined Group N (%)	Control Group N (%)	*P* Value
3	7 (20.0%)	23 (30.3%)	
4	3 (8.6%)	15 (19.7%)	
5	3 (8.6%)	8 (10.5%)	
Clinical risk assessment			
J-CAPRA score (mean)	6.38 ± 1.76	9.00 ± 2.32	.000
Intermediate risk	20 (57.1%)	6 (7.9%)	.000
High risk	12 (34.3%)	40 (52.6%)	
Missed	3 (8.6%)	30 (39.5%)	
Postoperative pathohistology			
Gleason grade group†			
2	1 (2.9 %)	N/A	
3	16 (45.7 %)	N/A	
4	15 (42.9 %)	N/A	
5	3 (8.6 %)	N/A	
T stage			
pT2	15 (42.9%)	N/A	
pT3	16 (45.7%)	N/A	
pT4	4 (11.4%)	N/A	
N stage			
cN0	21 (60.0%)	N/A	
cN1	14 (40.0%)	N/A	
Pelvic lymph node dissection			
Number of lymph nodes (mean)	12.8 ± 8.8	N/A	
Number of positive lymph nodes (Mean)	1.22 ± 2.01	N/A	
Positive surgical margins	10 (28.6%)	N/A	

J-CAPRA, Japan Cancer of the Prostate Risk Assessment.
* Eastern Cooperative Oncology Group (ECOG) performance-status scores are on a scale from 0 to 5, with higher scores indicating greater disability and a score of 5 indicating death. Suspicious retroperitoneal lymph nodes.
† Grade Group 1 = Gleason score ≤6, Grade Group 2 = Gleason score 3 + 4 = 7, Grade Group 3 = Gleason score 4 + 3 = 7, Grade Group 4 = Gleason score 8, Grade Group 5 = Gleason scores 9 and 10.

PSA response to treatment

Unequivocal PSA nadir was recorded for 22 (62.9%) patients in combined group and 66 (86.8%) patients in control group. The mean nadir was 6.77 ± 17.90 ng/mL and median nadir was 0.883 (IQR 0.308, 3.978) ng/mL in control group. In combined group, the mean nadir was 1.67 ± 6.10 ng/mL and median nadir was 0.011 (IQR 0.000, 0.198) ng/mL. There was no significant difference in PSA nadir between 2 groups (P = .196). Meanwhile, the means of variables which were associated with PSA decay kinetics were not significantly different between 2 groups (decline velocity: 30.2 ± 92.9 vs 78.6 ± 134.5 ng/mL/mo, P = .167; half time: 0.99 ± 1.80 vs 1.38 ± 1.06 month, P = .263). Our results did not imply that CRP plus ADT could lead to a faster decrease of PSA level than did ADT alone.

PSA relapse-free survival

There were 20 (57.1%) events of PSA relapse in combination group and 53 (69.7%) in control group (P = .184). The mean time from treatment initiation to PSA relapse was 22.05 ± 17.27 months in combined group and 16.66 ± 12.48 months in control group (P = .145). Median PRFS was 32.0 months (IQR, 16–57) in combined group vs 17.0 months (IQR, 9–46) in control group (P = .184). Three-year and 5-year PSA relapse-free rate were 38.2% and 15.3% in combined group and 26.0% and 13.7% in control group (P = .184), respectively (Fig. 2A). Unfortunately, statistical difference was not observed between 2 groups concerning PRFS which suggested CRP with ADT did not result in a significant lower risk of PSA relapse than did ADT alone.

Clinical progression-free survival

Finally, 18 patients (51.4%) in surgery group and 53 (69.7%) in control group progressed to CRPC. The mean time from treatment initiation to CRPC was 22.50 ± 15.60 months in combined group and 16.91 ± 11.20 months in control group (P = 0.103). Median CPFS was 35months (IQR, 18–59) in combined group vs 21 months (IQR, 10–49) in control group (P = .118). Three-year and 5-year clinical progression-free rate were 42.7% and 19.0% in combined group and 27.0% and 21.0% in control group, respectively (Fig. 2B). Although absolute difference in the median of CPFS (14 months) appeared obvious between 2 groups, statistical significance was not detected (P = .118) for CPFS in our study. This result suggested CRP combined with ADT still did not result in a lower clinical progression risk than did ADT alone.

Cancer-specific survival

The median CSS was not reached in either group. Finally, 4 patients (11.4%) in combination group and 11 patients (14.5%) in control group died due to prostate cancer (P = .663). Three-year and 5-year CSS rate were 90.8% and 63.6% in combined group and 87.9% and 74.9% in control group (P = .773), respectively (Fig. 2C). Combined therapy in our study did not confer a survival advantage over ADT alone.

Subgroup analysis

We further sought to evaluate the oncological benefit of CRP in prespecified subgroups. As this study was limited by the small sample size, subgroup analyses of CPFS were only performed for men with Gleason score 6-7, PSA 0-100 ng/mL, clinical stage of primary tumor T2-3, or radiological stage of regional lymph node N0. For

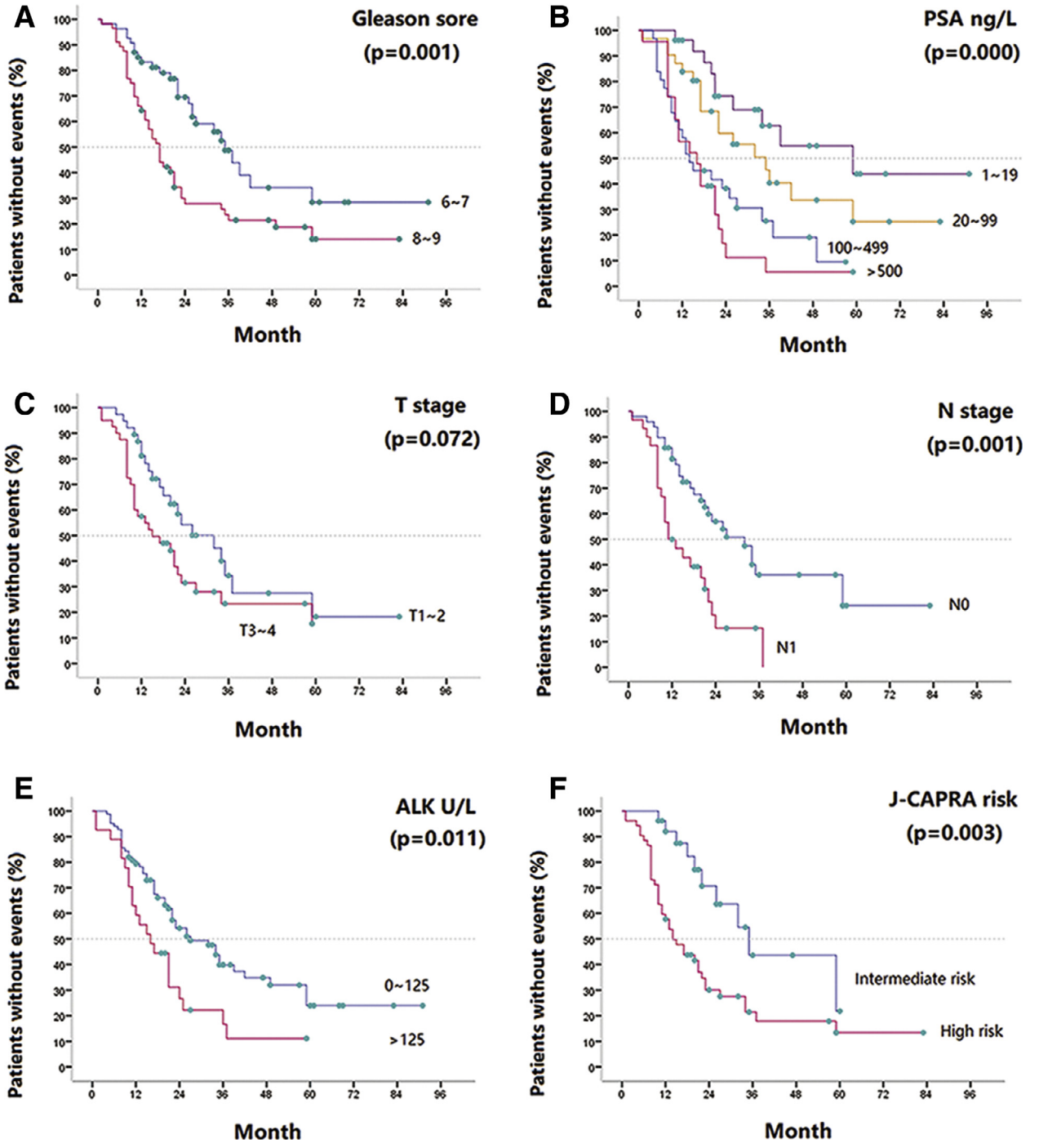

Figure 1. Kaplan-Meier estimates of CPFS in whole cohort according to the stratification with independent risk factors. A. Gleason score: 6-7 vs 8-10. B. PSA level at diagnosis: 0-19 ng/mL vs 20-99 ng/mL vs 100-499 ng/mL vs >500 ng/mL. C. Clinical T stage: cT1-2 vs cT3-4. D. Clinical N stage: N0 stage vs N1 stage. E. ALK level at diagnosis: 0-125 ng/mL vs >125 ng/mL. F. J-CAPRA risk-stratification: intermediate vs high. ALK, alkaline phosphatase; CPFS, clinical progression-free survival; J-CAPRA,Japan Cancer of the Prostate Risk Assessment. (Color version available online.)

patients with Gleason score 6-7, the median CPFS was 39 months (27 patients, IQR 26, not reached) in combined group and 26 months (27 patients, IQR 15, not reached) in control group (P = .266, Fig. 3A). For patients with PSA ranged from 0 to 100 ng/mL (29 in combined group and 28 in control group), median CPFS was 35 months (IQR 20-59) in combined group vs 59 months (IQR 21, not reached) in control group (P = .484, Fig. 3B). For patients with clinical T2-3 stage (29 of combined group and 23 of ADT alone group), the median CPFS was 32 months (IQR, 15-59) in combined group and 21 months (IQR, 8-34) in control group (P = .364, Fig. 3C). Meanwhile, for men with N0 stage (25 in combined group and 24 in control group), median PFS was 32 months (IQR, 15-59) in combined group and 27 months (IQR 13, not reached) in control group (P = .962, Fig. 3D), respectively. These results still suggested CRP plus ADT was not associated with a longer CPFS for the patients in prespecified subgroups.

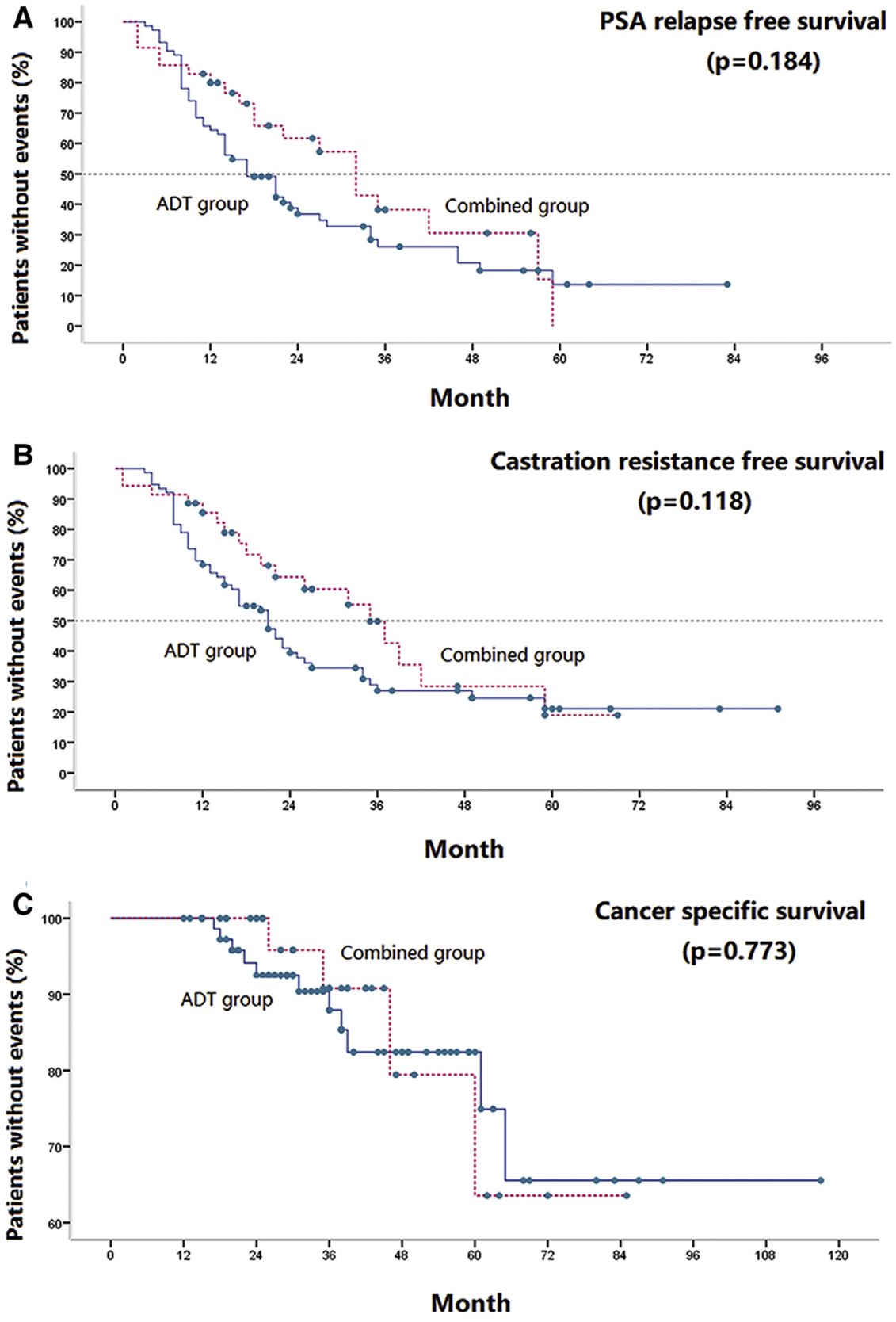

Figure 2. Kaplan-Meier estimates of time to (A) PSA biochemical relapse, (B) castration resistance prostate cancer, (C) prostate cancer-specific mortality between combined group and control group. (Color version available online.)

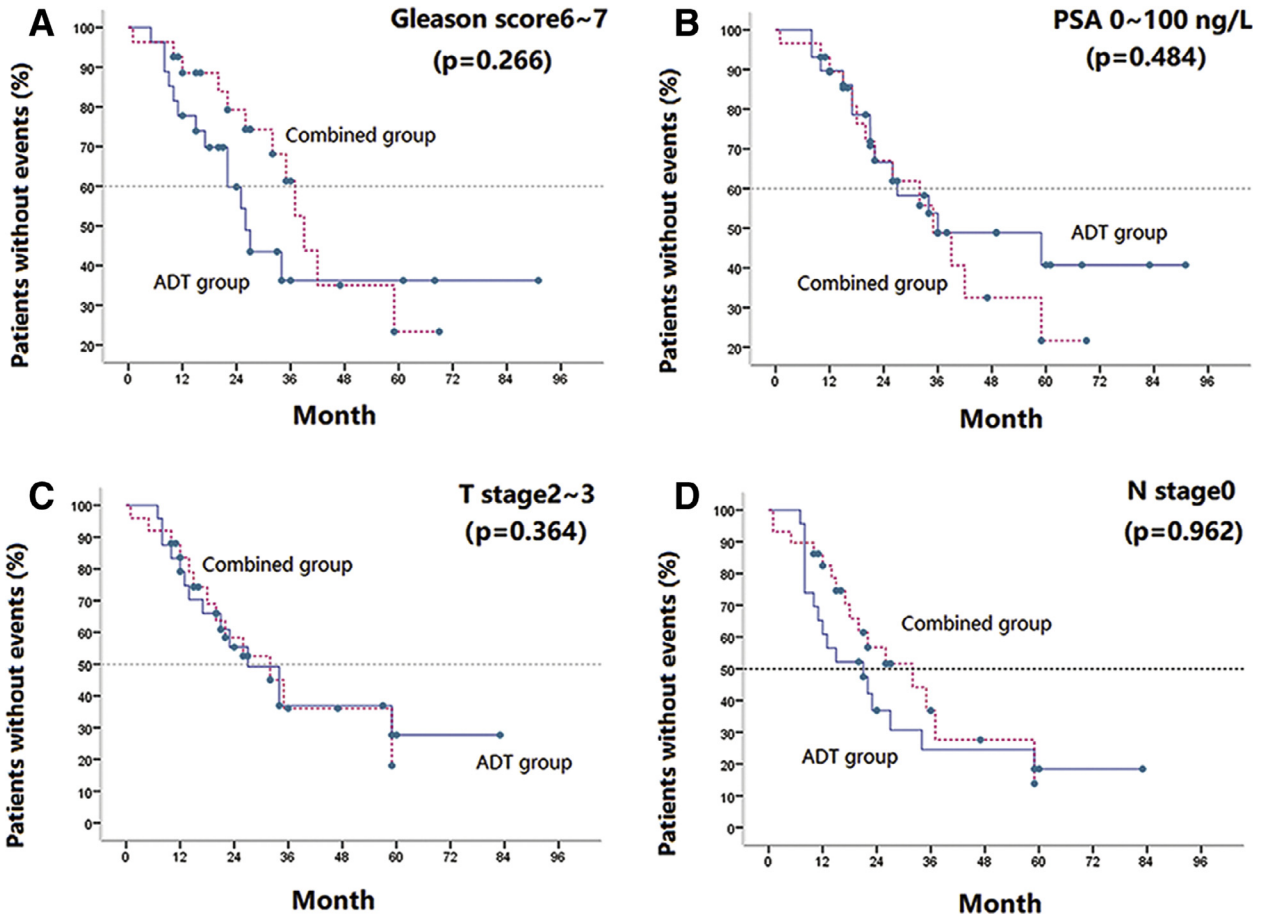

Figure 3. Kaplan-Meier estimates of CPFS between 2 groups by employing subgroup analyses. A Gleason score (6-7). B PSA level (0-100 ng/mL). C Clinical T stage (2-3) D Radiological N stage (N0 stage). CPFS, clinical progression-free survival. (Color version available online.)

DISCUSSION

By employing a comparison cohort consisted of consecutive patients in the same period, we reported the oncological outcomes for a series of well-selected men with oligometastatic CaP who were treated with systemic therapy and CRP. Significant benefit from cytoreductive surgery was still not observed in this retrospective study although patients in comparison cohort had more aggressive disease. Our result inferred that the refinement of inclusion criteria for cytoreductive surgery should depend on not only the definition of oligometastatic disease but also the other prognostic factors and risk-stratification models. Histopathologic classification,[15] serological biomarker,[16,17] TNM stage,[18,19] and metastasis status[20-22] are the strongest prognostic indicators for oncological progression. Meanwhile, J-CAPRA model offers a risk estimation on the progression-free survival for patients who were receiving primary ADT for metastatic CaP.[23,24] In addition, we also found the PSA nadir was also an independent prognostic factor for our patients regarding PRFS and CPFS (not shown in this article), which was consistent to the finding of SWOG trials.[25] These prognostic factors should be set in clinical trial for selecting the patients who would benefit from cytoreductive surgery.

It is worth mentioning that 16 (45.8%) patients aged from 70 to 80 years underwent cytoreductive surgery. The median age was 73.5 years old and median follow-up was 35 months (ranged from 16 to 82 months). Of them, 11 (68.8%) patients were under 75 years old. Nine (56.3%) cases finally progressed to castration resistance condition, and 1 died due to prostate cancer (35 months latter). As our sample size was relatively small we had not enough data to estimate the significance of CRP for elder patients regarding surgical complications, oncological outcomes, and life expectancy.

Major limitations of our study which impacted on statistical power were retrospective nature and small sample size. According to our design, we estimated the median PRFS or CPFS of our patients ranged from 24 to 36 months.[26-28] The median follow-up was 35 months in both groups, and there were 20 (57.1%) events of PSA relapse and 18 (51.4%) of clinical progression in combination group and 53 (69.7%) and 53 (69.7%) in control group, respectively. Since hazard ratio more depends on the time of follow-up and events rate, we encourage readers to focus on relative differences in risk (hazard ratio). Although absolute differences in medians between 2 groups appeared obvious, relative differences were statistically nonsignificant. Meanwhile, in subgroup analyses

relative differences in CPFS still had not statistical significance, which were consistent to the results derived from whole-cohort analysis. Therefore, systematic analysis was not further performed in multivariate model by employing more variables including Gleason grade group, T stage, N stage, serological biomarker, and et al. We assumed that such an adjustment would further reduce the levels of statistical significance of differences and verify that combined treatment was not an effective intervention for the oncological outcomes in our cohorts. Another limitation was the shorter follow-up which especially influenced CSS considerations. However, we emphasized our findings on time to CRPC since CPFS was an independent predictor of CSS in men with CRPC.[29] In addition, as neoadjuvant ADT might be an important consideration for suppressing early progression in some cases, the third limitation was that few patients (28.6%) in surgery group received a standard neoadjuvant treatment.[30]

CONCLUSION

In our study, significant benefit from CRP has not been detected in patients with oligometastatic CaP. At present, available information on preoperative assessment is lacking regarding patient selection. Data on examining tumor debulking in oligometastatic CaP are still hypothesis-generating, but should not direct current management.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.urology.2019.03.040.

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EDITORIAL COMMENT

Retrospective evaluations of the treatment of the primary tumor in the setting of metastatic hormone sensitive prostate cancer (mHSPC) are prevalent in the recent literature. The majority of these reports have favored the addition of local therapy[1] and form the hypothesis generating support for recently completed and ongoing prospective randomized studies.[2,3] Interestingly, in the present retrospective study, cancer-specific survival was not improved with local therapy. This is intriguing since the patients were subject to similar selection biases present in other retrospective reviews favoring local therapy. Information why the 35 patients who had surgery were selected for such is lacking, but a strong bias towards more favorable disease characteristics was evident. They had lower presenting PSA level, clinical T stage, radiographic N stage, lower Gleason score, and fewer number of bone metastases. Additionally, the median PSA nadir in the group that underwent surgery was 1.7 ± 6.1 ng/mL compared to 6.8 ± 17.9 ng/mL in the ADT alone group. Thus it is possible that some of these patients were selected based on their favorable response to ADT (30% received ADT prior to surgery). Since initial treatment response has been previously demonstrated as a predictor of survival,[4] it is somewhat surprising that in spite of the favorable profile of the patients that underwent surgery there was no statistically significant difference in cancer-specific survival between groups. However, given the small numbers it is likely underpowered and prone to type II error. Nevertheless, it provides opportunity to examine the nuances of the literature evaluating local treatment in mHSPC.

Similar to this study, 2 recently reported randomized trials evaluating radiotherapy to the primary tumor in mHSPC were also negative for survival benefit in unselected patients.[2,3] While the subgroup analysis of STAMPEDE Arm-H provides an encouraging signal of benefit from definitive treatment of the primary tumor with radiation in low-volume mHSPC, the generalizability of these results to contemporary practice is unclear. No patient received abiraterone in addition to ADT, and a minority (16%) received docetaxel. Quantification of early systemic treatment resistance was notably absent. Additionally, the radiation dose used was less than present standards and symptomatic local progression was substantial and no different between groups (42% control vs 44% radiotherapy).

Choice of initial systemic therapy and the patients' response, duration of response, initial and subsequent tumor profile will all be important to properly select patients' optimal treatment course, including the potential application of local therapy.[5] We await the results of the PEACE1 study (NCT01957436) which will provide data regarding radiation to the primary with contemporary systemic therapy (abiraterone and docetaxel). Analysis of the Phase II study of best systemic therapy or best systemic therapy plus definitive treatment (NCT01751438) which has fully accrued, as well the similar Phase III study (NCT03678025) which is actively enrolling will also be forthcoming. In addition to providing the first prospective data regarding prostatectomy in the mHSPC setting, these data will also provide insight to guide future trial design to evaluate for maximal local therapy benefit. There are still many unknowns regarding treatment of the primary tumor in mHSPC and support of ongoing clinical trials is critical to provide answers.

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AUTHOR REPLY

For men with localized prostate cancer (CaP), radical prostatectomy (RP) as well as radiotherapy (RT) was associated with lower incidences of progression and metastases than was active monitoring.[1] Meanwhile, prospective trial showed these patients with a long life expectancy would benefit from surgical intervention with a mean gain of almost 3-year of life.[2] Unfortunately, when localized CaP progressed to incurable metastatic disease ancestral subclones and stromal micro-environment evolved dynamically in space and time following principles of selective evolution, underpinning important emergent features such as therapeutic resistance and clinical aggressivity. Recently, emerging evidence from retrospective series suggests that cytoreductive prostatectomy might be a potential therapy to provide a survival benefit in selected patients with metastatic CaP. More

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importantly, using CHAARTED definition for low or high metastatic burden, STAMPEDE randomized controlled trial showed additional RT for primary tumor had improved 3-year overall survival compared with standard of care in a subgroup of patients with low metastatic burden.[3] Consequently, we spontaneously hypothesized that men with oligometastatic prostate cancer should benefit from RP although potential therapeutic mechanism was different between RP and RT.

"In the world of surgical oncology; biology is King; selection of cases is Queen; the technical details of surgical procedures are princes. And the princesses frequently try to overthrow the powerful forces of the King and Queen." It seems plausible given this hypothesis that an intact primary tumor may continue to shed metastases. However, there may be other radiation-specific mechanisms such as immunomodulation or an interplay between radiation and androgen deprivation, which contribute to the observed survival benefit by RT. Meanwhile, definitions of oligometastatic disease vary by number and location of lesions, with no consistency in current literature or ongoing clinical trials. Despite the clues to risk provided in patients population with the metastatic hormone sensitive CaP, ambiguity remains in defining the extent of metastatic burden that constitutes "oligometastatic disease."

Before cytoreductive RP was recommended for the patients with newly diagnosed oligometastatic CaP some stumbling blocks should be moved away firstly. First, defining a metastatic volume threshold above which patients are unlikely to benefit from RP is still an important area of further study. Admittedly, in current risk-stratification models including J-CAPRA[4] and Glass model,[5] the number of skeletal metastases was not the overarching factor for prognosing progression and mortality. Second, the standard definitions of resectable localized tumor and regional metastatic lymph-nodes should be further refined, which should be employed as a guide for surgical procedure. As each of pelvic regions has its own associated challenges to evaluation and resection the volume and distribution of disease within the pelvic cavity are consistently identified as an important prognostic factor for recurrence and survival. Third, PSA kinetics itself is an independent prognostic factor for metastatic CaP, and current data from published repositories have not yet elucidated the association between the responsibility to neoadjuvant androgen deprivation therapy and survival benefit of cytoreductive RP. The use of neoadjuvant treatment including hormonotherapy and chemotherapy in patients undergoing cytoreductive surgery has not been extensively studied.

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