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Neoadjuvant chemohormonal therapy combined with radical prostatectomy and extended PLND for very high risk locally advanced prostate cancer: A retrospective comparative study

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Abstract

Objective: Docetaxel has been shown to be an effective chemotherapy agent when combined with androgen deprivation therapy for hormone sensitive metastatic prostate cancer (CaP). Since very high risk CaP has a high rate of occult metastatic disease and early recurrence, we hypothesize that patients with very high risk locally advanced CaP may benefit from docetaxel-based neoadjuvant chemohormonal therapy (NCHT). Thus, we conducted a retrospective study to identify the outcome of these patients treated with NCHT followed by radical prostatectomy (RP).

Patients and Methods: We retrospectively analyzed data from 177 consecutive patients who had very high risk locally advanced CaP between March 2014 and July 2017. Patients received 3 different therapies: (i) 60 men in NCHT group, (ii) 73 men in neoadjuvant hormonal therapy (NHT) group, and (iii) 44 men received immediate RP without neoadjuvant therapy (No-NT group). Surgical outcomes were analyzed and survival differences were compared by the Kaplan-Meier method.

Results: The NCHT group had statistically significant higher preoperative Prostate-Specific Antigen (PSA) ($P < 0.002$), higher Gleason score ($P < 0.002$), and more advanced clinical stage ($P < 0.001$) than other groups. After RP, 81% (42/52) of patients in NCHT group, 73% (51/70) of patients in NHT group, and 48% (21/44) of patients in No-NT group achieved an undetectable PSA ($P < 0.001$). A total of 14% (6/42) patients achieving a postoperative undetectable PSA experienced biochemical recurrence in the NCHT group, with median biochemical progression-free survival (bPFS) time of 19 months; 47% (24/51) experienced biochemical recurrence in the NHT group, with median bPFS time of 13 months; 81% (17/21) experienced biochemical recurrence in the No-NT group, with median bPFS time of 9 months ($P < 0.001$). The median follow-up time of 3 groups was 12.5 months in the NCHT group, 18.3 months in the NHT group, and 22.8 months in the No-NT group ($P = 0.01$).

Conclusion: Despite having poorer prognostic factors, the NCHT group had better bPFS time after surgery compared to NHT and No-NT groups. Randomized controlled investigations are needed to validate these results and further follow-up is required for survival endpoints.

Keywords: Neoadjuvant chemohormonal therapy; Radical prostatectomy; Extended pelvic lymph node dissection; Biochemical recurrence

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1. Introduction

Prostate cancer (CaP) remains the most common malignancy diagnosed in men in the United States [1]. According to the latest Chinese cancer registry data, the age-standardized incidence rates showed an increasing trend for CaP, especially in urban areas [2], which might relate to more active Prostate-Specific Antigen (PSA) screening, popular western dietary habits as well as aging of population. Up till now, the majority of CaP cases in China were still diagnosed at an advanced stage [3]. Biochemical relapse and disease progression are more likely to occur in high risk or locally advanced disease after radical prostatectomy (RP). Neoadjuvant hormonal therapy before RP for locally advanced CaP has shown positive results for local disease control but not for survival outcomes in randomized clinical trials [4].

Docetaxel has been shown to be an effective chemotherapy agent when combined with androgen deprivation therapy (ADT) for hormone sensitive metastatic CaP in large randomized clinical trials with significant benefits in overall survival (OS) [5]. Moreover, in STAMPEDE study with high risk locally advanced prostate cancer patients included, additional docetaxel-based chemotherapy to standard hormone therapy also showed improved survival benefit [6]. Since very high risk locally advanced CaP has a high rate of occult metastatic disease and early recurrence, we hypothesize that patients with very high risk locally advanced CaP might also benefit from docetaxel-based treatment in a neoadjuvant setting.

To date, neoadjuvant systemic therapy followed by RP in high risk and very high risk prostate cancer has been proven to be safe without increased perioperative complications [7]. Also, several studies have investigated the role of neoadjuvant chemohormonal therapy (NCHT) in locally advanced high risk prostate cancer and reported high feasibility and positive effects [8–10]. Based on this data, we have been individually selecting cases at our center for RP after NCHT following multidisciplinary assessment. Considering that current studies were hindered by major limitations such as very small sample size, lack of control group or failure to identifying very high risk locally advanced CaP, we were prompt to explore the viability and efficacy of NCHT in our cohort.

In this study, we conducted a retrospective study to identify the outcome of patients with very high risk locally advanced disease who were treated with NCHT followed by RP. We compared their outcomes with men treated with neoadjuvant hormonal therapy followed by RP and with those undergoing immediate RP as monotherapy.

2. Materials and methods

2.1. Patient selection and grouping

We consecutively included 177 patients with locally advanced very high risk CaP newly diagnosed in department of urology, Renji Hospital affiliated to Shanghai Jiao Tong University, School of Medicine from March 2014 to July 2017. Patients were enrolled according to the following criteria: (i) patients had clinical stage more than cT3a, or primary Gleason pattern 5, or ≥5 cores with Gleason sum 8 to 10, or serum PSA ≥ 50 ng/ml, or with pelvic metastatic lymph node involvement, (ii) patient was initially diagnosed as locally advanced CaP with resectable tumor and could be treated with RP and ePLND, (iii) patients had a good general performance status with ECOG score 0 to 1.

According to the physical state of patients and decision based on surgeon's suggestion and patients' choices, patients received 1 of the 3 preoperative managements, NCHT (docetaxel-based neoadjuvant chemotherapy combined with maximal androgen blockage, NCHT group), NHT (neoadjuvant hormonal therapy, NHT group), and No-NT (immediate RP, No-NT group). Patients having other malignancies or with serious comorbidities were excluded from the study. The clinical data and pathological results were retrospectively reviewed. An informed consent was provided by all the patients and the study was approved by institutional Ethical Committee.

2.2. Neoadjuvant treatment and radical prostatectomy

For patients in NCHT group, 4 to 6 cycles of total androgen blockade and docetaxel-based systemic chemotherapy were administrated. Total androgen blockade consisted of subcutaneous administration of 3.6 mg goserelin acetate every 28 days and oral administration of bicalutamide 50 mg per day. Docetaxel was administrated intravenously at a dose of 75 mg/m^2 every 3 weeks along with oral administration of prednisone 5 mg twice a day. In the NHT group, only 4 to 6 cycles of total androgen blockade by goserelin acetate and bicalutamide were administrated. When all the cycles of the neoadjuvant therapy finished, a pelvic MRI along with a bone scan or a positron emission tomography-computed tomography were carried out to evaluate the tumor response to the treatment. Patient presented with severe Grade 3 to Grade 4 toxicities were initially managed medically while trying to continue therapy when safer. However, if toxicity could not be managed medically, treatment was withdrawn. The RP and extended pelvic lymph node dissection (ePLND) was performed in open retropubic approach, in laparoscopic transabdominal approach, or in robot-assisted laparoscopic transabdominal approach 3-4 weeks after the neoadjuvant therapy by 2 experienced surgeons. However, for No-NT group, the RP was performed 4 to 6 weeks after the prostate biopsy without neoadjuvant therapy.

2.3. Follow-up

The first postoperative serum PSA follow-up was scheduled at 6 weeks after RP and then tested every 3 months thereafter. The PSA recurrence was defined as 2 consecutive

rising PSA values of >0.2 ng/ml confirmed 2 weeks apart. The adjuvant therapy was not applied until the serum PSA went higher than 0.2 ng/ml even though in certain cases the positive surgical margin or lymph node involvement was presented. A whole pelvis external beam radiation combined with ADT was given to patient with a serum PSA higher than 0.2ng/ml during the follow-up.

2.4. Study endpoints and statistical analysis

The primary endpoint was the pathological down-staging in surgical specimens. The second endpoint was pathological complete remission rate, the proportion of undetectable PSA after RP and biochemical progression-free survival (bPFS) time. An undetectable PSA level after surgery was defined as PSA less than 0.2ng/ml at 6 weeks. bPFS was defined as the time of surgery to the date of first PSA recurrence in patients achieved an undetectable PSA after RP. The Kaplan-Meier method was applied to describe the bPFS, while survival differences were compared by the Log-rank test. Proportions of the variables were analyzed using chi-square test or Fisher's exact test while mean values were compared with 1-way ANOVA test and median values were analyzed with Kruskal-Wallis test. Statistical significance was set at $P < 0.05$ and all the P values were 2-sided. The SPSS 18.0 was applied to perform the data analysis.

3. Results

3.1. Patient demographic data

From March 2014 to July 2017, a total of 177 patients who had very high risk locally advanced CaP were consecutively included in this study. There were 60 men in NCHT group, 73 men in NHT group, and 44 men in No-NT group. In NCHT group, a total of 8 (8/60, 13.3%) patients failed to have surgery after neoadjuvant therapy due to disease progression or adverse effects. Among these patients, 4 (4/60, 6.7%) patients progressed on NCHT with 2 harboring de novo metastatic lesions in lumbar vertebrae and liver, 1 having progressive bladder invasion and 1 having enlarging lesion involving rectum. Of 4 (4/60, 6.7%) patients with severe adverse effects, 3 presented Grade 3 liver function impairment and 1 developed Grade 4 febrile neutropenia in whom the NCHT and surgery was abandoned. In NHT group, a total of 3 (3/73, 4.1%) patients with unresectable tumors in final assessment after neoadjuvant hormonal therapy dropped out of subsequent radical surgery. Thus, the RP and ePLND was carried out in 52 men in NCHT group, 70 men in NHT group and 44 men in No-NT group. As shown in Table 1, the average age was higher in No-NT group compared to NHT group and NCHT group ($P < 0.001$). The NCHT group had significantly higher initial PSA level ($P = 0.004$), higher Gleason score ($P = 0.042$), and more advanced clinical stage than the NHT and No-NT groups ($P < 0.001$). The median initial PSA level was 60.3 ng/ml, 71.2 ng/ml, and 93.2 ng/ml and the proportion of patients with clinical stage ≥T3 was 86%, 90%, and 98% in No-NT group, NHT group, and NCHT group, respectively. Moreover, the rate of clinical node positive disease was also higher in the NCHT group compared to the NHT group and the No-NT group($P < 0.001$). After 4 to 6 cycles of neoadjuvant therapy, the median serum PSA level in NHT group and NCHT group was 0.63 ng/ml and 0.41 ng/ml, respectively. The median follow-up time of the No-NT group, NHT group, and NCHT group was 22.8 months, 18.3 months, and 12.5 months, respectively. ($P = 0.01$)

Table 1
Demographic data of the patients in No-NT, NHT, and NCHT group.

	No-NT ($N = 44$)	NHT ($N = 73$)	NCHT ($N = 60$)	P
Age (median, range)	69 (57–78)	68 (56–78)	65 (46–78)	0.004
PSA_0 (median, range)	60.3 (13.7–150)	71.2 (9.7–289.0)	93.2 (6.1–722.9)	0.002
Gleason (N, %)				
6	5 (11.36%)	5 (6.8%)	1 (1.7%)	0.042
7	20 (45.45%)	29 (39.7%)	31 (51.7%)	
8	13 (29.55%)	23 (31.5%)	9 (15.0%)	
9	6 (13.63%)	16 (21.9%)	19 (31.7%)	
cT Stage (N, %)				
cT2	6 (13.64%)	7 (9.6%)	1 (1.7%)	0.000
cT3	37 (84.09%)	52 (71.2%)	39 (65.0%)	
cT4	1 (2.27%)	14 (19.2%)	20 (33.3%)	
cN Stage (N, %)				
cN0	38 (86.36%)	55 (75.3%)	27 (45.0%)	0.000
cN1	6 (13.63%)	18 (24.7%)	33 (55.0%)	
Neoadjuvant cycles prior to RP	/	5	5	0.142
PSA after NHT/NCHT (median, range)	/	0.63 (0.01–40.5)	0.41 (0.01–8.23)	0.314
Surgical approaches				
Open RP	24 (54.5%)	35 (50.0%)	18 (34.6%)	0.108
Laparoscopic and robot-assisted RP	20 (45.5%)	35 (50.0%)	34 (65.4%)	

3.2. Adverse events in NCHT group and NHT group

The adverse events in NCHT group and NHT group are shown in Table 2. All adverse events were graded according to National Cancer Institute's Common Terminology Criteria for Adverse Events Version 4.0 [11].

In NCHT group, the hematological toxicities were very common. About 53.33% (32/60) of the cases had Grade 1 to 2 leukopenia while 20.0% (12/60) of the cases had Grade 3 to 4 leukopenia treated by granulocyte colony-stimulating factor. One case presented Grade 4 febrile neutropenia and the NCHT was then abandoned. Mild transaminase increase was found in 9 cases (9/60, 15.0%) resolved by regular hepatoprotective therapy. However, the NCHT was stopped in 3 cases (3/60, 5%) who had presented Grade 3 liver function impairment. No severe allergic reaction occurred. Peripheral neuropathy and fluids retention were relatively rare. Nevertheless, hot flashes (36/60, 60.0%) and impotence (37/37, 100%) related to the administration of luteinizing hormone-releasing hormone (LHRH) analogue were quite common.

In NHT group, hot flushes (52/73, 71.23%), impotence (44/46, 95.65%), fatigue (33/46, 45.21%), and gynecomastia (10/73, 13.69%) were among most frequent complaints. Other adverse events were relatively rare in this group. The incidence of leukopenia and gastroenterological toxicities were significantly lower in NHT group than in NCHT group ($P = 0.000$).

3.3. Surgical outcomes

As shown in Table 3, there was no statistical difference in mean surgery time, mean blood loss ($P = 0.344$), hospital stay ($P = 0.286$), and surgical complications ($P = 0.581$) among the 3 groups. In both No-NT group and NHT group, rectal injury occurred in 1 case and treated by intraoperative rectum repair without colostomy. During the ePLND, iliac vessel injury occurred in 2 cases in No-NT group, 3 cases in NHT group, and 2 cases in NCHT group. However, the iliac vessel repair was all successful in these 7 cases.

After RP, 42 (42/52, 81%) of patients in NCHT group, 51 (51/70, 73%) of patients in NHT group and 21 (21/44, 48%) of patients in No-NT group achieved an undetectable PSA level, respectively ($P < 0.001$). In NCHT group, no residual cancer was found in surgical specimen in 9 (9/52, 17.31%) of the cases while it was only 6 (6/70, 8.57%) in NHT group, although there was no statistical difference between the groups. Positive surgical margin rates among 3 groups had no statistical difference with 31.82% (14/44), 22.86% (16/70), 17.31% (9/52) in the No-NT group, the NHT group, and NCHT group ($P = 0.244$). Among these groups, a significant pathological down-staging was found in surgical specimens with the highest rate of 61.5% (32/52) in the NCHT group ($P < 0.001$). There were more organ-confined diseases and significantly less pT3 and pT4 disease compared to preoperative evaluation, especially in NCHT group. By contrast, an obvious pathological up-staging was observed in No-NT group. There were only 2.27% of the cases in this group considered as cT4 disease in preoperative evaluation while 29.4% of the group was finally confirmed as pT4 disease in pathological diagnosis, as shown in Fig. 1. A total of 6 (6/42, 14%) patients achieving undetectable PSA after surgery experienced PSA-recurrence in the NCHT group, with median time of 19 months (19.26 ± 0.93) to develop biochemical recurrence; 24 (24/51, 47%) patients with undetectable PSA experienced PSA-recurrence in NHT group, with median time of 13 months (13.24 ± 0.98); 17 (17/21, 81%) patients with undetectable PSA experienced PSA-recurrence in No-NT group, with median time of 9 months (8.95 ± 1.06), respectively ($P < 0.001$). The bPFS survival profiles of patients in those 3 groups are shown in Fig. 2.

Table 2
Adverse events in the NCHT group and the NHT group.

	Adverse events	NCHT	NHT	*P*
Hematological toxicity	Leukopenia (Grade 1–2)	32 (53.33%)	1 (1.37%)	0.000
	Leukopenia (Grade 3–4)	12 (20.0%)	0 (0%)	0.000
	Anemia	7 (11.67%)	7 (9.60%)	0.698
	Thrombopenia	2 (3.33%)	0 (0%)	0.202
Gastroenterological toxicity	Transaminase increased	12 (20.0%)	1 (1.37%)	0.000
	Nausea/vomiting	16 (26.67%)	3 (4.11%)	0.000
	Diarrhea and constipation	11 (18.33%)	0 (0%)	0.000
Allergic reaction	Anaphylactic shock	0 (0%)	0 (0%)	/
	Rash	3 (5.0%)	1 (1.37%)	0.478
Neurological system toxicity	Peripheral neuropathy	3 (5.0%)	0 (0%)	0.178
Fluid retention	Edema of lower extremity	2 (3.33%)	1 (1.37%)	0.863
Musculoskeletal side effects	Fatigue	34 (56.7%)	33 (45.21%)	0.188
	Hormone-related fracture	0 (0%)	0 (0%)	/
Endocrine and reproductive system toxicity	Hot flashes	36 (60.0%)	52 (71.23%)	0.173
	Gynecomastia	9 (15.0%)	10 (13.69%)	0.831
	Impotence	37/37 (100.0%)	44/46 (95.65%)	0.5

Table 3
Surgical outcomes in No-NT, NHT, and NCHT group.

	No-NT ($N = 44$)	NHT ($N = 70$)	NCHT ($N = 52$)	P
Mean surgery time (min)	158	170	183	0.131
Mean blood loss (ml)	355	347	335	0.344
Hospital stay (d)	6.5	6.1	6.2	0.286
Surgical complications				
Rectal injury	1 (2.27%)	1 (1.43%)	0 (0.00%)	0.581
Iliac vessel injury	2 (5.54%)	3 (4.29%)	2 (3.85%)	0.985
Undetectable PSA after RP				
Yes	21 (47.73%)	51 (72.86%)	42 (80.77%)	<0.001
No	23 (52.27%)	19 (27.14%)	10 (19.23%)	
Pathological *T*stage				
pT2	2 (4.55%)	31 (44.29%)	24 (46.15%)	
pT3	29 (65.91%)	29 (41.43%)	18 (34.62%)	
pT4	13 (29.54%)	10 (14.28%)	10 (19.23%)	
Lymph nodes removed (median, range)	15 (9–17)	16 (8–20)	17 (9–22)	0.775
pT0 after RP	0 (0%)	6 (8.57%)	9 (17.31%)	0.146
Pathological downstaging	3 (6.82%)	35 (50.0%)	32 (61.5%)	<0.001
Pathological *N*stage				
pN0	35 (79.55%)	57 (81.43%)	30 (57.69%)	
pN1	9 (20.45%)	13 (18.57%)	22 (42.31%)	
Positive surgical margin	14 (31.82%)	16 (22.86%)	9 (17.31%)	0.244

4. Discussion

According to NCCN CaP classification [12], high risk CaP was defined as biopsy Gleason score sum ≥ 8 or PSA > 20 ng/ml or clinical stage ≥ T3a. However, the oncological outcomes, such as metastasis free survival and biochemical recurrence, vary significantly in this group [13,14]. Thus, Sundi et al. defined very high risk CaP as primary Gleason pattern 5, or ≥5 cores with Gleason sum 8 to 10, or multiple NCCN high risk features, which represents 15.1% of high risk CaP [15]. Compared to other high risk men, patients with very high risk CaP were at significantly higher risk for metastasis, cancer-specific mortality and had worse 10-year metastasis-free survival and cancer-specific survival [15]. In this study, we included 177 cases with very high risk locally advanced disease to evaluate the safety and the local tumor control as well as bPFS benefits of NHT or docetaxel-based NCHT before RP and ePLND.

For very high risk CaP, 10-year cancer specific survival was 0.62 (95% confidence interval [C.I.] 0.45, 0.76)

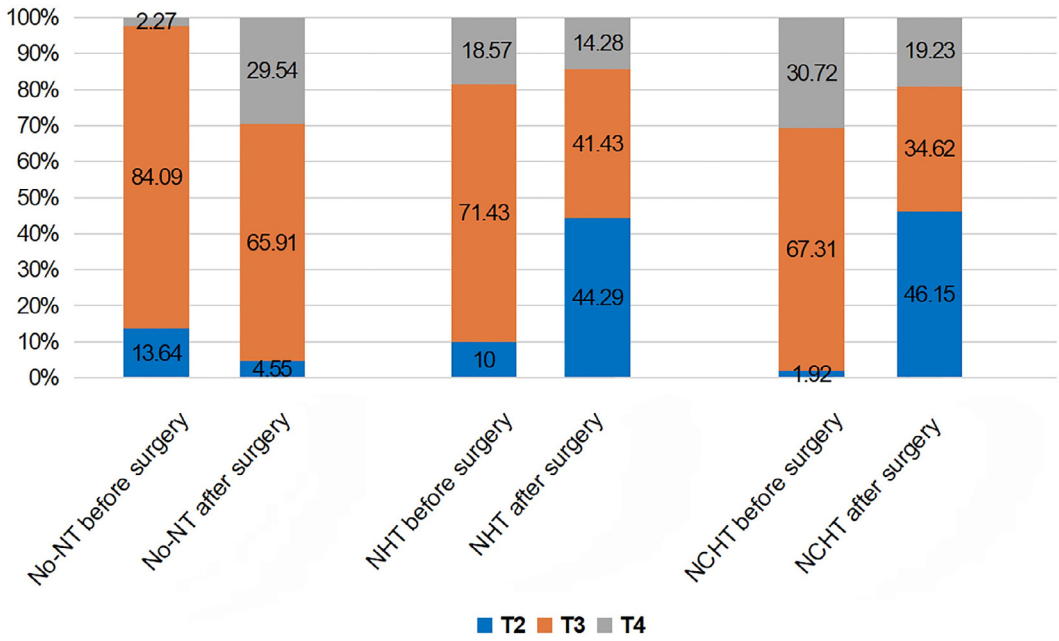

Fig. 1. *T* staging change before and after surgery in No-NT group, *T* stage change before neoadjuvant therapy and after surgery in NHT group and NCHT group.

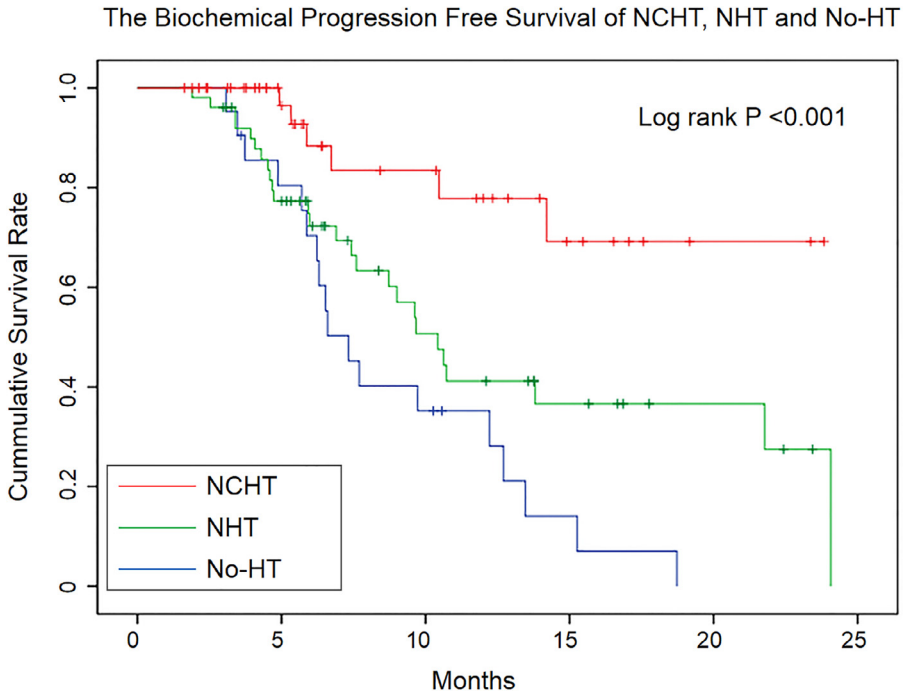

Fig. 2. The bPFS survival profiles of patients in 3 groups.

compared to 0.90 (95% C.I. 0.85, 0.93) for the rest of the high risk disease while metastasis-free survival was only 0.37 (95% C.I. 0.20, 0.54) compared to 0.78 (95% C.I. 0.72, 0.83) for the remainder of the high risk cohort [15]. To improve survival of high risk CaP, NHT has been used in this group. A meta-analysis of randomized trials of NHT in localized and locally advanced high risk CaP had proved NHT prior to RP could not improve overall or disease-free survival, but it did significantly reduce positive margin rates, organ confinement, and lymph node invasion [16]. The reasons for the failure of NHT in improving OS of high risk disease remain unclear. One possible reason is that despite maximum androgen synthesis and activity inhibition by complete androgen blockage, the residual levels of testosterone are still sufficient for the growth of CaP [17]. Great heterogeneities in CaP may also hinder tumoricidal effects of NHT and be responsible for development of castration resistance when selective hormonal resistant clones survive under androgen blockade [18,19]. Such theories prompted addition of cytotoxic agents as an important component of neoadjuvant therapy in very high risk disease in our study.

In early times, estramustine phosphate (EMP) had been used to treat locally advanced CaP before surgery. Several studies have found the NCHT might provide excellent long-term OS for high risk CaP. Fujita et al. [20] provided high risk CaP patients with NCHT followed by RP using EMP and the 10-year OS rate in the EMP group was significantly higher than the non-EMP group. Matsumoto et al. [21] compared the clinical outcomes of high risk CaP patients treated with RP plus ePLND or NCHT followed by RP with limited PLND. They found that the biochemical recurrence-free survival rate and OS rate in the neoadjuvant group were significantly higher and less patients progressed to castration-resistant CaP compared to control group.

To date, docetaxel has been proved to be a very efficacy chemotherapeutic drug for metastatic castration-resistant CaP, which could significantly improve the OS, the rates of response in terms of pain, serum total PSA level, and the quality of life as well [22]. Meanwhile, Sweeney et al. [5] has reported that 6 cycles of docetaxel at the beginning of ADT for high volume hormonal sensitive metastatic CaP significantly improved the OS with a longer time to the development of castration resistance than that with ADT alone.

Several studies have already proved that taxane-based NCHT was feasible and positive in nonmetastatic high risk CaP. Prayer-Galetti reported that patients had an 85% disease-free survival rate at 5 years after NCHT followed by RP and 1 patient (5%) had a pathological complete remission [8]. Thalgott reported that 55.2% of NCHT responders experienced PSA-recurrence after a median follow-up of 48.6 months and the estimated median time to PSA progression was 38.6 months while 85.3 months for OS [9]. In a phase II multicenter trial with median follow-up of 13.1 years, patients with high risk CaP was treated by ADT combined with paclitaxel, carboplatin, and estramustine before RP [23]. The oncological outcome showed that the probability of disease-specific survival at 10 years was 84% (95% CI 66%–93%) and OS was 78% (95% CI 60%–89%) [23]. However, even though this multi-institutional study had a longer follow-up, there were various chemotherapy

regimens rather than a standard protocol given to the patients. In addition, some of these studies only included a small number of patients, some of which were observational study without control group, and none of them focused on the oncological outcome of NCHT for very high risk locally advanced CaP.

The CALGB 90203 study was the only prospective randomized study to determine whether neoadjuvant chemotherapy combined with estramustine could improve the clinical outcome of high risk localized CaP (stage T1−T3a NxM0). In this study, resection of prostate will not be performed if the patient had gross, macroscopic, histologically confirmed lymph node metastasis [24]. The newly presented results of the CALGB 90203 (alliance) showed that NCHT followed by RP did not increase 3-year bPFS compared to RP alone in men with clinically localized high risk prostate cancer [25]. However, there was evidence that over time, bPFS and OS were improved in the men receiving NCHT and RP vs. the men receiving RP alone [25]. Compared to CALGB 90203, the NCHT arm in our study had a higher clinical stage with 98.3% of T3-4 tumor and 55% of clinical node positive disease. Although the NCHT group had significant higher initial PSA level, higher Gleason score, and more advanced clinical stage than No-NT group, a significantly longer bPFS time was achieved compared to RP as monotherapy. These results might suggest that the addition of preoperative cytotoxic chemotherapy could be more helpful in patients with higher tumor burden or more advanced clinical stage.

It has been proved that NHT had an important role in tumor down-staging in locally advanced CaP. In the current study, significant down-staging rates were found in both NHT group and NCHT group. In the NCHT group, such a down-staging effect was even more pronounced despite more T4 disease in this group, which implied that the addition of cytotoxic agent as a neoadjuvant therapy component might enhance the down-staging effect. In comparison, an obvious up-staging was observed in the No-NT group, which was also reported in high risk disease [26]. As previously reported, complete pathological remissions (pT0) ranging from 5% to 15% have been observed in studies exploring the clinical value of neoadjuvant therapy followed by RP [10,27]. In the present study, pT0 was found in 9 patients (17.31%) who had quite high tumor burden and clinical T-stage before the treatment in the NCHT group . Indeed, pT0 represents a powerful pathological outcome associated with favorable biochemical recurrence free survivals [8,25]. However, the translation from pT0 to survival benefit is still awaited validation by further follow-up. Moreover, patients in NCHT group also achieved the lowest positive surgical margin rate and the lowest biochemical recurrence rate with worse baselines although both rates were nonstatistically different from other groups. If preoperative parameters were identical in these 3 groups, like PSA level, Gleason score, and clinical stage, it is highly possible that NCHT group would have had much better oncological outcomes. Considering this situation, we speculated that the NCHT might have additional benefits for very high risk clinically localized CaP. Of note, there are 4 patients in the NCHT group and 3 patients in the NHT who progressed with unresectable lesions during neoadjuvant treatment and switched to radiotherapy. Indeed, resistance to neoadjuvant therapy poses a challenge to treatment selection, which warrants identification of better biomarkers to direct optimal treatment decisions.

The cytotoxicity remained the major concern for docetaxel-bases neoadjuvant chemotherapy. Since patients enrolled in the study were potential candidate for subsequent aggressive surgery, they were all in good general health status with 0 to 1 ECOG score. Overall, more adverse effects with those especially related to chemotherapy were observed in the NCHT group than in the NHT group. Notably, 1 case presented Grade 4 febrile neutropenia and 3 cases presented Grade 3 liver function impairment in the NCHT group in whom the NCHT was stopped. However, most of adverse effects could be well tolerated and managed medically in our study. In detail, hematological toxicity represented one of the most common adverse effects in the NCHT cohort. Grade 3 or 4 neutropenia, especially febrile neutropenia was relatively rare, which was consistent with the previous reports [18,19]. There was no febrile sepsis or septic shock presented in this study. Besides, gastroenterological problems, such as nausea, vomiting as well as transaminase increase, were also very frequent in NCHT group, but well tolerated in most cases. Hot flashes and impotence related to the administration of LHRH analogue were very common in the NCHT group as well as in the NHT group.

Since most cases enrolled in the study had a clinical stage more than T3b, RP and ePLND were somehow difficult. However, the docetaxel-based chemotherapy did not increase the surgical complications in our study, proving its safety in neoadjuvant setting. In fact, it significantly reduced the tumor burden, and helped to deliver the surgical plan between rectum and prostate and reduce the volume of adenopathy around the major vessels, which might make the surgery easier and safer.

Our study had several limitations. First of all, it was a retrospective study so that the possibility of selection bias could not be completely excluded. Second, although the oncological results seemed to be in favor of NCHT group despite its worst preoperative clinical parameters, the inhomogeneous baselines of the 3 groups remained an important imitation, which might be responsible for the statistical insignificance in oncological outcomes among the groups. Finally, significant differences of follow-up time among 3 groups with the shortest time in the NCHT may favor this arm regarding biochemical recurrence rates. Also, follow-up for bPFS was relatively limited in the absence of OS and metastasis-free survival. Thus, further validation in prospective larger cohorts with longer follow-up is warranted, especially with regard to prognostic value.

5. Conclusion

For very high risk CaP, men treated by NCHT and NHT had a higher probability of achieving an undetectable PSA level after RP with significant tumor downstaging. Despite having poorer prognostic factors, the NCHT group had better bPFS time after surgery compared to NHT and RP as monotherapy. Randomized controlled investigations are needed to validate the results and further follow-up is required for survival end points.

Conflict of interest

There is no conflict of interest to be declared.

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