The Clinical trials of Neoadjuvant chemo-hormonal therapy combined with radical prostatectomy for locally advanced prostate cancer

A prospective, multicenter, three-arm, randomized, controlled study comparing the efficacy of neoadjuvant hormonal therapy combined with systemic chemotherapy (NCHT), neoadjuvant hormonal therapy (NHT) and radical prostatectomy only in locally advanced prostate cancer

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Abbreviation

ACTH	Adrenocorticotropic hormone	ADR	Adverse drug reaction
AE	Adverse events	AKP	Alkaline phosphatase
ALT	Alanine aminotransferase	AST	Aspartate aminotransferase
CRF	Case Report Form	BPI-SF	Concise Pain Questionnaire
CT	Computed tomography	CR	Complete remission
ECOG	US Eastern Oncology Group	DBIL	Direct Bilirubin
GGT	Glutamyl transpeptidase	FACT-P	Quality of life scale
HCV	Hepatitis C Virus	GCP	Drug Clinical Trial Quality Management Practice
LH	Luteinizing hormone	HBsAg	Hepatitis B surface antigen
LLN	Lower limit of normal range	LDH	Lactate dehydrogenase
MRI	Magnetic Resonance Imaging	LHRH	Luteinizing Hormone Releasing Hormone
NE	Cannot evaluate	NCI-CTCAE	US National Cancer Institute Common Adverse Event Evaluation Criteria
NHT	Neoadjuvant hormonal therapy	NCHT	Neoadjuvant chemotherapy combined with hormone therapy
OS	Overall Survival	NYNH	New York Heart Association
PD	Disease progression	PCWG	Prostate Cancer Working Group
PSA	Prostate specific antigen	PR	Partial response
PFS	Progression-free survival	rPFS	Radiographic progression-free survival
SAE	Serious adverse events	RECIST	Solid tumor efficacy evaluation criteria
TBIL	Total bilirubin	TTPP	Prostate specific antigen progression time
SD	Disease stability	ULN	Normal range upper limit

Abstract

Study title	A prospective, multicentre, three-arms, randomized, controlled study comparing the efficacy of neoadjuvant hormonal therapy combined with systemic chemotherapy (NCHT), neoadjuvant hormonal therapy (NHT) and radical prostatectomy only in locally advanced prostate cancer
Study objectives	To evaluate of the value of radical prostatectomy and extended pelvic lymph node dissection in locally advanced prostate cancer after neoadjuvant hormonal therapy with or without docetaxel chemotherapy
Study design	Prospective， Multicenter, Open-label, Parallel group, Randomized (2:2:1) Controlled , Clinical Trial
Study group	Newly diagnosed, untreated cT3a-cT4 or any cT, cN1 in locally advanced hormone-sensitive prostate cancer
Study group number	Randomized 2:2:1
Inclusion Criteria	(1) 18≤ Aged <75 years, male; (2) Histology or cytology diagnosis: Prostate adenocarcinoma; (3) ECOG performance Status ≤1; Expected lifetime ≥10 years; (4) Without clinical or radiographic metastases in 6 months (Bone scan, MRI or pelvic enhanced CT scan, PET-CT) before randomized; (5) The patients of locally advanced prostate cancer need to satisfy at least one of the following requirements: clinical stageT3a-T4, N0, M0; any T, N1, M0; (6) Without Androgen Blockade Treatment in 4 weeks before randomized; (7) Without radiographic treatment towards primary tumour; (8) Without opioids (including codeine and dextropropoxyphene) relieving relevant pain of cancer; (9) Without azole drugs (such as fluconazole, itraconazole); (10) Important laboratory indicators are as follows: a、Haemoglobin ≥90g/L

	b、ANC ≥ 1500/μL c、PLT≥100*10^9/L d、K+≥3.5mmol/L e、AST or ALT ≤1.5 times upper limit of normal (ULN), TBIL should be ≤ULN (except patients with certified Gilbert syndrome) and ALP≤5ULN f、ALB≥30g / L g、calculated Ccr>60 ml/min, serum creatinine ≤ ULN (11) Without swallowing disease, able to swallow the whole piece of drugs; (12) Without other tumour chemotherapy history, without chemotherapy and endocrine therapy contraindications; (13) If patient's spouse is at her childbearing age, the patient needs to agree that effective contraception should be taken during the treatment and 4 months after the operation. (14) Subjects volunteer to participate, the subject must sign an informed consent form (ICF), indicating the understanding of the purpose and the required procedures of the study, and willing to participate in the study. Subjects must be willing to comply with the prohibitions and restrictions set forth in the program.
Exclusion Criteria	(1) The pathology result of prostate is neuroendocrine prostate cancer, including small cell carcinoma; (2) Previous cytotoxic chemotherapy or biological therapy for prostate cancer; (3) Contraindications to prednisone, such as active infections or other disorders; (4) Patients with chronic disease needed to be given dose of prednisone (each time 5mg, bid a day) exceed the dose in the study; (5) High blood pressure with poor control of drugs (systolic blood pressure ≥160mmHg or diastolic blood pressure ≥95mmHg); (6) Active or symptomatic viral hepatitis or other chronic liver disease, known infected with human immunodeficiency virus (HIV); (7) A disease history of pituitary or adrenal dysfunction; (8) Patients with active autoimmune disease who need hormone therapy; (9) Heart disease with clinical significance, including: myocardial infarction or arterial thrombosis occurred in the past 6 months; severe or unstable angina; New York Heart

	Association grade III or IV heart disease (Appendix 4); atrial fibrillation or other arrhythmias that require treatment; (10) Subjects who participated in other clinical studies within a month before the first use of chemotherapy; (the elution time is at least 5 times the half-life time of the study drug if the half-life time is too long.) (11) Patients with a history of hypersensitivity to Taxanes or docetaxel (12) Patients who are concomitantly receiving strong CYP3A4 inhibitors (13) Other circumstances considered inappropriate by investigator.
Treatment plan	Arm A: Docetaxel 75mg/m^2 IV (every 3 weeks) +Prednisone 5mg BID orally + HT (Bicalutamide Tablets, 50mg QD orally; Goserelin, 3.6mg, subcutaneous injection, q28d), 4-6 cycles Arm B: HT (Bicalutamide Tablets, 50mg QD orally; Goserelin, 3.6mg, subcutaneous injection, q28d), 3-6 cycles Radical Prostatectomy (RP)+ extended lymph node dissection: Within three months after neoadjuvant treatment. Arm C: RP+/- extended lymph node dissection alone Treatment after prostatectomy: There will not have any drug treatment after surgery until disease progression. Pelvic lymph node dissection is required to reach the level of bilateral iliac artery. If the postoperative pathology indicated positive incisional margin or pelvic lymph node metastasis, pelvic adjuvant radiotherapy should be performed within 3 months after surgery.
The time of follow-up	Neoadjuvant treatment period: Neoadjuvant hormone therapy combined with chemotherapy group has a follow-up period every 21 days, and it can be used continuously, with the longest time of 6 cycles. The neoadjuvant hormone therapy group has a follow-up cycle every 28 days. Postoperative follow-up period: one follow-up period every 4 weeks, after 3 consecutive weeks of monitoring, changed to a follow-up period every 12 weeks for a total of two years.
Efficacy evaluation	**<u>Primary</u>:** bPFS (Biochemical progression-free survival)

	Secondary: 1. First year biochemical progression-free survival rate The proportion of patients with PSA levels <0.2 ng/ml monitored continuously over 1 year and no postoperative adjuvant treatment in each group. 2. Overall survival (OS) 3. No imaging progression survival period (rPFS) 4. TTPP 5. Symptomatic progression occurred through the Quality of Life Assessment Scale (FACT-P) score. 6. The ECOG score indicates the time when the subject's physical condition deteriorated.
Safety evaluation	1. general physical examination indicators: respiration, pulse, blood pressure, body temperature and weight. 2. clinical examination: to observe whether the subjects have symptoms such as nausea, fatigue, backache and cough. 3. laboratory indicators related to safety of neoadjuvant therapy: blood routine, urine routine, liver function and blood electrolyte, renal function, coagulation function and other blood biochemistry. 4. ECG examination. 5. Surgical complications: deep vein thrombosis, pulmonary embolism, bone marrow suppression, infection, cardiovascular complications, fractures and other related or unrelated complications.
Estimated progress	Enrollment is planned to finish within 24 months
Project revision date	Jan 15th, 2020
Version number	V1.8

Study background

1.1 Prostate cancer

Prostate cancer (PCa) represents the most common malignancy in men and the second leading cause of death in Western countries. The incidence of prostate cancer in East Asian countries is much lower than in Western countries. But during the recent twenty years, the incidence of PCa in China has been increasing rapidly, likely due to a longer life expectancy and Westernized lifestyles associated with dramatic economic growth and sociocultural changes. The PCa incidence in Shanghai increased six fold from an age standardized rates (ASR) of 2.13/100,000 in 1973 to 12.96/100,000 in 2009, and its ranking ascended from the 17th to the 4th most common cancer during the period.

Prostate cancer is a highly heterogeneous tumor. The 5-year survival rate of early patients with low pathological grade is nearly 100%, while the 5-year survival rate of patients with advanced metastatic prostate cancer is only 30%. The European Association of Urology (EAU) guidelines defines patients with high-risk prostate cancer as PSA>20ng/ml, Gleason score >8 and clinical stage >T2c. Unlike Europe and the United States, in our country, because prostate specific antigen (prostate - specific antigen, PSA) screening has not been widely spread and other reasons, Chinese men with prostate cancer were often diagnosed with late-stage. The proportion of locally advanced tumor can reach 50-70%, and these patients become the threaten in patients with prostate cancer besides metastatic PCa.

The standard treatment for high-risk locally advanced prostate cancer has not been established yet. Radical prostatectomy is one of the important treatment methods, which is expected to provide long-term survival time for patients. Spahn et al. retrospectively analyzed the results of a multicenter study of 712 patients with prostate cancer diagnosed with PSA> 20ng/ml, who were followed for an average of 77 months after radical resection. The non-biochemical recurrence survival rate was 64.8% at 5 years, 51.9% at 10 years, 89.9% at 5 years, and 84.5% at 10 years. Similarly, Eggener et al. reported 1326 patients with GS 8-10 high-risk prostate cancer followed up for an average of 96 months after radical surgery, and the tumor-specific survival rate was 89% 10 years and 72% 15 years. However, the failure rate of these patients with radical prostatectomy alone was higher, and some patients had early PSA recurrence and distant micro-metastasis after operation. Ward et al. followed 1,179 patients with locally advanced (cT3) prostate cancer for an average of 2.4 years after radical surgery, and the biochemical recurrence rate was 52.6% in 5 years and 64.3% in 10 years. It can be seen that patients with high-risk or locally advanced prostate cancer are prone to recurrence and metastasis after simple radical prostatectomy, with low

long-term survival rate. It may be necessary to combine with HT, radiotherapy and chemotherapy to improve surgical efficacy and further improve the prognosis of patients.

Prostate cancer is an androgen-dependent malignant tumor, and HT is an effective treatment. Neoadjuvant endocrine therapy before radical resection of prostate cancer can reduce the clinical stage and pathological grade of high-risk or locally advanced tumors, reduce the positive rate of resection margin, and improve the rate of surgical resection. However, there is still controversy over whether it can ultimately benefit patients. Shelley's study showed that neoadjuvant HT did not improve the overall survival of the disease and the progression-free survival of the disease. However, the latest meta-analysis of 5194 patients showed that neoadjuvant HT had a significant effect on the downgrading and downstaging of high-risk prostate cancer. Although it significantly improved the non-biochemical recurrence disease free survival rate (bDFS) and overall survival rate (OS) of the patients, it was not helpful to improve the disease-free survival period (DFS) of the patients. Therefore, to further optimize the existing neoadjuvant treatment scheme for prostate cancer, in order to enable high-risk locally advanced prostate cancer patients to gain stable and definite long-term survival benefits from radical prostatectomy, is clinically needed.

1.2 Relevant research results at present

1.2.1 Relevant research conclusions conducted abroad

In 2004, Tannock et al. first reported in the New England journal of medicine that the systematic chemotherapy based on docetaxel could reduce the risk of death in PCa patients with advanced prostate cancer by 24%, increase the rate of progression-free survival (PFS), and increase the rate of tumor remission, pain remission and PSA remission. Docetaxel combined with prednisone (DP) has been listed as the first choice for the treatment of castration-resistant prostate cancer after the failure of HT. Based on this, some scholars tried to use this program to conduct neoadjuvant treatment for high-risk locally advanced prostate cancer and then conduct radical prostatectomy. Mark Thalgott et al. treated 30 cases of high-risk or locally advanced prostate cancer by RP combined with neoadjuvant therapy of DP. Long-term follow-up results showed that the therapy significantly reduced clinical staging but could not be pathologically completely relieved, and could extend 5 years without biochemical recurrence and survival. Preoperative joint application of docetaxel, estrostatin and triptorelin for the treatment of 21 patients with high-risk prostate cancer was performed, with an average follow-up of 53 months. 42% of the patients had no disease survival, and 85% of those who responded to the drug had no disease survival rate for 5 years. Sella et al studied 22 cases of high-risk prostate cancer, combined preoperative docetaxel, estrostatin and endocrine therapy, with an average follow-up of 23.6 months, and a disease-free survival rate of 54.5%.

1.2.2 The advance of previous research conducted by our center

From March 2014 to July 2017, a total of 166 patients who had very-high-risk locally advanced PCa were enrolled in this study. There were 56 men in NCHT group (2-10 cycles of DP chemotherapy), 70 men in NHT group and 44 men in No-NT group. 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.

Table 1 The basic characteristics of patients

	No-NT group	NHT group	NCHT group	P
age（y,SD）	68.8±5.3	67.8±5.5	63.9±7.5	RP vs NHT 0.652 RP vs NCHT 0.001 NHT vs NCHT 0.006
PSA0（ng/ml）	60.53±30.08	85.52±53.29	136.60±142.60	RP vs NHT 0.005 RP vs NCHT 0.001 NHT vs NCHT 0.052
Gleason score				0.040
<6	5(11.36%)	5(7.14%)	1(1.92%)	RP vs NHT 0.606 RP vs NCHT 0.020 NHT vs NCHT 0.031
7	20(45.45%)	27(38.57%)	28(53.85%)	
8	13(29.55%)	23(32.86%)	7(13.46%)	
≥9	6(13.63%)	15(21.43%)	16(30.77%)	
primary lesions				0.003
T2	5(11.36%)	5(7.14%)	1(1.92%)	RP vs NHT 0.035 RP vs NCHT 0.000
T3	37(84.09%)	50(71.43%)	35(67.31%)	

T4	1(2.27%%)	13(18.57%)	16(30.77%)	NHT vs NCHT 0.086
Local lymph node				0.000
N0	38(86.36%)	53(75.71%)	22(44.23%)	RP vs NHT 0.168 RP vs NCHT 0.000 NHT vs NCHT 0.000
N1	6(13.63%)	17(24.29%)	29(55.77%)	
PSA level After neoadjuvant therapy		4.65	0.99	NHT vs NCHT 0.006

All the patients in the three groups completed the surgery, and the intraoperative situation was as shown in table 2. In the no-HT group, 1 patient suffered with intraoperative mesenteric vessel injury and hemorrhagic shock after the surgery. Then he immediately recovered after the reoperation of small intestinal segment resection, and the patient was discharged successfully. In the NHT group, 1 patient presented intraoperative rectal injury, and intraoperative repair was performed. One patient underwent replantation of ureteral bladder due to tumor invasion. NCHT group: 1 patient underwent replantation of ureteral bladder due to tumor invasion. One case of laparoscopic prostate cancer underwent external iliac vein injury due to lymph node dissection during the operation.

Table 2 The operation summary of patients

	RP group	NHT group	NCHT group	P
surgery				0.012
RP	24(54.5%)	35(50.0%)	17(32.7%)	
LA-RP	8(18.2%)	14(20.0%)	5(9.6%)	
RA-RP	12(27.3%)	21(30.0%)	30(57.7%)	
lymph node dissection				0.000
lPLND	26(59.1%)	28(40.0%)	4(7.7%)	
ePLND	18(40.9%)	42(60.0%)	48(92.3%)	
Average operating time(min)	158	170	183	0.131

Intraoperative blood loss(ml)	355	347	335	0.344
post operation hospitalization duration(d)	6.5	6.1	6.2	0.286

The postoperative pathology of the patients was shown in table 3. All patients were followed up for 19.8 months. Without adjuvant drug treatment within 3 months after surgery, serum PSA decreased to the lowest point <0.2ng/ml, which is defined as reaching the value of 0. Two consecutive PSA test values of > 0.2ng/ml were defined as biochemical recurrence.

Table 3 Postoperative situations of patients

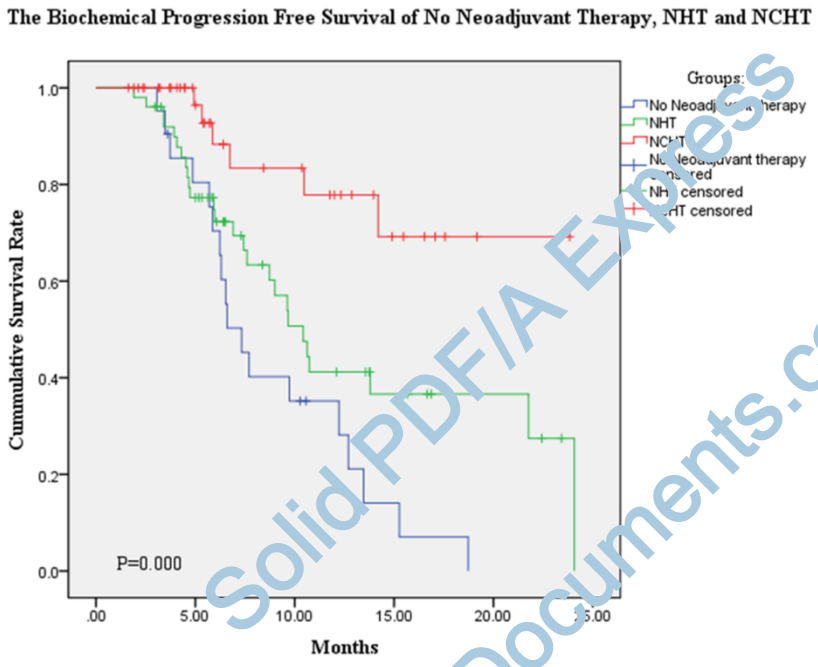
	RP group	**NHT group**	**NCHT group**	**P**
Gleason score				0.040
Unable to classification		**6(8.6%)**	**9(17.3%)**	
6	2(4.5%)	5(7.1%)	1(1.9%)	
7	16(36.4%)	18(25.7%)	14(26.9%)	
8	14(31.8%)	17(24.3%)	10(19.2%)	
≥9	12(27.3%)	24(34.3%)	16(30.8%)	
positive margin	14(31.8%)	16(22.9%)	9(17.3%)	0.244
primary lesion pT				0.000
0		**6(8.6%)**	**9(17.3%)**	
2	2(4.5%)	25(35.7%)	15(28.8%)	
3	29(65.9%)	29(41.4%)	18(34.6%)	
4	13(29.5%)	10(14.3%)	10(19.2%)	
lymph node pN+	9(20.5%)	13(18.6%)	22(42.3%)	0.003
Is it 0 value				0.001
yes	21(47.7%)	51(72.9%)	42(80.8%)	RP vs NHT 0.007

no	23(52.4%)	19(27.1%)	10(19.2%)	RP vs NCHT 0.001 NHT vs NCHT 0.310

The annual progression-free survival rate was 52.1% in the HCNT group, 27.9% in the NHT group and 19.3% in the direct surgery group, respectively. The biochemical progression-free survival curves of the three groups were shown in figure 1 (P<0.01).

Fig 1 The biochemical non-progression-free survival curve

Of patients in the three groups



1.3 Clinical research results and conclusions

Hormonal therapy combined with neoadjuvant chemotherapy for high-risk or locally advanced prostate cancer may be beneficial to improve patients' biochemical progression-free survival. To date, only a few small samples have been reported for disease-free progression-free survival and long-term survival, lacking a prospective and randomized controlled study. In addition, due to the strong racial specificity of prostate cancer, there are no clinical reports of endocrine therapy combined with systematic neoadjuvant chemotherapy for high-risk or locally advanced prostate cancer in Chinese population, so this field needs to be further explored.

Based on the previous work, this project intends to carry out a prospective, randomized, controlled study on the Chinese population with a large sample size, and

compares the clinical efficacy of endocrine therapy combined with or without system neoadjuvant chemotherapy in the treatment of locally advanced prostate cancer. The pathological characteristic changes before and after neoadjuvant treatment were analyzed. To find the important risk factors affecting the long-term prognosis of these patients, so as to provide the basis for the formulation of the optimal treatment plan for locally advanced prostate cancer, prolong the survival time of the patients and improve the quality of life.

2 Experiment purpose

Using larger sample prospective randomized controlled study design, and comparing neoadjuvant HT combined with docetaxel chemotherapy to neoadjuvant HT followed by RP and extended lymph node dissection to determine whether neoadjuvant HT combined with docetaxel chemotherapy can more effectively improve biochemical progression-free survival of locally advanced prostate cancer patients.

Further analysis was performed to determine whether the treatment regimen helped to prolong the radiologic progression-free survival (rPFS) and OS in these patients.

The pathological changes of tumor before and after neoadjuvant treatment were also analyzed. To search for the important risk factors influencing the long-term prognosis of these patients, the safety characteristics of patients in different treatment groups were analyzed. Therefore, it can provide the basis for the formulation of the optimal treatment plan for locally advanced prostate cancer, prolong the survival time of patients and improve the quality of life.

3 Experiment design

3.1 General design principles

Perspective, multi-center, three-arms, random, control.

3.2 Control group treatment selection

According to the 2018 guidelines for the diagnosis and treatment of EAU prostate cancer, radical prostatectomy and enlarged lymph node dissection in patients with cT3aN0M0, cT3b-cT4N0M0 or any cT, N1M0 are highly recommended. However, neoadjuvant HT is not recommended. Based on the above, direct radical resection of prostate cancer and pelvic enlarged lymph node dissection were used in the control group.

However, before radical surgery, HT of prostate cancer patients for a certain period of time can reduce tumor volume, reduce clinical stage, and reduce the positive rate of prostate

tumor excision margin. According to the existing retrospective study of our center, neoadjuvant endocrine therapy may still have possible benefits in bPFS for extremely high-risk patients. Therefore, neoadjuvant endocrine therapy was included in the study.

3.3 Number of cases and distribution

In this study, on the basis of combined HT, usage of neoadjuvant chemotherapy as a control group was tested for superior efficacy between groups. According to the retrospective study of our center, the median bPFS of patients in the three groups was 8.95 months, 13.24 months and 19.26 months respectively. According to the age =0.05, 90% grasp rate, 10% of each group were lost to follow-up, 24 months were enrolled, and the whole study was 48 months.

Two hypothesis tests are planned to declare that bPFS differs in NCHT vs. NHT and NCHT vs. RP group.

A two-sided log-rank test with a sample size of 340 subjects (170 in the NHT group and 170 in the NCHT group) achieves 80.2% power at a 0.025 significance level to detect a hazard ratio of 0.6842 when the NHT group median survival time is 13 months. (see report 1 as attached)

A two-sided logrank test with a sample size of 255 subjects (85 in the RP group and 170 in the NCHT group) achieves 99.9% power at a 0.025 significance level to detect a hazard ratio of 0.4737 when the RP group median survival time is 9 months. (see report 2 as attached)

The study lasts for 48 months over which subject accrual (entry) occurs in the first 24 months.

In total, 475 patients are enrolled after adjusted with a 10% drop-out rate (i.e. 190 for NCHT, 190 for NHT, and 95 for RP group, respectively).

3.4 Randomization methods

Use block randomization, to generate the random number table according to the SAS software simulation, set the seed number, segment length, and number of segments.

4 Subject selection and withdrawal

4.1 Subjects

New high-risk locally advanced hormone-sensitive prostate cancer.

4.2 Diagnostic criteria for prostate cancer

Referring to《Surgery》, People's medical publishing house, January 7, 2008

Combined with clinical symptoms, rectal examination, serum prostate-specific antigen (PSA) and imaging results, the early diagnosis of prostate cancer can be made, and the diagnosis requires the pathological diagnosis of prostate puncture biopsy.

4.3 Case inclusion criteria

(1) 18≤ Aged <75 years, male;

(2) Histology or cytology diagnosis: Prostate adenocarcinoma;

(3) ECOG performance Status ≤1; Expected lifetime ≥10 years;

(4) Without clinical or radiographic metastases in 6 months (Bone scan, MRI or pelvic enhanced CT scan, PET-CT) before randomized;

(5) The patients of locally advanced prostate cancer need to satisfy at least one of the following requirements: clinical stageT3a-T4, N0, M0; any T, N1, M0;

(6) Without Androgen Blockade Treatment in 4 weeks before randomized;

(7) Without radiographic treatment towards primary tumour;

(8) Without opioids (including codeine and dextropropoxyphene) relieving relevant pain of cancer;

(9) Without azole drugs (such as fluconazole, itraconazole);

(10) Important laboratory indicators are as follows:

a、Haemoglobin ≥80g/L

b、ANC ≥ 1500/μL

c、PLT≥100*10^9/L

d、K+≥3.5mmol/L

e、AST or ALT ≤1.5 times upper limit of normal (ULN), TBIL should be ≤ULN (except patients with certified Gilbert syndrome) and ALP≤5ULN

f、ALB≥30g/L

g、calculated Ccr>60 ml/min, serum creatinine ≤ ULN

(11) Without swallowing disease, able to swallow the whole piece of drugs;

(12) Without other tumour chemotherapy history, without chemotherapy and endocrine therapy contraindications;

(13) If patient's spouse is at her childbearing age, the patient needs to agree that effective contraception should be taken during the treatment and 4 months after the operation.

(14) Subjects volunteer to participate, the subject must sign an informed consent form (ICF), indicating the understanding of the purpose and the required procedures of the study, and willing to participate in the study. Subjects must be willing to comply with the prohibitions and restrictions set forth in the program.

4.4 Case exclusion criteria

(1) The pathology result of prostate is neuroendocrine prostate cancer, including small cell carcinoma;

(2) Previous cytotoxic chemotherapy or biological therapy for prostate cancer;

(3) Contraindications to prednisone, such as active infections or other disorders;

(4) Patients with chronic disease needed to be given dose of prednisone (each time 5mg, bid a day) exceed the dose in the study;

(5) High blood pressure with poor control of drugs (systolic blood pressure ⩾160mmHg or diastolic blood pressure ⩾95mmHg);

(6) Active or symptomatic viral hepatitis or other chronic liver disease, known infected with human immunodeficiency virus (HIV);

(7) A disease history of pituitary or adrenal dysfunction;

(8) Patients with active autoimmune disease who need hormone therapy;

(9) Heart disease with clinical significance, including: myocardial infarction or arterial thrombosis occurred in the past 6 months; severe or unstable angina; New York Heart Association grade III or IV heart disease (Appendix 4); atrial fibrillation or other arrhythmias that require treatment;

(10) Subjects who participated in other clinical studies within a month before the first use of chemotherapy; (the elution time is at least 5 times the half-life time of the study drug if the half-life time is too long.)

(11) Patients with a history of hypersensitivity to Taxanes or docetaxel

(12) Patients who are concomitantly receiving strong CYP3A4 inhibitors

(13) Other circumstances considered inappropriate by investigator.

4.5 Case withdrawal criteria

4.5.1 Subjects decided by researchers to withdraw

(1) patients with adverse events should be stopped according to the doctor's judgment.

(2) patients with local or systemic deterioration of prostate cancer during preoperative neoadjuvant therapy, such as new metastatic lesions or obstructive renal failure, should be stopped according to the doctor's judgment.

(3) subjects' poor compliance; Or automatic midway change of treatment regimen, hospital, or addition of drugs prohibited by this regimen, which has been confirmed by the researcher as having a serious effect on the judgment of curative effect.

(4) cases with various causes leading to treatment suspension.

4.5.2 Subjects withdrawal by themselves

(1) no matter what the reason is, the patient is unwilling or impossible to continue the clinical trial, and the patient discontinues the trial by asking the competent doctor to withdraw from the trial.

(2) although the subject did not explicitly propose to withdraw from the test, he/she will no longer receive the drug and test and lose the interviewee.

4.6 Management of withdrawal cases

When subjects fall out, the investigator should take measures to complete the last treatment evaluation as far as possible in order to analyze their efficacy and safety. All withdrawal cases should be filled in the case report form, the test conclusion form and the reason for withdrawal. If the patient is withdrawn from the trial due to allergic reactions, adverse reactions and ineffective treatment, the researcher should take corresponding treatment measures according to the actual situation of the subject.

4.7 Case elimination criteria

(1) after randomization, violation of inclusion criteria or exclusion criteria is found.

(2) patients who have not received treatment according to the protocol after randomization.

(3) after randomization, no patients were recorded after treatment.

(4) after randomization, patients in the treatment group were required to be replaced, that is, patients requiring combination chemotherapy during neoadjuvant endocrine therapy or patients requiring discontinuation of chemotherapy before neoadjuvant chemotherapy.

(5) others (such as serious violations of combined medication).

The final exclusion of cases is determined by the researchers.

4.8 Complete trial abortion criteria

(1) If a wide range of serious adverse reactions occur in the test, the test should be aborted in time.

(2) Significant errors were found in the clinical trial program, or serious deviations occurred in the implementation of the good program, which was difficult to evaluate the therapeutic effect, and the trial should be suspended.

(3) In the test, it was found that the treatment effect of the experimental group was significantly different from that of the control group, and it did not have clinical value. Therefore, the test should be suspended.

(4) The investigator demands to suspend the test due to irresistible factors;

(5) Administrative departments shall cancel the test.

5 Treatment Plan

5.1 Drugs involved

Casodex (bicalutamide tablets), specification 50mg, Manufacturer: Corden Pharma S.P.A, registration number of imported drugs: H20100390.

Zhaohuixian (bicalutamide tablets), specification 50mg; Manufacturer: Shanghai Zhaohui Pharmaceutical co., LTD. Approval number: H20064085.

Zoladex (goserelin sustained-release implant), 3.6mg/10.8mg; Manufacturer: AstraZeneca UK Limited, import drug registration number: H20100314.

Leuprorelin (Leuprorelin Acetate For Injection), specification: 3.75mg/11.25mg; Manufacturer: Takeda pharmaceutical industry co., LTD., registration standard for imported drugs: JX20090036.

Estracyt (Estramustine phosphate capsules), specification: 0.14g; Manufacturer: Pfizer Italia S.r.L.

Taxotere (Docetaxel injection), specification: 0.5ml:20mg; License holder: Aventis Pharma S. A., import drug registration standard: JX20130260.

Prednisolone acetate tablets, specification 5mg; Manufacturer: Shanghai Xinyi pharmaceutical co., LTD. Approval number: H3120771.

5.2 Different group treatment

5.2.1 Neoadjuvant HT combined with chemotherapy group

Neoadjuvant HT combined with docetaxel chemotherapy + radical resection of prostate cancer + extended pelvic lymph node dissection. Goserelin/Leuprorelin subcutaneous injection + docetaxel 75mg/m^2 intravenous drip every 3 weeks for a total of 4-6 cycles. Prednisolone acetate 5mg bid/ day started 14 days before docetaxel chemotherapy and stopped 3 weeks after the end of the last chemotherapy cycle. Radical prostatectomy was performed within 3 months after neoadjuvant therapy. Pelvic lymph node dissection was required to reach the level of bilateral common iliac artery. If the postoperative pathology indicated positive incisal margin or pelvic lymph node metastasis, pelvic adjuvant radiotherapy should be performed within 3 months after surgery.

Among them: selective oral bicalutamide tablets anti-male treatment. Acetaminophen tablets, if accidental omission, can be ignored, not to supplement.

5.2.2 Neoadjuvant HT group

Neoadjuvant HT with radical resection of prostate cancer plus extended pelvic lymph node dissection. Neoadjuvant endocrine therapy bicalutamide 50mg qd Po + subcutaneous injection of goserelin / leuprorelin, with a total of 3-6 cycles. Radical resection of prostate cancer was performed within 3 months after neoadjuvant therapy. Pelvic lymph node dissection was required to reach the level of bilateral common iliac artery. If the postoperative pathology indicated positive incisal margin or pelvic lymph node metastasis, pelvic adjuvant radiotherapy should be performed within 3 months after surgery.

Among them: selective oral bicalutamide tablets anti-male treatment.

5.2.3 Direct operation group

Radical prostatectomy and extended pelvic lymph node dissection. The enrolled patients received direct radical prostatectomy, during which pelvic lymph node dissection was required to reach the level of bilateral common iliac artery. If the postoperative pathology indicated positive incisal margin or pelvic lymph node metastasis, pelvic adjuvant radiotherapy should be performed within 3 months after surgery.

5.2.4 Neoadjuvant therapy course and follow-up

The experimental group received docetaxel chemotherapy on the first day of each cycle, followed by outpatient visits on the 18th to 20th day to assess the safety of the next chemotherapy, which was continuously conducted, with a maximum of 6 cycles.

In the control group, LHRH-α was injected every 28 days, and outpatient visits were conducted on the 25th to 27th days of each cycle. Use up to 6 cycles.

In all three groups, PSA test will be conducted within 2-4 days before each cycle ends, and radiographic evaluation will be conducted every three cycles of neoadjuvant therapy, including (bone scan, pelvic MRI/CT, or PET-CT).

Termination of neoadjuvant therapy in the presence of either of the following:

(1) according to the researcher's judgment, the comprehensive conditions of the patient were in line with the surgical conditions, and the surgical treatment was performed, including obvious reduction of prostate volume, reduction of local invasion, reduction of lymph node enlargement, and obvious relief of PSA.

(2) prostatic cancer disease progression (Appendix 2), or castration-resistant prostate cancer, is no longer suitable for continuing the current treatment. Special note: in the first 2 cycles of neoadjuvant therapy, if PSA alone is elevated but no imaging progress, this condition is not disease progression.

(3) start new anticancer therapies, such as second-line endocrine therapy (enzalutamide, abiraterone, etc.), radiotherapy, change of chemotherapy regimens, and immunotherapy.

(4) the use of the study drug will be terminated after the inadmissibility of drug toxicity or other adverse events are confirmed by the researcher.

(5) poor compliance during treatment, with potential risk of medical disputes.

(6) withdraw informed consent.

(7) subjects are lost to visit.

(8) other reasons, such as major protocol violations confirmed by the researcher, occurred during the study.

5.2.5 Follow-up after radical prostatectomy

Postoperative follow-up nodes of the three groups were 4 weeks postoperative, 8 weeks postoperative, 12 weeks postoperative and 6 months postoperative. Necessary laboratory and imaging examinations were performed to determine the curative effect of surgery and the prognosis of treatment.

Six months after the operation, the follow-up period of the patients was adjusted to 3 months. At least one imaging examination and four PSA examinations (each interval of more than 2 months) shall be conducted in our hospital every year.

5.3 Principles of management of adverse reactions during neoadjuvant therapy

5.3.1 General principles of management of adverse reactions to chemotherapy drugs

Adverse event classification	Management of adverse events	Drug adjustment
Grade 1-2	The researchers made their own decisions about the treatment	No reduction or adjustment based on the researcher's experience
Grade 3 or above	The researchers made their own decisions about the treatment	In the first case of grade 3 or above toxicity, the patient was given symptomatic treatment after 1 week of delayed chemotherapy. In the case of recurrence, the patient was treated with symptomatic treatment for 1 week after reprieve of chemotherapy, and the drug was restored to 50mg/m^2 when the toxicity level was no more than 1 If reappeared, the chemotherapy was terminated, symptomatic treatment was given, and the surgery was assessed by direct imaging.

5.3.2 General principles for the management of adverse drug reactions in endocrine therapy

Common adverse reactions such as castration syndrome and male breast development require no special treatment. If liver toxicity occurs, symptomatic treatment is required. The treatment principles are as follows.

Adverse event classification	Management of adverse events	Drug adjustment
Grade 1-2	The researchers made their own decisions about the treatment	No dosage reduction, oral or intravenous hepatoprotective therapy is required
Grade 3 or above	The researchers made their own decisions about the treatment	If the transaminase is more than 2 times the normal value, the anti-male drug will be discontinued, the castrated drug alone will be combined with chemotherapy, and the oral or intravenous

		hepatoprotective drug will be treated until the transaminase decreases to 1.5uln.

For patients with bone pain, a bone scan or magnetic resonance imaging (MRI) is needed to identify pain caused by new metastases or osteoporosis caused by drugs. Combination therapy with bisphosphonate is allowed.

5.4 Surgical treatment and postoperative adjuvant therapy

Radical prostatectomy (RP) is one of the most effective methods to cure localized prostate cancer. The main operative methods included in this study were: open transcranial retropubic radical prostatectomy, laparoscopic radical prostatectomy and robot-assisted laparoscopic radical prostatectomy.

Extended pelvic lymph node dissection, which covers bilateral obturator lymph nodes, external iliac nodes, internal iliac nodes, general iliac nodes, including or excluding anterior sacral nodes.

According to the actual situation, if the scope of surgery is expanded but the tumor is finally removed, including not only total cystectomy, partial cystectomy, ureteral bladder replantation, colorectal bowel segment resection and colonic ostomy, etc. are also included in this study.

Surgical evaluation will be performed at least twice, at the screening stage and at the end of the third cycle of neoadjuvant therapy. Preoperative evaluation should take into account the level of risk factors for tumors, life expectancy and overall health status.

5.4.1 Surgical indications

(1) imaging showed that the tumor could be completely excised, and there was no evidence of distant lymph node metastasis (diagnosed preoperatively by imaging or lymphatic biopsy), bone metastasis or other viscera metastasis, and no other tumors were combined.

(2) good treatment compliance and adequate understanding and preparation for surgical treatment and complications.

(3) health status: the physical status score of the eastern cancer cooperative group (ECOG) is no more than 1, and the life expectancy is no more than 10 years. After neoadjuvant treatment, the patient was in good condition and the results of laboratory examination were still qualified for inclusion.

5.4.2 Surgical contraindication

(1) patients with diseases that significantly increase the risk of surgery, such as serious cardiovascular diseases and pulmonary dysfunction.

(2) suffering from severe bleeding tendency or coagulation disorder.

(3) there are distant lymph node metastases (diagnosed preoperatively by imaging or lymphatic biopsy), bone metastases, other viscera metastases, or other tumors.

(4) the fitness score of the eastern cancer cooperative group (ECOG) was greater than or equal to grade 2, or the life expectancy was less than 10 years.

5.4.3 Postoperative adjuvant therapy

The postoperative adjuvant treatment was determined according to the postoperative pathology. The details are as follows:

(1) if the postoperative pathological cutting edge is positive, remedial external radiotherapy shall be performed immediately after the recovery of urinary incontinence.

(2) no matter the postoperative pathological stage, lymph node metastasis, seminal vesicle and Vas deferens invasion, postoperative positive observation was adopted and auxiliary drug was discontinued.12 weeks after the operation, if the patient has biochemical recurrence or the postoperative PSA fails to reach the radical treatment level (PSA>, 0.2ng/ml), the endocrine therapy is started (accompanied by castration therapy combined with anti-androgen therapy).

5.5 Treatment compliance

Four days before the end of each cycle, the subjects were evaluated in sequence. In addition to suspension due to drug toxicity, if the subject takes prednisolone acetate and Bicalutamide tablets for two consecutive drug cycles, the compliance is no more than 75%;Or adherence to a medication cycle is no more than 75%;Or the patient refused or delayed docetaxel chemotherapy more than 2 times, then the subjects will stop participating in the clinical trial, complete the treatment termination visit within the specified time limit, and enter the survival follow-up. Subject's medication compliance is determined by drug count combined with inquiry, and test medication compliance = (total number of prescriptions used/total number of drugs to be prescribed) x l00%.

5.6 Rules for combine medication

From the beginning of the incorporation of clinical trials, all the combined drugs need to be recorded during the observation period, and the study program stipulates that the combination of Estracyt, prednisolone acetate tablets and Bicalutamide tablets are not included in this program. The cutoff time for the combined medication was 28 days after the last administration of the study drug. If there is combined therapy due to adverse events, it is necessary to record the disappearance of adverse events or the stable state considered by the researcher.

5.6.1 Combination medication allowed for use

Patients who cannot tolerate bicalutamide can switch to another generation of anti-male drugs, such as flutamide.

Conventional vitamin formulation;

On the day of chemotherapy, systemic glucocorticoid, highly selective 5-HT3 receptor antagonist antiemetic, prolactin or antacids, bisphosphonates, immune modulators and hepatoprotective agents are allowed.

Use bisphosphonates orally or intravenously;

Oral liver protection drugs;

Oral selective α blockers, such as doxazosin mesylate, tamsulosin hydrochloride, etc.

Blood transfusion and hematopoietic growth factor;

Short or long term recombinant human granulocyte stimulating factor;

If the body is combined with other diseases, it can be used on demand without violating the following prohibition.

5.6.2 prohibited drugs

Other chemotherapy drugs;

Other anti-androgenic drugs: Nilutamide, methadone acetate, cyproterone acetate, estradiol valerate, Enzalutamide, abiraterone;

Immunotherapy drugs;

Chinese traditional medicine with anticancer indications;

Ketoconazole;

5 α - reductase inhibitor;

Diethylstilbestrol, and Chinese herbal medicine containing estrogen;

Radioactive drugs such as strontium (89Sr), samarium (153Sm) and radium (223Ra);

Coumarin anticoagulants such as warfarin: competing with bicalutamide protein binding sites, resulting in abnormal prothrombin time;

Pomegranate juice: may affect the stability of prostate specific antigen;

Linseed oil: has the estrogen activity and the anti-androgen function; Potentially reduces the role of potassium in blood.

5.7 Study conditions and treatment of termination

Termination of the clinical study if either of the following occurs to the subject:

(1) the disease progression of prostate cancer (annex 2), or castration-resistant prostate cancer, is no longer suitable for continuing the current treatment. Special note: in the neoadjuvant drug cycle, if PSA alone is elevated but no imaging progress, this condition is not a disease progression.

(2) start new anticancer therapies, such as second-line endocrine therapy (enzalutamide, abiraterone, etc.), radiotherapy, change of chemotherapy regimens, and immunotherapy.

(3) the use of the study drug will be terminated after the inadmissibility of drug toxicity or other adverse events are confirmed by the researcher.

(4) poor compliance during treatment, with potential risk of medical disputes.

(5) withdraw informed consent.

(6) subjects are lost to visit.

(7) other reasons, such as major protocol violations confirmed by the researcher, occurred during the study.

After termination of the study, subjects will enter the stage of survival follow-up after completing all examinations for treatment termination visits.

Definition of treatment termination visits: subjects who have terminated neoadjuvant therapy for any reason or have not received surgical treatment shall complete the relevant clinical and laboratory evaluation within 28 days after the last neoadjuvant treatment.

5.8 Patients requiring changing the treatment group

In this study plan, patients in the control group and experimental group were required to change the treatment group, that is, neoadjuvant endocrine therapy patients were required to combine with chemotherapy, or neoadjuvant endocrine therapy combined with chemotherapy group were required to stop chemotherapy. Both are deemed to have withdrawn the informed consent. Follow-up treatment, including neoadjuvant and surgical treatment, will be performed clinically on a case-by-case basis, but this data will not be included in the trial statistics.

6 Observation indicators and observation time points

6.1 Relevant time Windows

The time window of the screening period was 28 days before the first use of the study drug.

During the neoadjuvant treatment period, each visit window was + / - 2 days (except the time window of each imaging examination and ECG examination was + / - 4 days).

The time window from neoadjuvant treatment to surgical treatment is 3 months.

In patients who were followed up after the operative treatment period, the time window of outpatient visit was + / - 7 days.

6.2 Demographic and general clinical data

Including the age, gender, height and ethnicity of the subjects; Medical history, previous treatment history, associated diseases and medication. This class of data is recorded once during the filter period.

Prior treatment for prostate cancer/prostate cancer before screening should be traced back to 6 months before prostate biopsy.

A copy of the most recent histological or cytological diagnostic report of prostate cancer will be provided as a diagnostic document.

6.3 Screening indicators

The following indexes are tested only once during the screening period:

Hepatitis b surface antigen (HbsAg), anti-hcv, HIV antibody;

Chest CT or MRI;

Echocardiogram;

Paclitaxel gene detection before chemotherapy is recommended for patients in the experimental group.

6.4 Efficacy indicators and efficacy evaluation criteria

6.4.1 Efficacy indicators

(1) Serum prostate specific antigen (PSA): before prostate biopsy, screening period after prostate biopsy, 2-4 day, before the end of each cycle of neoadjuvant treatment period, 1 day before surgery, 4 weeks after surgery, 8 Weeks, 12 weeks, 3 months, and 6 months, each subsequent follow-up visit should be performed once. In particular, if the subject is to undergo a digital rectal examination, the blood sample collection of the PSA should be performed prior to the digital rectal examination.

(2) Overall survival of the patient (OS): OS is starts from the neoadjuvant therapy to death for any reasons, and the time of the last time the lost participant was contacted was censored data. For subjects who discontinue treatment for various reasons, the investigator

should call the subject once every 3 months to obtain information on overall survival, with the total survival follow-up stopped at 24 months after last patient enrollment.

(3) CT (or MRI), bone scan or PET-CT: during the screening period, every 3 cycles during the neoadjuvant treatment period, before surgery, every six months after surgery. PET-CT examination can replace CT/MRI and bone scan. During the neoadjuvant treatment, if a metastasis is observed by bone scan, it will take at least 6 weeks to confirm with a bone scan. One can be checked by CT or MRI. The imaging assessment is valid for 28 days and does not need to be repeated. It can be done before the date of the informed consent form signed by the subject, but to ensure that the relevant examination is traceable and effective.

(4) Relevant quality of life scores: including:

a. ECOG fitness status,

b. Pain Scale (BPI-SF),

c. Analgesic use score,

d. Quality of Life Scale (FACT-P).

The three indicators a, b, and c were examined at the end of each screening period and before the surgical treatment in the screening period and neoadjuvant treatment period. The d item (FACT-P) is in the screening period, every 2 cycles of the neoadjuvant treatment period, and before the surgical treatment.

6.4.2 Evaluation criteria for efficacy

6.4.2.1 Main efficacy evaluation (primary endpoint)

Biochemical recurrence-free survival (bPFS): defined as the time from randomization to biochemical recurrence. The definition of biochemical recurrence is as follows: in the case of normal testosterone levels, the PSA was >0.2 ng/ml twice for more than 4 consecutive weeks.

6.4.2.2 Secondary efficacy assessment (secondary endpoints)

(1) The 1-year biochemical progression-free survival (bPFS) rate: the ratio of patients whose consecutive postoperative PSA ＜0.2ng/ml within 1-year.

(2) Overall survival (OS): the time from randomization to death due to all causes.

(3) Radiographic progression-free survival (rPFS): the time from randomization to first confirmed imaging progression or death (whichever first is counted). Imaging progression was defined as one of the following: a. Progression of soft tissue lesions as defined in the

revised RECIST 1.1 (Appendix 8) found by CT or MRI. b. Confirmation of bone metastasis lesions by ECT or PET-CT examination.

(4) TTPP: the time from randomization to the time when PSA increased by 25%.

(6) ECOG score progression-free survival: the time from treatment to the time of ECOG score progression.

6.5 Safety indicators

6.5.1 General physical examination indexes

Respiratory rate, pulse rate, blood pressure, body temperature and body weight.

Tested at the time of screening, the end of each cycle of neoadjuvant therapy (every 21 days in the experimental group, 28 days in the control group), 1 day before surgery, and 4 weeks after surgery.

6.5.2 Clinical symptom examination

During the study, the investigator should promptly record the symptoms such as nausea, fatigue, back pain, and cough, and record them in the adverse event tables timely.

6.5.3 Laboratory safety indicators related to neoadjuvant therapy

Complete blood count: red cell count, hemoglobin, platelet count, and white cell count. Tested at the time of screening, during each cycle of neoadjuvant therapy (the 5th, 10th, and 20th days of the experimental group, every 28 days in the control group), 1 day before surgery, and 4 weeks after surgery.

Urine routine: urine sugar, urine protein, urinary red cell count, white cell count. Tested at the time of screening, the end of each cycle of neoadjuvant therapy (every 21 days in the experimental group, 28 days in the control group), 1 day before surgery, and 4 weeks after surgery.

Liver function, renal function and blood electrolytes: ALT, AST, GGT, TBIL, DBIL, AKP, LDH, albumin, total protein, urea nitrogen, serum creatinine, uric acid, potassium, sodium, chlorine. Tested at the time of screening, the end of each cycle of neoadjuvant therapy (every 21 days in the experimental group, 28 days in the control group), 1 day before surgery, and 4 weeks after surgery.

Blood lipids and blood sugar: triglycerides, cholesterol, high-density lipoprotein, low-density lipoprotein, fasting blood sugar. Tested at the time of screening, 1 day before surgery, and 4 weeks after surgery.

Note: The date of the laboratory screening test should be ⩽ 14 days from the start of the neoadjuvant medication.

6.5.4 Electrocardiogram

Electrocardiogram (12-lead): Recorded at the time of screening period, 1 day before surgery, and half a year after surgery. If necessary, add an ECG test. When the blood potassium concentration is <3.5mmol/L, the electrocardiogram should not be performed. The hypokalemia should be corrected before the electrocardiogram performed.

6.5.5 Chemotherapy related complications

For the patients who received 75 mg/m^2 of docetaxel alone, the response was described according to the NCI General Toxicity Criteria (Grade 3 = G3, Grade 3-4 = G3/4; Grade 4 = G4) and COSTART terminology. The frequency is defined as: very common (1/10), common (1/100-1/10); uncommon (1/1000-1/100); rare (1/10000-1/1000); rare (< 1/10000). The report is as follows:

Hematologic abnormalities: bone marrow suppression and other hematological adverse reactions.

Very common: neutropenia (89.8%; G4: 54.2%); anemia (93.3%; G3/4: 10.8%); infection (10.7%; G3/4: 5%); thrombocytopenia (10%; G4: 1.7%).

Common: febrile neutropenia (6.2%).

Abnormal immune system: Most of the allergic reactions occur in the first few minutes of docetaxel infusion, usually mild to moderate. The most commonly reported symptoms are erythema and rash with or without itching, chest tightness, back pain, difficulty breathing, and drug-induced fever or chills. Severe reactions include hypotension and/or bronchospasm or systemic rash/erythema, which can be resumed after stopping the infusion and symptomatic treatment.

Common (2.5%, no serious reaction)

Abnormal skin and subcutaneous tissue: The skin reaction is usually mild to moderate and reversible, often manifested as a local rash that is mainly found in the hands, feet, arms, face, or chest, often accompanied by itching. The rash occurs mostly within a week after infusion of docetaxel. Less common severe symptoms is severe rash that causes disturbance or discontinuation of docetaxel treatment followed by peeling. Severe nail lesion is characterized by hyperpigmentation or hypopigmentation, sometimes causes pain and nail loss.

Very common: hair loss (38%); skin reaction (15.7%; G3/4: 0.8%).

Common: nail changes (9.9%; severe 0.8%).

Body fluid retention: such as peripheral edema, there are a few reports of pleural effusion, pericardial effusion, ascites and weight gain. Peripheral edema usually begins at the lower limb and may progress to the whole body with a weight gain of 3 kg or more. The incidence and extent of body fluid retention can be accumulated.

Very common (24.8%; weighed 0.8%).

Gastrointestinal discomfort:

Very common: nausea (28.9%; G3/4: 3.3%); stomatitis (24.8%; G3/4: 1.7%); vomiting (16.5%; G3/4: 0.8%); diarrhea (11.6%; G3/ 4:1.7%).

Common: constipation (6.6%).

Abnormal nervous system: When severe peripheral neurotoxic symptoms occur, the dose of docetaxel should be reduced. Mild to moderate sensory neuropathy includes paresthesia, sensory disturbances or pain including burning pain. The main motor neurological event is weakness.

Very common: sensory neurological symptoms (24%; G3: 0.8%).

Common: motor neurological events (9.9%; G3/4: 2.5%).

Abnormal heart:

Common: arrhythmia (2.5%; no severe events); hypotension (1.7%).

Abnormal hepatobiliary system:

Common: bilirubin increased (G3/4 <2%).

Metabolic and nutritional abnormalities:

Very common: anorexia (19%).

Ocular abnormalities: transient visual impairments (sparkling, flashing, blind spots) are rarely reported, especially when the drug is infused intravenously with an allergic reaction. It can be reversed after stopping the infusion. Tears with or without conjunctivitis, tear duct obstruction due to excessive tearing are rarely reported.

Ear and labyrinth abnormalities: Other ototoxic drugs related ototoxicity, hearing abnormalities, and/or hearing loss are rarely reported.

Musculoskeletal, connective tissue and bone abnormalities:

Common: myalgia (5.8%).

Respiratory, thoracic and mediastinal abnormalities:

Very common: difficulty breathing (16.1%; severe 2.7%).

Whole body and injection site abnormalities:

Very common: weak (48.8%; severe 12.4%); pain (10.7%).

6.5.6 Surgery related complications

Perioperative complications (7 days before surgery to 28 days after surgery): hemorrhage, anastomotic leakage, obturator nerve injury, iliac vascular injury, lymphocystosis, deep vein thrombosis, pulmonary embolism, infection, cardiovascular complications and other related or unrelated complications. Recorded timely and reported as required.

Long-term complications: erectile dysfunction, urinary incontinence, anastomotic stricture, and pseudo-dwelling.

6.5.7 Other adverse events and serious adverse events

Record Instantly and reported as required.

7. Adverse events

7.1 Adverse events definitions

Adverse events: Any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

Serious adverse events: any untoward medical occurrence that, at any dose: result in death; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent disability/incapacity; is a congenital anomaly/birth defect; or is considered an important medical event.

Adverse reactions: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. “Responses to a medicinal product” means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.

7.2 Recording and handling of adverse events

The investigator should observe any adverse events that occur during the clinical trial of the subjects and ask the patients to truthfully reflect the disease changes after treatment and avoid inducing questions. The investigator should observe adverse effects or

unexpected clinical manifestations and side effects (including symptoms, signs, and laboratory tests) while observing the effects. Regardless of the relevance of adverse event and study intervention , it should be recorded in the CRF, including the time, symptoms, signs, degree, duration, laboratory test indicators, treatment methods, development process, results, follow-up time, etc. of the adverse event. Meanwhile, the concomitant medication should be detailed recorded to analyze the association of adverse events with study procedures and study medications, and signed and dated are needed.

All AE and SAE will be collected from the date of signed the informed consent until the end of study. Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor or designate.

Medical treatment of the subjects: When an adverse reaction occurs, the investigator should take necessary treatments according to the condition, such as surgical intervention, adjustment of chemotherapy dose, temporary interruption of treatment, etc., and decide whether to terminate the study drug. When a serious adverse event occurs immediate treatment should be taken to protect the safety of the subject.

7.3 Classification of adverse events

All AEs are graded using NCI's CTCAE standard (CTCAE V5.0).

If an adverse event is not covered by the CTCAE standard, it is recorded according to the following criteria:

(1) Mild: Does not affect the normal function of the participants, causing minimal discomfort and not interfering with everyday activities.

(2) Moderate: Affects the normal function of the subject to some extent, causing sufficient discomfort, and interferes with normal everyday activities.

(3) Severe: Significantly affects the normal function of the subject, preventing normal everyday activities.

Pay attention to the severity and intensity of adverse events. When the intensity of adverse event is severe, it may not be SAE. For example, a severe headache in intensity may not be included in the SAE unless it meets the SAE criteria.

7.4 Evaluation of causality between adverse events and study drugs/study procedures

Researchers should make full use of their medical knowledge and clinical experience to comprehensively analyze when reporting adverse events. During the evaluation, the reporter should first understand the patient's treatment and various examination data, ask the patient's medication history to prevent the omission of suspicious drugs or medical behavior, and initially find the association between adverse events and study drugs/study procedures.

The analysis methods of adverse events used in China mainly follow the following five principles:

1. Is there a reasonable time relationship between study drugs/study procedures and the occurrence of adverse events?

For example, it takes only a few seconds for cyanide poisoning to die; anaphylactic shock or death caused by penicillin occurs several minutes to several hours after administration; phenothiazine-induced liver damage usually occurs after 3-4 weeks of taking the drug.

2. Does it meet the type of adverse reactions known in clinical trials?

For example, docetaxel chemotherapy can cause bone marrow suppression and liver damage; endocrine therapy can lead to osteoporosis, breast pain and so on.

3. Does the reaction disappear or reduce after adjusting the medication or changing the treatment plan?

4. When the suspicious drug or clinical operation is resumed again, does the same reaction event occur again?

5. Whether the reaction events can be explained by the effects of combined medication, the progression of the patient's condition, and the effects of other treatments?

Under the premise of consulting the reference literatures and analyzing the relevant information of the report, the adverse events will be evaluated as required. For serious adverse events or adverse events with difficult evaluation, the relevant experts can be consulted; if necessary, an expert discussion will be held, among which difficult cases will be re-evaluated. According to the five principles of adverse event analysis, the relevance evaluation is divided into six levels: affirmative, very likely, possible, possibly irrelevant, to be evaluated, and unevaluable.

Affirmation: The adverse reactions occurs reasonably in the time; the response stops or rapidly reduces or improves after discontinuation of treatment (some ADR responses may occur after several days depending on the body's immune status); the response reappears after re-use, and may be significantly aggravated (ie, the positive re-priming test); at the same time, there is literature evidence; and other confounding factors such as the original disease have been excluded.

Very likely: no repeated exposure history, the rest is the same with "affirmation ", or although there is a combination of drugs, the possibility of combined use of drugs to cause the reaction can be ruled out basically.

Possibly: The clinical trial is closely related to the time of occurrence of the reaction, and there is literature supported; however, there is more than one drug that causes ADR, or the progression of the original disease cannot be excluded.

Possibly irrelevant: ADR is not closely related to the clinical trial, and the response is not consistent with the known ADR of the drug. The progression of the original disease may also develop similar clinical manifestations.

To be evaluated: the content of the report is not completed, the supplement and then evaluation are wanted, or the causal relationship is difficult to determine, and literatures and evidence are insufficient.

Unevaluable: There are too many missing items in the report, the causal relationship is difficult to determine, and the information cannot be supplemented.

Detailed description is in the table below.

	1	2	3	4	5
Affirmation	+	+	+	-	-
Very likely	+	+	+	?	-
Possibly	+	±	±?	?	±?
Possibly irrelevant	-	-	±?	?	±?
To be evaluated	Additional materials needed				
Unevaluable	The necessary information for the evaluation is unavailable				

Note: + affirmation; - negation; ± hard to be affirmative or negative; ? unknown.

7.5 Serious adverse events reporting

Any serious adverse events that occur during the clinical trial, should be promptly dealt with and reported to the Sponsor or designee and the ethics committee responsible for the clinical trial within 24 hours, Regardless of the relevance of serious adverse events and clinical trial. The investigator should quickly investigate the serious adverse events and take some necessary measures to ensure the safety and rights of subjects, and timely report to the departments of management and health administration. The investigator should bear

the cost of rescue, treatment and give the corresponding economic compensation if the serious adverse event is determined to be related to clinical trial.

The investigator must complete the “Serious Adverse Event Report Form” and record when, how, and to whom the serious adverse event was reported in the original data.

7.6 Follow-up of unresolved adverse events

All adverse events (including adverse drug reactions) that have not been fully resolved at the end of the course of treatment should be followed up to time of proper resolution or stable condition.

8. Data management

8.1 Requirements of filling the clinical trial observation form

The investigator should carefully fill the case record. The outpatient medical records at the time of follow-up shall be used as the original records and shall not be altered. The original records shall not be altered during other corrections, and only the additional narratives can be used to explain the reasons and be signed and dated by the physician participating in the clinical trial. All the laboratory data in the clinical trial should be recorded.

8.2 Data traceability

The outpatient medical records of all the tested cases, whether they are in accordance with the clinical trial plan or the cases of shedding, should be written timely, completely and accurately, and the laboratory and examination records can be traced to the hospital CIS system and imaging system. For the subject whose examinations were performed in other hospitals, a copy of the patient's relevant medical record to be retained is needed, and the original image archive is available for imaging.

8.3 Filling the case report form

The data in the case report form are derived from the outpatient medical record and are filled in by the investigator. The case report form must be filled in for each case. The various data or descriptions recorded in the case report form should be checked with the original records and test reports in the research medical records. The researcher performs data entry and management based on the case report.

8.4 Data entry

Data entry and management is the responsibility of the designated researcher. Data administrators use Excel software for data entry and management. To ensure the data accuracy, the enrollment/exclusion criteria, integrity, logical consistency, outlier data, time window, combined drug, adverse event, etc. are checked again, after all the case report forms have been inputed and verified.

9. Statistical Analysis

9.1 Analytical data set

Full Analysis Set (FAS): All subjects that have received neoadjuvant therapy after randomization.

Per Protocol Set (PPS): a subset of FAS, all the subjects that meet the test protocol and have good compliance (the actual use of neoadjuvant drugs accounts for 80%-120% of the applied dose), and successfully complete the radical surgery and 3 months outpatient follow-up after surgery, the entire clinical observation and the contents of CRF.

Safety Analysis Set (SAS): all the subjects with at least one safety assessment after randomization and neoadjuvant therapy.

In this trial, baseline data are analyzed using FAS. The primary and secondary efficacy indicators are analyzed by FAS and PPS simultaneously. However, the conclusions are from the FAS analysis. When the conclusions obtained by FAS and PPS are consistent, the credibility of the conclusion can be increased.

In the safety analysis, adverse events and adverse reaction data, vital signs, and laboratory indicators are analyzed by SAS. Subjects who are prematurely terminated due to adverse events and various non-therapeutic reasons are included in the safety analysis.

9.2 Statistical methods

Statistical analysis was carried out using SPSS. All the statistical tests were two-sided. Differences were considered to be statistically significant if $p < 0.05$. 95 % confidence interval (CI) were computed.

Baseline data were analyzed by FAS. All efficacy indicators were analyzed according to FAS and PPS; the safety analysis used SAS.

- Effectiveness analysis:

For the primary endpoint bPFS, The survival curves will be estimated using Kaplan-Meier estimates: cumulative incidence of events at 6 months and by year, and appropriate confidence interval will be presented by treatment arm using Kaplan-Meier estimates.

Kaplan-Meier curves will be displayed by treatment arm. The Log-Rank test is used to compare the survival indicators of three groups.

For the secondary endpoint

(1) First year biochemical progression-free survival rate: cumulative incidence of events at one year will be presented by treatment arm using Kaplan-Meier estimates. The χ2 test or Fisher's exact test is used to compared the biochemical progression-free survival rate of subjects.

(2) Overall survival (OS)

(3)No imaging progression survival period (rPFS)

(4)TTPP

(5)Symptomatic progression occurred through the Quality of Life Assessment Scale (FACT-P) score.

(6) The ECOG score indicates the time when the subject's physical condition deteriorated.

All the above time to events secondary endpoint will use the same statistical methods as primary endpoint.

- Safety analysis: Descriptive statistical analysis is the main method. The AEs that occurred in this clinical trial are described in the list. If necessary, Fisher's exact test method is used to compare the incidence of AEs between groups. Laboratory test results that are normal pre-test but abnormal post-treatment and the relationship with the test drug should be descriptive statistical analysis.

10. Quality control and assurance of clinical trial

In the course of this study, the personnel participating in the clinical trial is relatively fixed. The clinical trial plan and clinical trial manual must be carefully studied and discussed, and the recording methods and judgment criteria should be unified.

Researchers should use the pen or carbon pen to fill in the CRF in a realistic, detailed and serious manner.

All observations and findings in clinical trial should be verified to ensure the data reliability and to ensure that conclusions of clinical trial are derived from raw data. There are corresponding data management measures in the clinical trial and data processing stages.

Outpatient medical records are the original records and cannot be changed generally. The original records shall not be altered during other corrections, and only the additional

narratives can be used to explain the reasons and be signed and dated by the physician participating in the clinical trial.

Researchers should take active measures (such as notification of follow-up) to control the case drop rate within 20%.

In order to ensure the compliance of subjects, researchers should make the subjects fully understand the significance of the trial and the importance of neoadjuvant therapy. The researchers shall record the medication on the outpatient medical record. Those who do not fully follow the requirements should be persuaded in time and the reasons should be recorded in detail.

Laboratory data should be recorded in the CRF and can be traced to the hospital's CIS system and imaging system. For the subject whose examinations were performed in other hospitals, a copy of the patient's relevant medical record to be retained is needed, and the original image archive is available for imaging.

11. Ethical principles

Before the clinical trial begins, the trial protocol (ie, the program) discussed, revised, and signed by the investigator must be submitted to the ethics committee for approval. If the program has problems during the actual implementation of the clinical trial, and needs to be revised, it should be re-submitted to the ethics committee for approval. If new information related to clinical research is found, the informed consent form must be modified in writing and sent to the ethics committee for approval. After that, the subject's consent should be obtained again.

Before the start of the clinical trial, the investigator must provide the subject with details about the clinical trial, including the nature and purpose of the trial, the possible benefits and risks, alternative treatment options, and the subject's rights and obligations that are compliance with the Helsinki Declaration, etc, to enable the subject and his legal representatives to fully understand and agree to and sign the informed consent form before starting clinical trial. Each patient should leave a detailed contact address, telephone number, ID card, etc., and the doctor should leave his contact number to the patient so that the patient can find the doctor at any time when the condition changes, which is also helpful for the doctor to understand the condition changes, remind the subject to return to hospital in time to avoid loss of follow-up.

Throughout the study period, the researchers in our center strictly protect the rights of each subject in accordance with the GCP requirements and the Helsinki Declaration. The specific implementation method is leaving the contact number of ourselves and the second researcher (24 hours remain unblocked) to the patients and their guardians, in addition, the research team is equipped with a dedicated call system, each member has a short call

number to ensure that the subject contacts his or her supervisor in case of any discomfort. It also ensures that the investigator is fully aware of the subject's condition throughout the study period.

12. Data preservation

According to GCP regulations, research medical records are archived as raw materials. After the data input are completed, the investigator saved them 5 years after the end of the clinical trial.

13. Modification of the trial

After the program has been approved by the ethics committee, the main researcher should write a “program modification manual” and sign it, if it needs to be revised during the implementation process, and the program may be modified after the agreement of the sponsor.

After the plan is revised, it must be approved by the ethics committee before implementation.

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Appendix 1 Prostate Cancer Clinical Trials Working Group (PCWG2) Standards

Excerpted from “Design and End Points of Clinical Trials for Patients With Progressive Prostate Cancer and Castrate Levels of Testosterone: Recommendations of the Prostate Cancer Clinical Trials Working Group” published by Scher et al at 2008.

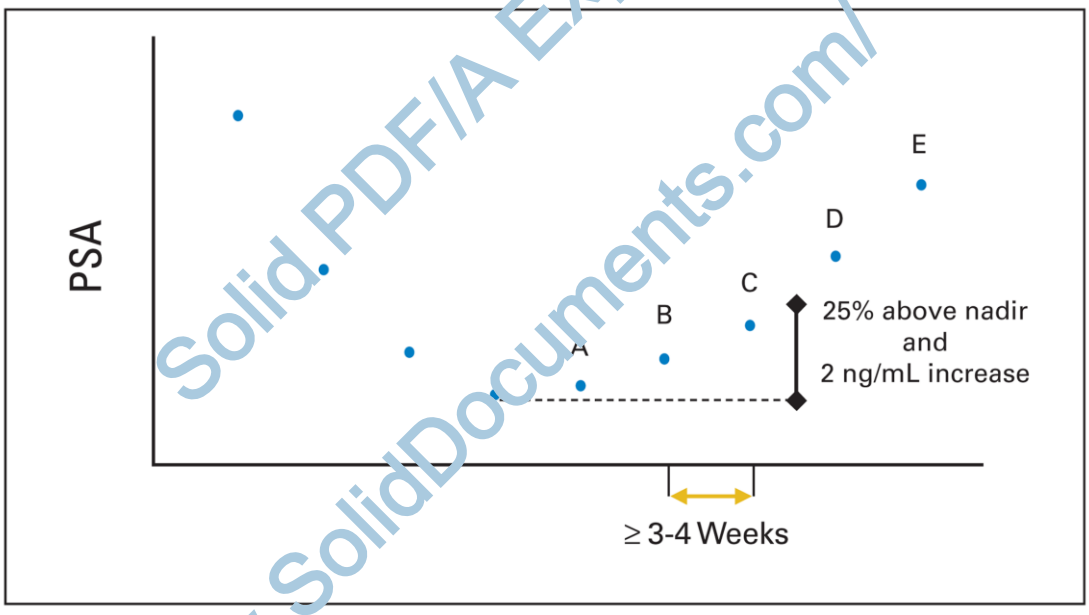
Journal of Clinical Oncology 2008; (26), 1148-1159.

Screening period: high-risk or locally advanced prostate cancer

Patients should meet one or more of the following three criteria: PSA > 20 ng / ml, Gleason score(GS) 8-10, clinical stage ≥ T3a.

Follow-up period: The criteria used for efficacy judgment during the study observation stages:

Early changes in PSA should not be used as the basis for developing the clinical trial protocol. PSWG2 defines PSA progression as a 25% or greater increase and an absolute increase of 2 ng/mL or more from the nadir, which is confirmed by a second value obtained 3 or more weeks later (as shown below).



Schematic illustration: Prostate-specific antigen (PSA) progression. An increase of 25% and absolute increase of 2 ng/mL or more above the nadir. Values A, B, and C show rising PSA values that do not meet the criteria. Value D is the first PSA value that is greater than 25% and more than 2 ng/mL above the nadir, confirmed with a further rise in PSA shown by value E. For reporting purposes, PSA progression would be recorded on the date value D was obtained.

Appendix 2 Prostate Cancer Progression Standards

After treatment, subjects who meet any of the following criteria will be identified as disease progression:

1.PSA progression as determined by the PCWG2 standards.

2.Progression in imaging.

3.Clinical progression.

Definition of progression:

● Prostate specific antigen progression:

See " The criteria used for efficacy judgment during the study observation stages " of Annex 1

● Progression in imaging, at least one of the followings:

1. Bone scan showed disease progression, new lesions appeared and did not meet tumor flare, and was confirmed in the second bone scan after ≥6 weeks, this bone scan showed ≥1 additional new lesions;

2.Compliance with soft tissue (lymphatic or visceral) disease progression as defined by the modified RECIST criteria (baseline lymph nodes must be ≥ 2.0 cm to be considered as target lesions or evaluable lesions)

● Clinical progression, meeting any of the followings:

1. Pain progression: Aggravation of pain due to metastatic bone disease, which was observed in two consecutive evaluations 4 weeks apart, refers to that the most severe pain score is increased by ≥30% based on the Concise Pain Questionnaire in the past 24 hours in the case of an undecreased analgesic drug score, or an increase in analgesic use scores of ≥30% is observed in two consecutive assessments 4 weeks apart, and the subject's brief pain questionnaire score must be ≥4.

2. Skeletal-related events: pathological fractures, spinal cord compression, bone palliative radiotherapy, or bone surgery associated with progression of prostate cancer in the bone.

3. Increase the prednisone dose or replace with a more potent glucocorticoid such as dexamethasone, or add opioid analgesics to treat prostate cancer related symptoms and signs, such as pain and fatigue.

4. Therapist decides to start a new systemic anticancer treatment (whether or not there is evidence of PSA or imaging disease progression.

Appendix 3 Physical Status (ECOG PS) Scoring Criteria

0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead.

Appendix 4 The New York Heart Association (NYHA) Functional Classification

The heart function is generally divided into four levels, and the heart failure is divided into three degrees (slightly added according to the NYHA classification).

Level I: No symptoms and no limitation in ordinary physical activity, e.g. no shortness of breath when walking, climbing stairs etc.

Level II: Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.

Level III: Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m).Comfortable only at rest.

Level IV: Severe limitations. Experiences symptoms even while *at rest*. Mostly bedbound patients.

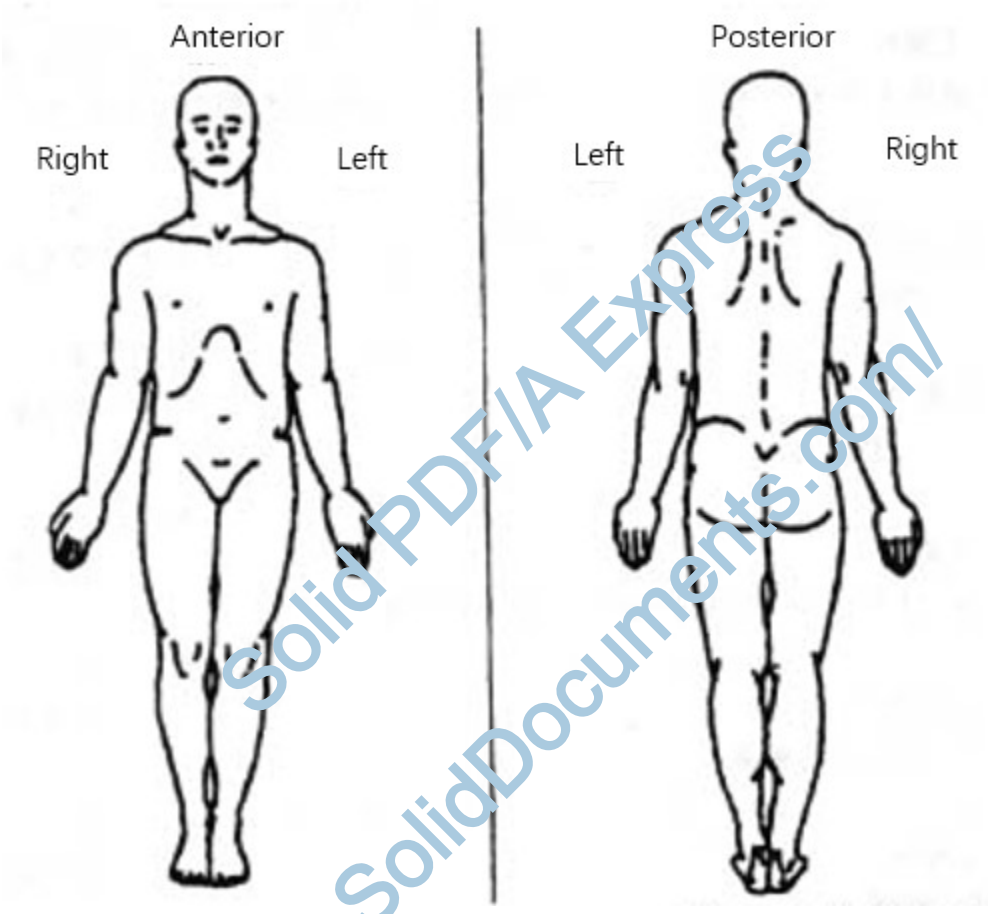
Appendix 5 Brief pain inventory

Brief pain inventory (BPI)

1.Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every- day kinds of pain today?

(1) Yes (2) No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

(No Pain)0 1 2 3 4 5 6 7 8 9 10(as bad as Pain you can imagine)

4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.

(No Pain)0 1 2 3 4 5 6 7 8 9 10(as bad as Pain you can imagine)

5. Please rate your pain by circling the one number that best describes your pain on the average.

(No Pain)0 1 2 3 4 5 6 7 8 9 10(as bad as Pain you can imagine)

6. Please rate your pain by circling the one number that tells how much pain you have right now.

(No Pain)0 1 2 3 4 5 6 7 8 9 10(as bad as Pain you can imagine)

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

（ No Relief）0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%（Complete Relief）

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with you:

A. General Activity

(Not affected)0 1 2 3 4 5 6 7 8 9 10(Completely affected)

B. Mood

(Not affected)0 1 2 3 4 5 6 7 8 9 10(Completely affected)

C. Walking Ability

(Not affected)0 1 2 3 4 5 6 7 8 9 10(Completely affected)

D. Normal Work (includes both working outside home and housework)

(Not affected)0 1 2 3 4 5 6 7 8 9 10(Completely affected)

E. Relations with other people

(Not affected)0 1 2 3 4 5 6 7 8 9 10(Completely affected)

F. Sleep

(Not affected)0 1 2 3 4 5 6 7 8 9 10(Completely affected)

G. Enjoyment of life

(Not affected)0 1 2 3 4 5 6 7 8 9 10(Completely affected)

Appendix 6 Analgesic Usage Score

According to the WHO pain level grading ladder

0: Do not use analgesics

1: Non-opioid analgesics (including paracetamol, acetaminophen, antidepressants, drugs for the treatment of neuropathic pain)

2: (weak) Opioids for moderate pain

3: (weak) Strong tablets for severe pain

Appendix 7 Functional Assessment of Cancer Therapy-Prostate cancer

FACT-P (Version 4)

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days.</u>

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy.....	0	1	2	3	4
GP2	I have nausea.....	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family.....	0	1	2	3	4
GP4	I have pain.....	0	1	2	3	4
GP5	I am bothered by side effects of treatment.....	0	1	2	3	4
GP6	I feel ill.....	0	1	2	3	4
GP7	I am forced to spend time in bed.....	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends.....	0	1	2	3	4
GS2	I get emotional support from my family.....	0	1	2	3	4
GS3	I get support from my friends.....	0	1	2	3	4

GS4	My family has accepted my illness……	0	1	2	3	4
GS5	I am satisfied with family communication about my illness……	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)…… ……	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box □ and go to the next section.*					
GS7	I am satisfied with my sex life……	0	1	2	3	4

FACT-B (version 4)

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad……	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness……	0	1	2	3	4
GE3	I am losing hope in the fight against my illness……	0	1	2	3	4
GE4	I feel nervous……	0	1	2	3	4
GE5	I worry about dying……	0	1	2	3	4
GE6	I worry that my condition will get worse……	0	1	2	3	4

FUNCTIONAL WELL-BEING

		Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home).....	0	1	2	3	4
GF2	My work (include work at home) is fulfilling.....	0	1	2	3	4
GF3	I am able to enjoy life.....	0	1	2	3	4
GF4	I have accepted my illness.....	0	1	2	3	4
GF5	I am sleeping well.....	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun.....	0	1	2	3	4
GF7	I am content with the quality of my life right now.....	0	1	2	3	4

-AUT-P (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

ADDITIONAL CONCERNS

		Not at all	A little bit	Some-what	Quite a bit	Very much
C2	I am losing weight.....	0	1	2	3	4
C6	I have a good appetite.....	0	1	2	3	4
P1	I have aches and pains that bother me.....	0	1	2	3	4
P2	I have certain parts of my body where I experience pain.....	0	1	2	3	4
P3	My pain keeps me from doing things I want to do.....	0	1	2	3	4

P4	I am satisfied with my present comfort level……	0	1	2	3	4
P5	I am able to feel like a man……	0	1	2	3	4
P6	I have trouble moving my bowels……	0	1	2	3	4
P7	I have difficulty urinating……	0	1	2	3	4
BL2	I urinate more frequently than usual……	0	1	2	3	4
P8	My problems with urinating limit my activities……	0	1	2	3	4
BL5	I am able to have and maintain an erection……	0	1	2	3	4

Appendix 8 Response Evaluation Criteria in Solid Tumors(RECIST)

（RECIST Version 1.1)

Measurability of tumor at baseline

1.1. Definitions

At baseline, tumour lesions/lymph nodes will be categorized measurable or non-measurable as follows:

1.1.1. Measurable

Tumour lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10mm by CT scan (CT scan slice thickness no greater than 5 mm).
- 10mm callipers measurement by clinical exam (lesions which cannot be accurately measured with callipers should be recorded as non-measurable).
- 20mm by chest X-ray.
- Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed (see Schwartz et al. in this Special Issue15). See also notes below on 'Baseline documentation of target and non-target lesions' for information on lymph node measurement.

1.1.2. Un-measurable

All other lesions, including small lesions (longest diameter <10mm or pathological lymph nodes with ≥10 to <15mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, and inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

1.1.3. Special considerations regarding lesion measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

• Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

• Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

• Blastic bone lesions are non-measurable.

Cystic lesions:

• Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

• 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:.

• Tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

1.2. Specifications by methods of measurements

1.2.1. Measurement of lesions

All measurements should be recorded in metric notation, using callipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 28days (4 weeks) before the beginning of the treatment.

1.2.2. Method of assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and P10mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilisation of these techniques for objective tumour evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumour markers: Tumour markers alone cannot be used to assess objective tumour response. If markers are initially above the upper normal limit, however, they must normalise for a patient to be considered in complete response. Because tumour markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer), have been published. In addition, the Gynaecologic Cancer Intergroup has developed CA125 progression criteria which are to be integrated with objective tumour assessment for use in first-line trials in ovarian cancer.

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumour types such as germ cell tumours, where known residual benign tumours can remain). When effusions are

known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumour has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

2. Tumour response evaluation

2.1. Assessment of overall tumour burden and measurable disease

To assess objective response or future progression, it is necessary to estimate the overall tumour burden at baseline and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included in protocols where objective tumour response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion. In studies where the primary endpoint is tumour progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether patients having non-measurable disease only are also eligible.

2.2. Baseline documentation of 'target' and 'non-target' lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumour. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of P15mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumour. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the

axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20mm× 30mm has a short axis of 20mm and qualifies as a malignant, measurable node. In this example, 20mm should be recorded as the node measurement**.** All other pathological nodes (those with short axis ≥10mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterise any objective tumour regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

2.3. Response criteria

2.3.1. Evaluation of target lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

2.3.2. Special notes on the assessment of target lesions

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10mm on study. This means that when

lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure': While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5mm should be assigned in this circumstance as well). This default value is derived from the 5mm CT slice thickness (but should not be changed with varying CT slice thicknesses). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5mm.

Lesions that split or coalesce on treatment: When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

2.3.3 Evaluation of non-target lesions

This section provides the definitions of the criteria used to determine the tumour response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol. Complete Response (CR): Disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (<10mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

2.3.4. Special notes on assessment of progression of non-target disease

The concept of progression of non-target disease requires additional explanation as follows:

When the patient also has measurable disease. In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy**.** A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease. This circumstance arises in some phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition, if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumour burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to large', an increase in lymphangitic disease from localised to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

2.3.5 New lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be

unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

b. No FDG-PET at baseline and a positive FDG-PET at follow-up:

If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.

If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).

If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

2.4. Evaluation of best overall response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols

should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomised trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the 'best overall response'.

2.4.1. Time point response

It is assumed that at each protocol specified time point, a response assessment occurs. Table 1 on the next page provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

2.4.2. Missing assessments and inevaluable designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

2.4.3. Best overall response: all time points

The best overall response is determined once all the data for the patient is known.

Best response determination in trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

Best response determination in trials where confirmation of complete or partial response IS required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as in Table 3.

2.4.4. Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

In trials where confirmation of response is required, repeated 'NE' time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with time point responses of PR-NE-PR as a confirmed response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Tables 1–3.

Conditions that define 'early progression, early death and inevaluability' are study specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/ sensitivity.

For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled

assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Table 1 – Time point response: patients with target (+/–non-target) disease.

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease,

PD = progressive disease, and NE = inevaluable.

Table 2 – Time point response: patients with non-target disease only.

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD

Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = inevaluable.

A 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Table 3 – Best overall response when confirmation of CR and PR required.

Overall response First time point	Overall response Subsequent time point	Best overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

Note: CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

a: If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

2.5. Frequency of tumour re-evaluation

Frequency of tumour re-evaluation while on treatment should be protocol specific and adapted to the type and schedule of treatment. However, in the context of phase II studies where the beneficial effect of therapy is not known, follow-up every 6–8 weeks (timed to coincide with the end of a cycle) is reasonable. Smaller or greater time intervals than these could be justified in specific regimens or circumstances. The protocol should specify which organ sites are to be evaluated at baseline (usually those most likely to be involved with metastatic disease for the tumour type under study) and how often evaluations are repeated. Normally, all target and non-target sites are evaluated at each assessment. In selected circumstances certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

After the end of the treatment, the need for repetitive tumour evaluations depends on whether the trial has as a goal the response rate or the time to an event (progression/death). If 'time to an event' (e.g. time to progression, disease-free survival, progression-free survival) is the main endpoint of the study, then routine scheduled re-evaluation of protocol specified sites of disease is warranted. In randomised comparative trials in particular, the scheduled assessments should be performed as identified on a calendar schedule (for example: every 6–8 weeks on treatment or every 3–4 months after treatment) and should not be affected by delays in therapy, drug holidays or any other events that might lead to imbalance in a treatment arm in the timing of disease assessment.

2.6. Confirmatory measurement/duration of response

2.6.1. Confirmation

In non-randomised trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data

where response has traditionally required confirmation in such trials (see the paper by Bogaerts et al. in this Special Issue10). However, in all other circumstances, i.e. in randomised trials (phase II or III) or studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6–8 weeks) that is defined in the study protocol.

2.6.2. Duration of overall response

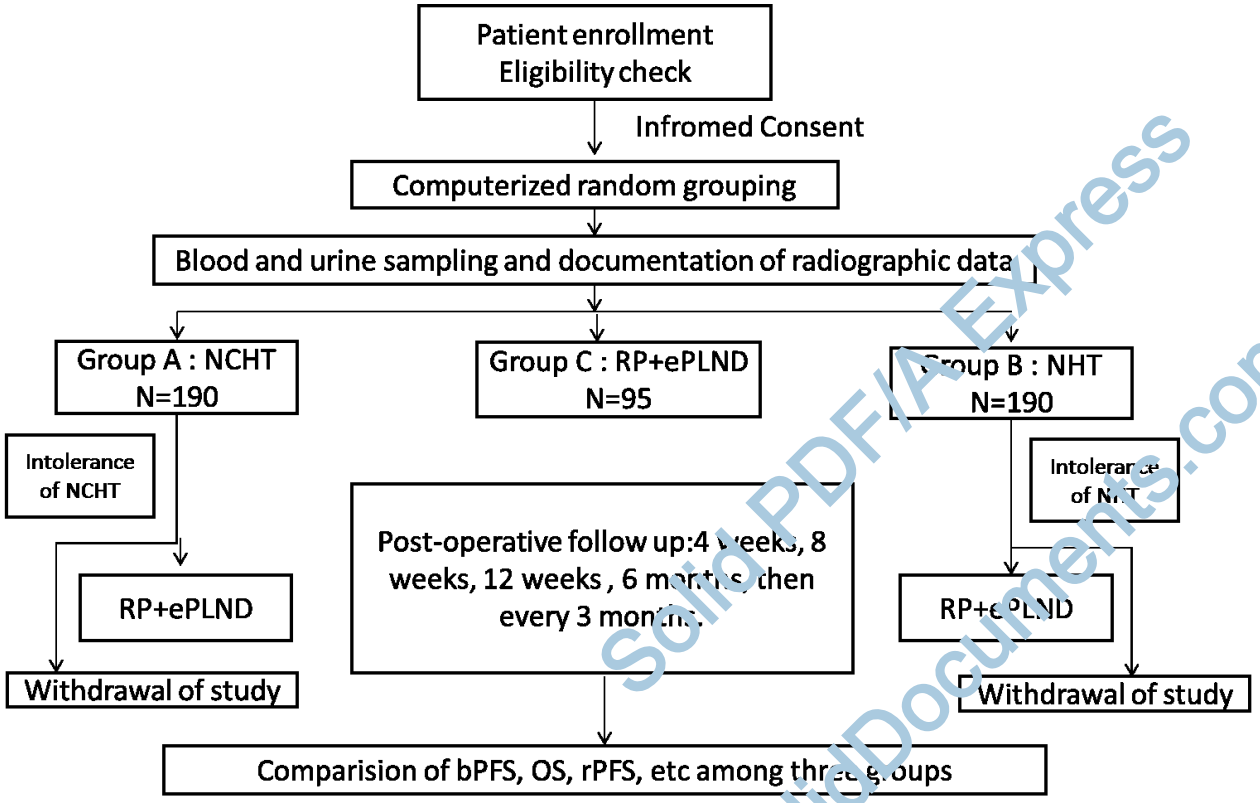
The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study). The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

2.6.3. Duration of stable disease

Stable disease is measured from the start of the treatment (in randomised trials, from date of randomisation) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest this is the reference for calculation of PD). The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between two measurements for determination of stable disease.

Note: The duration of response and stable disease as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between trials are to be made.

Appendix 9 The trial flowchart



	Screening period	Neoadjuvant treatment period (21 days per cycle in the experimental group and 28 days per cycle in the control group)[A]	Before surgery	Postoperative visit[G]	Long term survival

Time / Items												visit[G]
	-28~0天	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6		4 weeks after surgery	8 weeks after surgery	12 weeks after surgery	Half year after surgery	Every 3 months
informed consent	X												
Demographics, medical history, past treatment history	X												
（FACT-P）[B]	X	X	X	X	X	X	X	X^D					
（BPI-SF）	X	X	X	X	X	X	X	X^D					
Analgesic usage score	X	X	X	X	X	X	X	X^D					
Vital sign, weights	X	X	X	X	X	X	X	X^D				X	X^H
ECOG Performance Status	X	X	X	X	X	X	X	X^D	X	X	X	X	X
CT, MRI, bone scan [C]	X			X			X	X^D				X	X^H
PET-CT[C]	O			O			O	O^D				O	O^H
ECHO	X												
EKG[E]	X							X				X	
Liver function, renal function,	X	X	X	X	X	X	X	X^D	X	X	X	X	X

electrolytes													
Complete blood count	X	X	X	X	X	X	X	X[D]			X	X	X
Urine routine	X	X	X	X	X	X	X	X[D]			X	X	X
Blood lipids and blood sugar	X	O	O	X	O	O	X	X[D]			X	X	X
PSA	X	X	X	X	X	X	X	X[D]	X	X	X	X	X
Testosterone	X	O	O	X	O	O	X	X[D]	O	O	X	X	X
HbsAg, HCV antibody, HIV antibody	X							X					
Paclitaxel related gene detection	O												
Adverse event records	X	X	X	X	X	X	X	X	X	X	X	X	X
Combined medication records		X	X	X	X	X	X	X	X	X	X	X	X
Disease progression assessment [F]				X			X	X		X	X	X	X
Survival follow-up												X	X

Note (X: necessary test; O: selective test):

A: The neoadjuvant chemotherapy in the experimental group is planned to be carried out for 4 cycles, and if necessary, it can be increased to 6 cycles; in the control group, neoadjuvant hormone therapy is planned to be carried out for 3-6 cycles, which is not extended in principle.

The time window is specified: the time window of the screening period is 28 days before the first use of the study drug; the visit window of the neoadjuvant treatment period is ± 2 days (except for the time window of each imaging examination and electrocardiogram examination is ±4 days); The time window from the adjuvant treatment period to the surgical treatment period is 3 months; during the follow-up period after the surgical treatment period, the outpatient visit time window was ±7 days.

B: The Quality of Life Scale (FACT-P) is carried out at the screening period, every 8 weeks after the study drug usage, and at the end of the treatment visit.

C: CT (or MRI), bone scan or PET-CT: Complete imaging test during the screening period, every 3 cycles during the neoadjuvant treatment, before surgery, and every six months after surgery. PET-CT examination can replace CT/MRI and bone scan. During the neoadjuvant treatment, if a metastasis is observed by bone scan, confirmatory bone scan will be done after at least 6 months. Either CT or MRI is qualified for assessment. Imaging assessments are valid for 28 days and no repetitive test is needed.

D: Participants whose preoperative examination are within 14 days of final assessment of neoadjuvant therapy are spared of repetitive test.

E: Performed once in the screening period, 1 day before surgery, and half a year after surgery. If necessary, add an ECG test. When the potassium concentration is <3.5mmol/L, the electrocardiogram should not be performed. The hypokalemia should be corrected before the electrocardiogram can be performed.

F: The assessment of disease progression is usually evaluated at the end of the third and sixth follow-up cycles of neoadjuvant therapy, before surgery and after each outpatient visit.

G: Long-term survival assessment are in principle every 3 months, and all examinations are carried out according to the requirements of the program. If the patient is unable to come to the hospital on time, visit can be done by video or to extend the follow-up period to 6 months.

H: Imaging examination during long-term survival assessment needs to be completed in our hospital. The inspection period can be extended to half a year to once a year as needed.