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Clinical Efficacy of Neoadjuvant Endocrine Therapy in Non-Metastatic Prostate Cancer and Preliminary Experiences of Bone Metastasis Patients

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Abstract: Objective To explore the short-term efficacy of neoadjuvant endocrine therapy (NET) for localized prostate cancer and preliminary exploration of NET in patients with bone metastases. Methods Analyze clinical data of patients undergoing radical prostatectomy (RP) in the First Affiliated Hospital of Chongqing Medical University from January 2017 to January 2021 retrospectively. Patients with localized prostate cancer undergoing NET+RP were selected as the experimental group. The ones who only received RP were chosen as the control group, and the peri- and post-operative outcomes such as down-staging, pathological complete response, positive margin, intraoperative blood loss, and operation time were compared between the two groups. In addition, collect the information of patients with bone metastatic prostate cancer, excluding organ metastases, who received NET+RP over the same time-period and analyzed the short-term efficacy and quality of life. Results In the experimental group, there were more down-staging (13.08% vs. 4.67%, P=0.031), more pathological complete response (12.15% vs. 0.93%, P=0.001), less positive margin (9.35% vs. 29.91%, P< 0.001) and less blood loss (171.45±16.19 vs. 177.76±23.28, P=0.022). NET+RP also showed a satisfying short-term efficacy in patients with bone metastases, with well quality of life. Conclusion NET combined with RP can provide good short-term prognosis and patient satisfaction in patients with prostate cancer, and it is a potential option for patients with bone metastases without organ metastases.

Keywords: Prostate Cancer; Neoadjuvant Endocrine Therapy; Bone Metastasis.

1. Introduction

Prostate cancer (PCa) is one of the most common malignancies of the genitourinary system. As of 2022, it has surpassed lung cancer to become the leading cancer in men in terms of incidence, and is also the second leading cause of cancer death in men[1]. Organ-confined prostate cancer is defined as prostate cancer confined within the prostatic capsule, while locally advanced prostate cancer is defined as prostate cancer with tumor foci extending beyond the prostatic capsule but without distant metastasis. Treatment of organ-confined prostate cancer varies depending on the risk stratification of prostate cancer[2]. According to Chinese guidelines, high-risk prostate cancer is defined as organ-confined prostate cancer with prostate-specific antigen (PSA) levels greater than 20 ng/mL, a Gleason score of 8 or higher, or a clinical stage of cT2c or greater[3]. For low-risk prostate cancer, even if radical prostatectomy (RP) is not performed immediately, active surveillance is still satisfactory in the long-term[4]. However, the long-term prognosis for patients with high-risk and advanced prostate cancer is usually poor. Therefore, various adjuvant or neoadjuvant therapies are usually performed during the perioperative period for high-risk prostate cancer patients undergoing surgery. In recent years, neoadjuvant endocrine therapy (NET) related studies have been reported frequently, and clinical trials of various new endocrine therapy drugs for prostate cancer are ongoing[5, 6]. Existing evidence suggests that neoadjuvant endocrine therapy may reduce tumor burden and demonstrate advantages in reducing positive surgical margins[7]. After appropriately extending the duration of NET, the positive surgical margin rate may be even lower[8]. This study retrospectively analyzed the data of patients undergoing RP at the First Affiliated Hospital of Chongqing Medical University to explore the efficacy and clinical value of NET in Chinese prostate cancer patients.

2. Methods

2.1. Clinical Data

This retrospective study collected data from prostate cancer patients who underwent neoadjuvant endocrine therapy (NET) followed by radical prostatectomy (RP) at the First Affiliated Hospital of Chongqing Medical University between January 2017 and January 2021 as the experimental group, and collected data from prostate cancer patients who underwent RP alone as the control group. Inclusion criteria were: 1) RP surgery with or without neoadjuvant endocrine therapy, 2) pathology diagnosed as prostate adenocarcinoma. Exclusion criteria were: 1) previous treatment with other neoadjuvant therapies, 2) severe underlying conditions, including cardiovascular and pulmonary diseases, and coagulation disorders, 3) concurrent tumors originating from other organs or tissues, 4) allergy to study drugs. All patients provided informed consent for the use of their medical data for research purposes upon admission, and this study was approved by the hospital ethics committee.

2.2. Treatment Procedure

All patients in the experimental group received preoperative subcutaneous injection of goserelin or leuprorelin combined with bicalutamide tablets orally. Studies have shown that goserelin and leuprorelin have comparable potential in suppressing testosterone levels[9], therefore, the preoperative treatment plan in the experimental group is collectively referred to as neoadjuvant endocrine therapy (NET) in the following text. Patients in the NET group visited our hospital outpatient clinic every 4 weeks

after NET to check PSA, testosterone, and liver function levels, evaluate their general condition, and determine whether to be admitted based on the clinical judgment of the attending physician. The RP procedure followed the surgical norms and recommendations for radical prostatectomy after pubic bone in Hinman's Atlas of Urologic Surgery[10]. It is worth noting that all NET patients were informed that the efficacy of NET is still not fully understood, and for all patients with bone metastases undergoing RP, they were informed before surgery that the efficacy of RP for metastatic prostate cancer is still uncertain. All patients agreed to close follow-up in the outpatient clinic after surgery.

2.3. Outcome Measures

The following patient information was collected: age, BMI, preoperative PSA score, preoperative biopsy Gleason score, and ISUP grouping. The tumor stage was determined by preoperative prostate magnetic resonance imaging (MRI) and postoperative gross specimen evaluation of the primary tumor growth, combined with preoperative bone scans and chest CT to determine whether bone and lung metastases were present. The general condition before surgery was evaluated according to the Eastern Cooperative Oncology Group (ECOG) rating scale, and postoperative quality of life was evaluated using the SF-36 health scale. The main endpoints after surgery were positive margin rate and postoperative tumor downstaging, and the secondary endpoints included operative time, intraoperative blood loss, and drainage tube removal time.

2.4. Statistical Analysis

All data processing was performed using SPSS 25.0. The t-test and rank-sum test were used to compare the quantitative data, while the chi-square/corrected chi-square test or Fisher's exact test was used to compare the count data. A P-value <0.05 was considered statistically significant.

3. Results

3.1. Baseline Data

Table 1. Preoperative baseline data of prostate cancer patients

Characteristics	Experimental group (n=172)	Control group (n=268)	*P* value
Age, years (*x±s)*	67.50±6.19	67.97±6.67	0.459
BMI, kg/m^2 (*x±s)*	23.84±1.85	24.29±1.84	0.013*
Initial T stage (n, %)			<0.001*
T1	0	6(2.24%)	
T2a	38(22.09%)	130(48.51%)	
T2b	50(29.07%)	62(23.13%)	
T2c	68(39.53%)	54(20.15%)	
T3	16(9.30%)	16(5.97%)	
Initial PSA, ng/ml [M (P_{25}, P_{75})]	31.82(13.45, 49.16)	31.52(15.36, 43.18)	0.591
Preoperative PSA, ng/ml [M (P_{25}, P_{75})]	0.167(0.106, 0.244)		
	P<0.001*		
ISUP grade group (n, %)			<0.001*
1	4(2.33%)	36(13.43%)	
2	56(32.56%)	138(51.49%)	
3	32(18.60%)	38(14.18%)	
4	80(46.51%)	52(19.40%)	
5	0	4(1.49%)	
ECOG score (n, %)			0.146
1	32(18.60%)	50(18.66%)	
2	130(75.58%)	212(79.10%)	
3	10(5.81%)	6(2.24%)	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; BMI, Body Mass Index; PSA, prostate specific antigen.
* Statistical significance

Table 2. Preoperative baseline data of prostate cancer patients after propensity score matching

Characteristics	Experimental group (n=107)	Control group (n=107)	*P* value
Age, years (*x±s)*	67.95±6.26	67.91±6.47	0.957
BMI, kg/m^2 (*x±s)*	24.09±1.79	24.33±1.88	0.335
Initial T stage (n, %)			0.225
T2a	31(28.97%)	20(18.69%)	
T2b	34(31.78%)	45(42.06%)	
T2c	38(35.51%)	36(33.64%)	
T3	4(3.74%)	6(5.61%)	
Initial PSA, ng/ml [M (P_{25}, P_{75})]	17.56(12.72, 42.30)	26.52(14.62, 40.38)	0.144
ISUP grade group (n, %)			0.308*
1	3(2.80%)	1(0.93%)	
2	45(42.06%)	43(40.19%)	
3	17(15.89%)	27(25.23%)	
4	42(39.25%)	36(33.64%)	
ECOG score (n, %)			0.657*
1	19(17.76%)	14(13.08%)	
2	84(78.50%)	89(83.18%)	
3	4(3.74%)	4(3.74%)	

*Fisher's exact test

There was a total of 172 patients involved in the experimental group and 268 patients in the control group. There were no statistically significant differences between the two groups in terms of age (P=0.459), initial PSA level (P=0.591), and ECOG score (P=0.146). Based on the initial diagnostic results, 16 patients (9.30%) in the experimental group were classified as T3 stage, and 80 patients (46.51%) were in ISUP grouping 4 or above based on biopsy results; in the control group, 4 patients (1.49%) were in ISUP grouping 5 based on biopsy results (Table 1). After 1:1 propensity score matching, a total of 107 patients were selected in both the experimental group and the control group, and there were no statistically significant differences in baseline data between the two groups (Table 2). Subsequent intergroup comparisons were based on patient data matched by propensity score.

3.2. Perioperative Outcomes

Table 3. The short-term prognostic data during perioperative period

Perioperative outcomes	Experimental group (n=107)	Control group (n=107)	*P* value
Operation time, min (*x±s)*	146.86±19.85	148.83±19.94	0.471
Estimated blood loss, ml (*x±s)*	171.45±16.19	177.76±23.28	0.022*
Downstaging of T stage (n, %)	14(13.08%)	5(4.67%)	0.031*
Positive margin (n, %)	10(9.35%)	32(29.91%)	<0.001*
pathologic complete response (n, %)	13(12.15%)	1(0.93%)	0.001*
drain removal time, days (*x±s)*	4.36±1.44	4.64±1.59	0.177

* Statistical significance

After surgery, the number of positive surgical margins was significantly lower in the experimental group than in the control group (9.35% vs. 29.91%, P<0.001), and there were more cases of postoperative T-stage downgrade in the experimental group (13.08% vs. 4.67%, P=0.031). The estimated intraoperative blood loss (ml) was less in the experimental group than in the control group (171.45±16.19 vs. 177.76±23.28, P=0.022). A total of 13 cases (12.15%) achieved complete pathological remission in the experimental group (partially shown in Figure 1), while there were no cases of pathological remission in the control group. There were no

statistically significant differences in operative time and drainage tube removal time (Table 3).

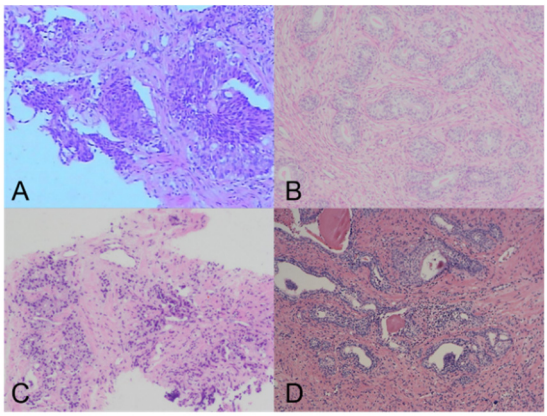

Figure 1. Pathological slides from two patients with pathological complete responses. A. The biopsy of prostate gland of Patient "a" before surgery, which had a Gleason score of 5+4=9. B. The biopsy of prostate gland of Patient "a" after surgery, which showed hyperplasia without cancer cells. C. The biopsy of prostate gland of Patient "b" before surgery, which has a Gleason score of 4+4=8. D. The biopsy of prostate gland of patient "b" after surgery, which showed inflammatory cell infiltration without cancer cells

3.3. Information of Advanced Patients

After propensity score matching, 22 patients with oligometastases in the experimental group were excluded. The clinical characteristics, perioperative related indicators, and short-term prognosis data of the remaining patients are shown in Table 4. Among them, 7 patients with bone metastases showed a significant reduction in the density of bone metastatic lesions on whole-body bone scans after neoadjuvant endocrine therapy (partially shown in Figure 2), and the mean SF-36 scores of patients followed up for six months after surgery were greater than 500 points.

Table 4. The brief information of NET patients with bone metastases

Characteristics	**n=22**
Age, years (*x±s)*	65.23±5.94
Initial PSA, ng/ml [M (P_{25}, P_{75})]	50.17(42.62, 57.96)
Preoperative PSA, ng/ml [M (P_{25}, P_{75})]	0.203(0.122, 0.583)
ISUP grade group (n, %)	
3	3(13.64%)
4	13(59.09%)
5	6(27.27%)
ECOG score (n, %)	
1	1(4.55%)
2	11(50%)
3	10(45.45%)
NET duration (n, %)	
1~3 months	7(31.81%)
3 months	14(63.64%)
6 months	1(4.55%)
SF-36 score* (*x±s)*	552.01±110.90
Operation time, min (*x±s)*	175(135, 185)
Estimated blood loss, ml (*x±s)*	200(200, 400)
Positive margin (n, %)	5(22.72%)

* Following up 6 months after surgery.

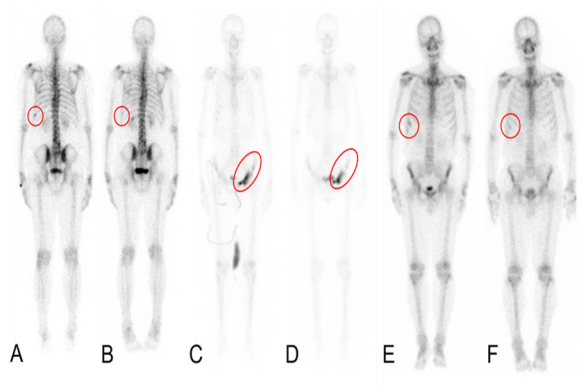

Figure 2. Comparison of three patients' bone scans before and after NET, which showed the partial thinning of shadow (marked with red circles). A. The bone scan of Patient "a" before NET. B. The bone scan of Patient "a" after three-month NET, showing the partial thinning of shadow in the left 10th rib. C. The bone scan of Patient "b" before NET. D. The bone scan of Patient "b" after three-month NET, showing the partial thinning of shadow in the left iliac crest and pubis. E. The bone scan of Patient "c" before NET. F. The bone scan of Patient "c" after three-month NET, showing the partial thinning of shadow in the right 7 and 8 ribs.

4. Discussion

Currently, there is no consensus on the standard treatment for localized prostate cancer, especially for locally advanced prostate cancer without organ metastasis. It is believed that a combination of radiation therapy (RT) and RP, augmented with other drug treatments, can lead to good prognosis for patients with prostate cancer[11]. In this study, we retrospectively analyzed data from prostate cancer patients who underwent RP at the First Affiliated Hospital of Chongqing Medical University in recent years. Initial grouping data showed that for localized and locally advanced prostate cancer, compared with the neoadjuvant endocrine therapy group, the pure RP group had lower initial T-stage and Gleason scores and better preoperative general condition, indicating that in clinical practice, when making the final treatment plan, physicians and patients tend to choose RP surgery for patients with early stage and good pathological grading. According to a retrospective study by Teppei Matsumoto et al. that included 640 high-risk prostate cancer patients, patients who received combined NET therapy had significantly better biochemical recurrence-free survival (BCRFS) and overall survival (OS) than those who received simple RP combined with lymph node dissection[12]. In the formulation of subsequent treatment plans, different patients may choose different adjuvant treatments, and the heterogeneity among patients may lead to biased judgments about whether patients benefit in terms of BCRFS and OS. Therefore, this study used short-term surgical-related indicators in follow-up to partially exclude the interference of subsequent treatment plans.

The prognosis of prostate cancer patients is related to the residual tumor status at the surgical margin, and existing evidence suggests that neoadjuvant endocrine therapy before radical prostatectomy can improve surgical-related indicators, including the positive margin rate[13]. In this study, the perioperative related indicators of the NET RP group and RP group were analyzed, and it was found that NET was beneficial in reducing the positive margin rate. In addition, compared with the clinical stage of the tumor determined according to MRI and biopsy at the initial diagnosis of prostate cancer, the proportion of postoperative T-stage downgrade in the NET RP group was significantly higher than that in the RP group, which suggests that NET can to some extent reduce the tumor volume and lower the surgical difficulty for the surgeon. Furthermore, although there was no statistically significant difference in the surgical time and the time to remove the drainage tube between the two groups, the NET RP group had less intraoperative bleeding and a trend toward shorter surgical time. In the future, with the continuous improvement of prostate cancer surgery, the intraoperative advantages of NET may become more apparent. However, some studies have shown that tumor cells and tissue inflammation can promote each other, and tissue inflammation reactions can lead to fibrosis in the surrounding tissues[14]. Although NET can reduce the positive margin rate, whether the fibrosis caused by the tumor will weaken the help of NET for surgery needs further exploration.

Currently, there is no consensus on the treatment of primary lesions in metastatic prostate cancer. The "seed-soil" theory regards tumor disseminating cells as "seeds" and the body microenvironment that can accept tumor disseminating cells as "soil"[15]. The primary tumor can spread to other parts through various pathways and then promote the development of the primary lesion, forming a vicious cycle[16]. This self-spreading phenomenon relies on the intact presence of the primary tumor lesion[17], so the treatment of the primary lesion cannot be ignored. Currently, RT seems to be one of the available treatment options for prostate cancer patients with bone metastases[2]. Boeve et al. concluded in a trial on the efficacy of RT in CRPC that the median time to PSA progression was significantly better in the RT combined with androgen deprivation therapy (ADT) group than in the ADT-alone group[18]. In addition, a phase III randomized controlled trial (STAMPEDE study) comparing the efficacy of ADT and ADT RP in patients with hormone-sensitive prostate cancer in the M1b stage suggested that the ADT RP group showed survival benefits in the low tumor burden subgroup[19]. However, there is currently insufficient evidence to extend the research results of RT to RP treatment. Recently, a prospective randomized controlled study described the role of RP in patients with oligo-bone metastases (1 to 3 skeletal lesions on bone scan, without visceral metastasis) with prostate cancer, and the results showed that RP combined with a systemic treatment regimen was safe in this population, but there were no subsequent statistics on the long-term prognosis[20]. In this study, we retrospectively analyzed the efficacy of NET RP treatment in prostate cancer patients with oligometastases, and the results showed that it performed well in perioperative-related indicators such as positive margin rate, intraoperative bleeding, and surgical time, and provided satisfactory quality of life for patients. In addition, seven patients showed a significant reduction in the density of bone metastatic lesions on whole-body bone scans after NET treatment, suggesting that neoadjuvant endocrine therapy may provide a new idea for oligometastatic patients to regain clinical cure opportunities. Although the number of screened patients was small, the overall data of the study results showed good tolerance and good prognosis after NET RP treatment for prostate cancer patients with oligometastases, which reflects the feasibility of NET RP treatment in clinical practice to some extent.

In summary, neoadjuvant endocrine therapy combined with radical prostatectomy has advantages in reducing surgical

difficulty and positive margin rate, even achieving pathological complete remission for patients with localized and locally advanced prostate cancer. For bone metastatic patients without organ metastasis, NHT RP can provide good short-term prognosis and patient satisfaction, and may provide a chance for some patients to achieve tumor cure, which is a potentially promising option. With the continuous development of new endocrine therapy drugs, its advantages may become more apparent. However, there are still some areas for improvement in this study. Firstly, this was a retrospective study, and although propensity score matching was used to reduce the differences in baseline levels between the two groups of patients, retrospective data still have bias. In addition, further large-scale prospective randomized controlled studies are needed to validate the clinical efficacy of NET RP for bone metastatic patients.

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