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Original Article

Neoadjuvant hormonal deprivation for patients undergoing radical prostatectomy

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Abstract

The purpose of this study is to evaluate the therapeutic effect of radical prostatectomy combined with preoperative neoadjuvant hormonal ablation therapy for prostate cancer (PCa). In this study, a total of 31 patients with local PCa underwent radical prostatectomy; of these, 12 patients underwent preoperative hormonal deprivation with a combination of goserelin and flutamide for a period of 5.6 months. Data regarding clinical characteristics were compared between the neoadjuvant therapy and radical prostatectomy groups. A total of 31 patients received pelvic lymph node clearance, and the rate of positive lymph nodes was 12.9% (4/31). Serum prostate-specific antigen (PSA) was 8.9 ± 1.2 μg L^{-1} after the neoadjuvant therapy and 0.4 ± 0.3 μg L^{-1} one month after the radical prostatectomy. There were significant differences in the positive surgical margins, seminal vesicle invasion and lymph node metastasis between the neoadjuvant therapy group (n = 12) and the radical prostatectomy group (n = 19, $P < 0.01$). The resulsts indicates that preoperative hormonal deprivation induced by goserelin and flutamide can decrease clinical and pathological staging, but assessment of its influence on long-term prognosis requires further study.

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1 Introduction

Radical prostatectomy is still the 'gold standard' of treatment for local prostate cancer (PCa). However, for nearly 66% of men undergoing prostatectomy, the preoperative clinical stage underestimates the extent of disease, and positive margin rates may be as high as 30%–60% [1]. In patients diagnosed with stage B PCa, the extracapsular extension rate was as high as 63% [2]. Incomplete resection of cancer may lead to increased risk for local recurrence, distant metastases and shorter overall survival. When PCa was present at the surgical margin, biochemical disease-free survival decreased to 37%–70% [3], whereas the long-term progression-free survival rate for patients with pT2N0 tumours and negative margins ranged from 84% to 98%.

Neoadjuvant hormone therapy (NHT) prior to radical prostatectomy had a significant impact in lowering the positive surgical margin rate, increasing the organ-confined rates, lowering the pathological staging and decreasing lymph node involvement. Therefore, NHT prior to prostatectomy may result in the achievement of significant local control, which may improve the patients' quality of life [4]. We present here our clinical experience in a retrospective series of 31 patients with localized PCa who underwent radical prostatectomy at our hospital from April 1999 to December 2003, including 12 patients who underwent preoperative hormonal deprivation with goserelin combined with flutamide.

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2 Materials and methods

2.1 Population

The mean age of the 31 patients was 61.3 years (range: 53–71 years). All the patients were suspected of having PCa on the basis of positive results of digital rectal examination (DRE), serum prostate-specific antigen (PSA) and transrectal ultrasound. All the patients underwent transrectal ultrasound-guided prostate biopsy, and PCa was confirmed by pathology. Clinical stage was established by computer tomography, magnetic resonance imaging and bone scanning. A total of 31 patients with local PCa underwent radical prostatectomy; of these, 12 patients underwent neoadjuvant hormonal deprivation with a combination of goserelin and flutamide before surgery. Of the 31 patients, 4 had a clinical stage of T1c, 6 of T2a, 9 of T2b, 4 of T2c, 5 of T3a and 3 of T3b. The mean prostate volume measured by transrectal ultrasound was 34.5 ± 21.7 mL. The mean serum PSA was 31.8 ± 13.7 μg L^{-1}. The mean Gleason score was 5.4 ± 1.2.

2.2 Methods

Patients in the neoadjuvant therapy group were treated with goserelin and flutamide for an average of 5.6 months (3–8 months) before radical prostatectomy. Serum PSA levels were measured every month, and radical prostatectomy was performed after the PSA level reached its nadir. Biopsy of pelvic lymph nodes was routinely performed during radical prostatectomy. The key steps in performing radical prostatectomy were as follows: dissection of the urethra at the apex of the prostate; retrograde dissection of the prostate; preservation of the urinary sphincter at the bladder neck; and wide excision of the nerve plexus on the tumour side and soft tissue near the prostate, preserving, if possible, the nerve plexus on the opposite side.

2.3 Statistical analysis

The paired Student's *t*-test and chi-square analysis were used for statistical analysis.

3 Results

All the patients undergoing neoadjuvant therapy showed good tolerance to Zoladex. Two men treated with flutamide experienced severe hepatic dysfunction; another patient stopped taking flutamide after a severe gastrointestinal reaction. Serum PSA was 8.9 ± 1.2 μg L^{-1} after neoadjuvant therapy and 0.4 ± 0.3 μg L^{-1} one month after the radical prostatectomy. The clinical stage before the hormonal deprivation was T2a in two patients, T2b in two patients, T2c in three patients, T3a in three patients and T3b in two patients, and the clinical stage after the hormonal deprivation was T1c in three patients, T2a in four patients, T2c in two patients, T3a in two patients and T3b in one patient. One patient with stage T2a, two patients with T2b, two patients with T2c, two patients with T3a and one patient with T3b were downstaged after radical prostatectomy. The postoperative pathological stage was T1c in one patient, T2c in five patients, T3a in three patients, T3b in two patients and T3c in one patient.

In the group of patients who underwent radical prostatectomy alone, serum PSA was 1.3 ± 0.4 μg L^{-1} 1 month after surgery. The preoperative clinical stage was T1c in four patients, T2a in four patients, T2b in seven patients, T2c in one patient, T3a in two patients and T3b in one patient, and the postoperative pathological stage was T2a in two patients, T2b in two patients, T2c in three patients, T3a in five patients, T3b in three patients and T3c in four patients.

Our study showed higher rates of positive surgical margin rates and extracapsular extension and greater seminal vesicle invasion, pelvic lymph node involvement and prostate volume in the radical prostatectomy group than in the neoadjuvant therapy group ($P < 0.05$). There were no significant differences in Gleason grade, blood loss and operation time between the two groups (Table 1).

4 Discussion

NHT, which refers to androgen deprivation therapy

Table 1. Characteristics of patients undergoing radical prostatectomy and neoadjuvant therapy.

Index	The radical prostatectomy group	The neoadjuvant therapy group	*P*
Positive margin rates (%)	36.8 (7/19)	16.7 (2/12)	< 0.05
Extracapsular extension rates (%)	47.3 (9/19)	25.0 (3/12)	< 0.05
Seminal vesicle invasion rates (%)	21.1 (4/19)	8.3 (1/12)	< 0.05
Lymph node involvement rates (%)	15.8 (3/19)	8.3 (1/12)	< 0.05
Prostate volume (mL)	32.7 ± 22.5	14.6 ± 5.7	< 0.05
Operation time (h)	3.2 ± 0.4	3.8 ± 0.7	> 0.05
Blood loss (mL)	760 ± 431	771 ± 397	> 0.05
Gleason grade (score)	5.2 ± 1.3	4.8 ± 1.7	> 0.05

prior to radical treatment for PCa (radical prostatectomy or radiotherapy), can lower the clinical stage and increase the possibility of cure [5]. It can also affect tumour behaviour and biology, as evaluated by changes in metabolic patterns of atrophy on magnetic resonance spectroscopy, lowering of the serum PSA level and histological atrophy (fibrosis, vacuolization and glandular collapse). Studies [6] have shown that NHT has a significant impact on reduction in prostate volume (30%–50%), tumour volume and PSA level (90%). NHT comprises androgen deprivation therapy, antiandrogen therapy and combined androgen blockade (CAB), which entails adding an antiandrogen to surgical castration or luteinizing hormone-releasing hormone (LHRH) agonists [6]. In a randomized controlled study, as compared with 300 patients receiving leuprolide and placebo, patients treated with leuprolide and flutamide had a longer progression-free survival and an increase in the median length of survival [7]. The results of our study indicate that NHT prior to radical prostatectomy significantly reduced serum PSA and lowered the clinical stage of PCa. Sassine and Schulman [8] showed that after 3 months of neoadjuvant hormone treatment, PSA showed promise as a useful predictor for patient selection for radical surgery, as 86% of patients with undetectable PSA had tumours confined to the gland. In their study, clinical downstaging was observed in one-third of the patients, but the result was not confirmed by the final pathological staging. Oesterling and coworkers [9] reported that the decrease in serum PSA and downstaging after preoperative androgen deprivation therapy were misleading, because there was no difference between the neoadjuvant therapy group and the radical prostatectomy group with regard to maximal tumour dimension, pathological stage and deoxyribonucleic acid ploidy status. Fair and associates [5] also stated that the significance of reduced clinical stage was unclear.

A meta-analysis revealed that NHT prior to radical prostatectomy resulted in a significant reduction in the positive surgical margin rate and a significant improvement in other pathological variables such as lymph node involvement, pathological staging and organ-confined rate [4]. Positive surgical margin rate is an important independent predictor for prognosis. The presence of a positive surgical margin was associated with the greatest relative risk (4.37; range 2.90–6.58) [6]. Iselin and coworkers [10] reported that after radical prostatectomy in patients with local PCa, the 5-year recurrence rate and positive surgical margin rate were 8% and 65%, respectively. Neoadjuvant hormonal ablation therapy can reduce the positive surgical margin rate. Compared with only 3 months of treatment, the use of a longer duration of neoadjuvant hormones was associated with a significant reduction in positive surgical margins [4]. Meyer and coworkers [11] reported that, compared with the radical prostatectomy group, patients undergoing neoadjuvant therapy showed decreased extracapsular extension and seminal vesicle invasion and fewer positive lymph nodes. Our study showed the same results, indicating that neoadjuvant androgen deprivation could lead to pathological downstaging. In our study, there was no significant difference in Gleason grade before vs after the hormonal therapy. However, studies have shown that androgen deprivation therapy may obscure pathological interpretation, and many pathologists do not recommend assigning a Gleason score to prostatectomy specimens from patients who have received NHT [12].

As has been reported, stage T2 cancer is the best indication for neoadjuvant treatment, as this treatment can significantly reduce the positive surgical margin rate. Although T1 and T3 are relative indications, the positive surgical margin rates do not show a significant difference [13]. Overall, only 20% of the patients with clinical stage T3 cancer have organ-confined disease at the time of radical prostatectomy, despite clinical downstaging in 32%–90% of patients. In one study, in 402 patients with cT2-T3N0M0 tumours, pathological downstaging was seen more frequently in the neoadjuvant group (15%) than in the prostatectomy-alone group (7%; $P < 0.01$); however, in men with cT3 disease, there was no difference in the rate of pathological downstaging and the incidence of lymph node metastases [6]. As neoadjuvant treatment delays the operation, short-term (3 months) treatment has been the traditional approach. However, some investigators have recently argued that 3 months of androgen deprivation therapy is not enough. Gleave and coworkers demonstrated that PSA levels became undetectable or reached their nadir in 22% of patients by 3 months, in 42% by 5 months and in 84% by 8 months [14]. In a follow-up study conducted by the same researchers, of the patients who received 3 months of neoadjuvant therapy, 23% had positive surgical margins, compared with 12% of those who received 8 months of neoadjuvant therapy [15].

In conclusion, preoperative hormonal deprivation with goserelin and flutamide can lower the clinical and pathological staging. As there has not been a large, serial, long-term randomized controlled trial on neoadjuvant hormonal ablation therapy, its degree of influence on long-term prognosis requires further observation.

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