Original Article

Efficacy of radical prostatectomy combined with endocrine drugs in treatment of elderly patients with prostate cancer

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Abstract: Objective: This study aimed to explore the efficacy of radical prostatectomy (RP) combined with endocrine drugs on elderly patients with prostate cancer (PCa). Methods: A retrospective analysis was performed for the data of 70 patients with PCa, who were divided into the control group (RP) and the observation group (RP combined with endocrine drugs) according to treatment methods. Patients in the two groups were compared in terms of prostate volume, serum prostate specific antigen (PSA) concentration, operative time, intraoperative bleeding, volume of drainage fluid, time of indwelling catheter, time of lymph node dissection, hospital stay, positive margin rate, rate of positive lymph nodes, bladder neck invasion, seminal vesicle invasion and bone metastasis. The patients were followed up to record the biochemical recurrence-free rate and grouped based on different parameters to analyze the biochemical recurrence-free survival rates. Results: Compared with the control group, patients in the observation group had significantly lower prostate volume and serum PSA level (both P < 0.05), significantly greater operative time and intraoperative bleeding but significantly lower volume of drainage fluid and time of indwelling catheter (all P < 0.05), significantly lower positive margin rate, rate of positive lymph nodes, and bone metastasis (P < 0.05). The 5-year biochemical recurrence-free rate in the observation group was significantly higher than that in the control group (P < 0.05), and the rate in patients with postoperative positive bone and lymph node metastases was significantly higher than that in patients with negative bone and lymph node metastases. Conclusion: RP combined with endocrine drugs in the treatment of elderly patients with PCa reduces prostate volume, PSA level, positive margin rate of tumors and rate of positive lymph nodes, and significantly reduces the 5-year biochemical recurrence rate, with a good long-term effect.

Keywords: Prostate cancer, radical prostatectomy, endocrine therapy, biochemical recurrence

Introduction

With high incidence rates worldwide, prostate cancer (PCa) is a malignant lesion that affects the health of elderly males. The incidence rate in developed countries is higher than that in developing countries, and patients in the United States, Britain, France, Germany and Japan currently account for 70% of the total number [1, 2]. However, patients with PCa in China have significantly increased with the increasing elderly people, the aggravation of environmental pollution and the changes in dietary habits and daily routines. There were 120,000 new patients with the disease in 2016, and 5% of all patients who died of it lived in China [3, 4]. The disease has serious influences on patients' quality of life and work, so how to prevent and treat it has been increasingly valued by urologists, which is also a hot topic in the medical field [5, 6]. With a complex natural history and great individual differences, PCa has fewer obvious early symptoms and is prone to be undetectable, whose low predictability leads to unpredictable outcomes [7].

As the best method to treat localized low- or intermediate-risk PCa (T1-T2c), radical prostatectomy (RP) may cause postoperative impotence, urinary incontinence and other adverse reactions [8]. Radiotherapy or other physical therapies damage surrounding organs while killing cancer cells, thereby causing serious side effects. The mortality risk of radiotherapy for non-metastatic patients with PCa is much higher than that of RP [9]. Currently, combined
RP combined with endocrine drugs in treating elderly patients with PCa

therapies are usually used to improve the postoperative effect on patients with PCa, and the most common one is RP combined with endocrine therapy, which reduces prostate volume, prostate specific antigen (PSA) level and positive surgical margin. However, according to a study, endocrine therapy before RP leads to tissue adhesion around prostate and increases fibrosis, which relatively increases the difficulty of surgery [10]. Therefore, whether to combine endocrine therapy with RP in the treatment of patients with PCa remains a dilemma in the medical field.

Materials and methods

General information

This study was approved by the Ethics Committee of Tongliao City Hospital. A retrospective analysis was conducted for the medical records of 70 patients with PCa admitted to this hospital from January 2010 to January 2013, who were divided into the combination group and the operation group (n = 35) according to treatment methods. Patients and their families have signed informed consent. Inclusion criteria: (1) Patients diagnosed with localized PCa by transrectal prostate biopsy; patients excluded from pelvic lymph nodes and distant metastasis by abdominal color Doppler ultrasound, pelvic and prostate magnetic resonance and systemic radionuclide bone scanning; (2) patients in a clinical stage of T2c or below without metastasis, based on the tumor node metastasis (TNM) staging criteria (the 7th edition in 2010) for gastric cancer developed by the American Joint Committee on Cancer; (3) patients without contraindications to related operations or anesthesia; (4) hormone-dependent patients who had not received endocrine-related therapies within half a year; (5) patients with a postoperative pathological result of adenocarcinoma; (6) patients diagnosed with PCa within 1 year. Exclusion criteria: (1) Patients with incomplete medical records; (2) patients with coagulation disorders, immune system dysfunction and endocrine diseases; (3) patients with poor underlying disease, diabetes, hypertension or other endocrine diseases that were not effectively controlled, and severe complications, who were intolerable to surgery; (4) patients with a postoperative pathological result of involved pelvic lymph nodes; (5) hormone-resistant patients.

Research methods

Routine physical examination was conducted on patients to ensure homeostasis in the body and increase the tolerance to surgery. Patients in the control group were treated with RP. After generally anesthetized (dexmedetomidine hydrochloride injection, Jiangsu Hengrui Pharmaceutical Co., Ltd., China), the patients under a Trendelenburg position were indwelled with a three-cavity catheter and injected with water. The surgical site was routinely disinfected and laid with a surgical drape. With the scalpel perpendicularly inserted into the skin 2 cm below the umbilical region, the skin was separated from abdominal wall muscles using a blunt dilator, and the incision site was gently covered with the hemostatic gauze, installed with a laparoscope (STORZ 26003BA, Germany), and connected to a gas-assisted machine to increase the abdominal pressure (with an inlet condition of 12 mmHg). Then, the prostate was exposed to dissociate the prostate and surrounding fat, the prostate and superior margin of pubic symphysis, and obturator lymph nodes on both sides of prostate were fixed and gently pulled into one side with hemostatic forceps. An ultrasonic scalpel was used to longitudinally cut the pelvic fascia to the apex of prostate and the pubic ligament, and the ligated great vessels on the dorsal side of prostate were sutured to dissociate both sides of prostate. After complete dissociation, the bladder neck was incised to expose the urinary catheter. The incision was enlarged and the anterior wall of the bladder was pulled to expose the seminal vesicle, so as to dissociate the vas deferens and the tissue around the seminal vesicle. With the seminal vesicle pulled, the lateral ligament to the apex of prostate was ligated successively, and the vascular complex at the dorsal side and the apex were cut off. After complete dissociation of prostate, the bladder neck was anastomosed with the posterior urethra, and a catheter was inserted to observe whether there was seepage at the anastomotic stoma. A pelvic drainage tube was indwelled, and the umbilical incision was enlarged to remove the prostate. With ECG monitoring performed 24 h after operation, the patients were intravenously supplemented with nutrition, infused with broad-spectrum antibiotics (cefalotin sodium for injection, Harbin Pharmaceutical Group General Pharmaceutical Factory, China) to prevent infection. Patients in the observation group were orally
RP combined with endocrine drugs in treating elderly patients with PCa

Biochemical recurrence: PSA concentration in the reexamination was greater than or equal to 0.2 ng/mL for consecutive twice, with increasing PSA ≥ 0.2 ng/mL for the first time as time of biochemical recurrence [18].

Statistical methods

SPSS21.0 software was used to statistically process the data. Measurement data are expressed as mean ± standard deviation (X ± sd), and a t test was used for measurement data conforming to normal distribution between the two groups. Count data are expressed as number of cases/percentage (n/%) and tested by a χ² test. P < 0.05 indicated a statistically significant difference.

Results

General information

There were no statistically significant differences in age, body mass index and the proportion of cancer staging between the two groups (P > 0.05). More details are shown in Table 1.

Comparison of prostate volume and PSA

Before treatment, there were no differences between the two groups with respect to prostate volume and PSA concentration (P > 0.05), which were significantly lower in the observation group than in the control group after treatment (both P < 0.05). More details are shown in Figure 1.

Comparison of surgical conditions

Compared with the control group, patients in the observation group had significantly greater operative time and intraoperative bleeding, but significantly smaller volume of drainage fluid and shorter time of indwelling catheter (all P < 0.05), without differences in time of pelvic drainage and hospital stay (both P > 0.05). More details are shown in Figure 2.

Comparison of postoperative pathological results

The positive margin rate, rates of positive lymph nodes and bone metastasis in the obser-

<table>
<thead>
<tr>
<th>Group</th>
<th>Control group (n = 35)</th>
<th>Observation group (n = 35)</th>
<th>t/χ²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>68.1 ± 9.3</td>
<td>65.8 ± 10.6</td>
<td>0.957</td>
<td>0.342</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.00 ± 3.17</td>
<td>22.22 ± 4.04</td>
<td>0.896</td>
<td>0.373</td>
</tr>
<tr>
<td>Cancer staging</td>
<td></td>
<td></td>
<td>0.385</td>
<td>0.943</td>
</tr>
<tr>
<td>T1c</td>
<td>1 (2.86)</td>
<td>1 (2.86)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2a</td>
<td>3 (8.57)</td>
<td>2 (5.71)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2b</td>
<td>5 (14.29)</td>
<td>4 (11.43)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2c</td>
<td>26 (74.29)</td>
<td>28 (80.00)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: BMI, body mass index.
vation group were significantly lower than those in the control group (all P < 0.05). There were no differences in bladder neck and seminal vesicle invasions between the two groups (all P > 0.05). More details are shown in Table 2.

Comparison of 2- and 5-year biochemical recurrence-free rates

There was no difference in the 2-year biochemical recurrence-free rate between the two groups ($\chi^2 = 0.674, P = 0.412$), but the 5-year biochemical recurrence-free rate in the observation group was significantly higher than that in the control group ($\chi^2 = 4.259, P = 0.039$). More details are shown in Figure 3.

Relationship between 5-year biochemical recurrence-free rate and postoperative relevant indexes

The 5-year biochemical recurrence-free rate in patients with postoperative positive bone and lymph node metastases was significantly higher than that in patients with negative bone ($\chi^2 = 8.525, P = 0.004$) and lymph node metastases ($\chi^2 = 7.444, P = 0.006$). However, there was no statistically significant difference in the 5-year biochemical recurrence-free rates between patients with a postoperative Gleason score ≥ 8 points, TNM stage ≥ pT2c and patients with a Gleason score < 8 points ($\chi^2 = 2.291, P = 0.087$), TNM stage < pT2c ($\chi^2 = 0.764, P = 0.087$).
RP combined with endocrine drugs in treating elderly patients with PCa

Table 2. Comparison of postoperative pathological results (n/%)

<table>
<thead>
<tr>
<th>Group</th>
<th>Control group (n = 35)</th>
<th>Observation group (n = 35)</th>
<th>t/χ²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive margin rate</td>
<td>18 (51.43)</td>
<td>8 (22.86)</td>
<td>3.982</td>
<td>0.043</td>
</tr>
<tr>
<td>Rate of positive lymph nodes</td>
<td>14 (40.00)</td>
<td>3 (8.57)</td>
<td>7.769</td>
<td>0.005</td>
</tr>
<tr>
<td>Bladder neck invasion</td>
<td>3 (8.57)</td>
<td>1 (2.86)</td>
<td>0.265</td>
<td>0.607</td>
</tr>
<tr>
<td>Seminal vesicle invasion</td>
<td>5 (14.29)</td>
<td>2 (5.71)</td>
<td>0.635</td>
<td>0.426</td>
</tr>
<tr>
<td>Bone metastasis</td>
<td>17 (48.57)</td>
<td>5 (14.29)</td>
<td>8.021</td>
<td>0.005</td>
</tr>
</tbody>
</table>

0.382) (P > 0.05). More details are shown in Figure 4.

Discussion

As a clinically common malignant tumor in the elderly, PCa in most patients can be detected in China with the improvement of medical technology and popularization of PSA detection [19]. However, most patients are still unaware of the importance of early detection of PCa, so they are diagnosed with high-risk localized or locally advanced PCa at the initial visit, even accompanied by bone metastasis [2]. PCa is diagnosed in the early stage in USA with a low mortality rate, and the 5-year survival rate is 98.9%, which is only 50% in China. In the past, patients with the disease were mainly treated with radiotherapy and chemotherapy to prolong their lives; RP was not considered, because the patients were easy to suffer from severe postoperative complications due to their older ages and intraoperative uncertain factors, which further reduced patients’ quality of life. However, with the updating of clinical surgical equipment and the proficiency and optimization of personnel technology, the number of patients with postoperative adverse reactions and damages to the functional area have significantly reduced, who have a longer survival time after surgery, especially after laparoscopy is applied to RP [3, 20]. There are also patients with postoperative positive pathological margins, seminal vesicle invasion and regional lymphatic metastasis, which are signs of poor prognosis; therefore, it is urgent for relevant clinical personnel to solve.

It was generally believed in the past that the tumor is only spread and transferred to the whole body after breaking through its capsule. However, according to Chung et al., tumor cells of patients with PCa have micrometastasis in the early stage, and the patients pathologically diagnosed in the high-risk stage are most likely to have distant metastasis, which explains the reasons for recurrence of high-risk PCa after RP [21]. In 1941, Huggins and Hodges first reported the benefits of castration and estrogen injection in patients with metastatic PCa. In 2006, American Society of Clinical Oncology announced the dependence of PCa cell growth on androgen and the importance of endocrine therapy for PCa [22]. Endocrine therapy mostly chooses analogues of luteinizing hormone releasing hormone and antiandrogen as drugs, which is significantly effective in the treatment of bladder, breast and lung cancers [23]. Theoretically, endocrine therapy can reduce tumor volume and treat undetected micrometastasis, and some patients are pathologically cured after endocrine therapy without residual tumor in pathological examination. However, according to a study, endocrine therapy blurs the anatomical level of the tissues around prostate and increases the difficulty of surgery [24].

As a non-steroidal antiandrogen drug, bicalutamide used in endocrine therapy binds with androgen receptors and inhibits expression activity of androgen, further promoting atrophy of the prostate [25]. However, the production of PSA is regulated by testosterone/dihydrotestosterone level in vivo, which leads to cell apoptosis and stops PSA synthesis in the case of androgen deficiency. The prostate volume and PSA concentration in patients with endocrine therapy before RP are significantly reduced. According to Helgstrand et al., endocrine therapy for some patients aggravates the adhesion between prostate, the surrounding tissues and the seminal vesicle, which increases the difficulty of surgery, operative time and bleeding [26]. This is consistent with the results of this study that patients in the observation group had significantly greater operative time and intraoperative bleeding than those in the control group, which will be effectively solved with the accumulation of surgical experience and improvement of medical equipment. According to the postoperative pathological results, positive margin rate and rate of positive lymph nodes in the observation group were signifi-
RP combined with endocrine drugs in treating elderly patients with PCa

Significantly lower than those in the control group, suggesting that endocrine therapy is effective in reducing tumor stages and the risk of local recurrence and metastasis. The 5-year bio-

Figure 3. Comparison of 2- and 5-year biochemical recurrence-free rates. A. 2-year biochemical recurrence-free rates. B. 5-year biochemical recurrence-free rates, with a higher biochemical recurrence-free rate indicates a better treatment effect. *P < 0.05.

Figure 4. Relationship between 5-year biochemical recurrence-free rate and postoperative relevant indexes. A. The relationship between bone metastasis and biochemical recurrence. The biochemical recurrence rate in patients with bone metastasis is significantly higher than that in patients without bone metastasis. B. The relationship between Gleason score and biochemical recurrence. Whether the Gleason score is higher than 8 points is not associated with biochemical recurrence. C. The relationship between tumor node metastasis staging and biochemical recurrence. Whether the pathological staging is higher than pT2c is not associated with biochemical recurrence. D. The relationship between lymph node metastasis and biochemical recurrence. The biochemical recurrence rate in patients with lymph node metastasis is significantly higher than that in patients without lymph node metastasis. **P < 0.01.
RP combined with endocrine drugs in treating elderly patients with PCa

chemical recurrence-free rate in the observation group was significantly higher than that in the control group. RP combined with endocrine therapy effectively prevents tumor recurrence, controls disease progression and improves the survival rate. In this study, the 5-year biochemical recurrence-free rate in patients with postoperative positive bone and lymph node metastases was significantly higher than that in patients with negative bone and lymph node metastases, consistent with the findings of Nyushko et al. [27]. This suggests that dissection of pelvic lymph nodes during RP should be specially valued to reduce the possibility of tumor recurrence, and patients with bone and lymph node metastases need regular checks in order to improve the long-term survival rates. However, there was no difference in the 5-year biochemical recurrence-free rate between patients with a postoperative Gleason score ≥ 8 points, TNM staging ≥ pT2c and patients with a Gleason score < 8 points, TNM staging < pT2c. The errors in clinical and postoperative pathological staging may be due to the limitation of imaging diagnostic techniques and the blurring of artificial staging criteria or the unreasonable dividing line between the Gleason score and TNM staging in this study. Therefore, the Gleason score and TNM staging may be correlated with the biochemical recurrence-free rate, which needs further research.

Studies have confirmed that the occurrence and development of PCa is significantly different in race and heredity [28, 29]. Therefore, the natural history and treatment prognosis of the disease in China should be better understood, and the patient’s condition should be evaluated more objectively, so as to develop the best individualized treatment plan. However, there may be errors in conclusions of this study due to the few patients and the retrospective clinical study. Next, a large number of randomized clinical studies will be conducted, and the mechanism of PCa occurrence and metastasis will be jointly explored with relevant departments to improve the survival rate. In addition, PSA census should be further promoted in places with backward economic and medical standards, so that more patients can be timely treated in the early stage.

To sum up, RP combined with endocrine drugs in the treatment of PCa reduces prostate volume, PSA concentration, positive margin rates and rates of positive lymph nodes, and increases the 5-year biochemical recurrence-free rates; hence, it is worthy of clinical promotion and application.

Disclosure of conflict of interest

None.

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