Laparoscopic Radical Prostatectomy plus Extended Lymph Nodes Dissection for Cases with pT3-4N0-1M0 Prostate Cancer: a Study of 8-year Follow-up

Yi Yang^{*1}, Yun Luo^{*1}, Guo-Liang Hou², Qun-Xiong Huang¹, Jun Pang¹, Xin Gao^{#1}.

*These authors contributed equally to this work.

¹Department of Urology, The Third Affiliated Hospital, Sun Yat-sen University, Tianhe Road 600, Guangzhou, 510630, China

²Department of Urology, Foshan First Municipal People's Hospital, Foshan, 528000, China

To whom correspondence should be addressed.

Xin Gao, Department of Urology, The Third Affiliated Hospital, Sun Yat-sen University, Tianhe Road 600, Guangzhou, 510630, China

Telephone: +86-20-85252990; Fax: +86-20-85252678

Email: urologygx@126.com

Conflict of Interest

We declare that we have no conflicts of interest. All co-authors, who have made a significant contribution to the findings and methods in the paper, have seen and agree with the contents of the manuscript and there is no financial interest to report.

MicroAbstract

To evaluate therapeutic effects through the long-time survival analysis of patients with or without locallymphnode metastatic prostate cancer treated by laparoscopic radical prostatectomy (LRP).The results showed that LRP plus extended lymph nodesdissectionwas a feasible approach to these patients and many clinical pathological parameters influenced the postoperative survival results.

Abstract

Purpose

To investigate the functional and oncologic outcomes of patients with locally advanced or lymph node metastatic prostate cancer (PCa) treated by laparoscopic radical prostatectomy (LRP) with extended lymph node dissection (ePLND).

Methods

From June 2004 to March 2014, a total of 232 cases (pT3-4N0-1M0) including 160 locally advanced PCa and 72 lymph node metastatic PCa who were treated by LRP with ePLND were enrolled in our study. The patients were followed up for 12-124 months. Surgical records, surgical margin status, complications, urinary continence, and oncologic outcomes were presented.

Results

The mean operation time and bleeding were 230 min and 105 ml, respectively. The rates of urinary continence were 91.4 and 94.8 % at 6 and 12 months, respectively. We observed 122 biochemical recurrent cases. The 5- and 8-year biochemical relapse-free survivals were 47.3 and 46.7 %, respectively. The 5- and 8-year overall and cancer-specific survivals were 81.2, 80.1 and 90.6, 90.6 %, respectively. The survival analysis showed that biochemical recurrence-free survival rates were significantly lower for patients with higher Gleason score (77.3 vs. 39.6 vs. 30.8 %, $P = 0.003$ log rank), higher T stage (55.7 vs. 41.4 vs. 21.4 %, $P = 0.039$ log rank), positive surgical margin (51.1 vs. 29.3 %, $P = 0.000$ log rank), and higher CAPRA-S score (68.6 vs. 35.0 vs. 29.2 %, $P = 0.000$ log rank). There were no significant differences in biochemical relapse-free (40.9 vs. 49.3 %, $P = 0.286$), overall (75.6 vs. 81.9 %, $P = 0.398$), and cancer-specific survivals (87.3 vs. 92.1 %, $P = 0.284$) between lymph node-positive and -negative PCa.

Conclusions

LRP plus ePLND is a feasible approach to patients with pT3-4N0-1M0 PCa as favorable functional and oncologic outcomes were presented postoperatively.

Keywords Laparoscopic radical prostatectomy; Extended lymph node dissection; Locally advanced prostate cancer; Biochemical recurrence; Survival

Introduction

Either androgen deprivation therapy (ADT) or a combination with radiotherapy has been long accepted for treating locally advanced or lymph node metastatic PCa [1]. However, the efficacy of ADT alone is limited (often 2-3 years) for the consequent castration resistance, and high positive rate of biopsy (10–91 %) after radiotherapy and local tumor progression (up to 40 %) still challenge us [2]. Radical prostatectomy (RP) is always recognized as a golden standard modality only for organ-confined PCa. Recent reports said that patients treated by RP before the progression of metastatic disease had a higher sensitivity to ADT and longer survival [3]. Moreover, some studies showed that the cancer-specific survival of patients with advanced non-bone metastatic PCa treated by radical prostatectomy (RP) was higher than endocrinotherapy and equivalent to radiotherapy [4]. Our previous study also showed that pathologically advanced PCa may benefit from LRP [5]. In this regard, a longer-term outcome study of patients with pT3-4N0-1M0 prostate cancer (PCa) treated by LRP may still be necessary.

In China, prostate-specific antigen (PSA) screening has not been widely carried out. Of all initially diagnosed PCa, nearly 80 % is locally advanced or metastatic [6]. Moreover, there were part of the preoperatively diagnosed organ-confined PCa by imaging and biopsy whose postoperatively (RP or LRP) pathological TNM indicated a local advanced stage or positive lymph node [7]. Thus, to evaluate the value of LRP in treating locally advanced or lymph node metastatic PCa is important. As a Chinese institute, LRP has become a routine treatment modality which we use to treat localized PCa [8]. Here we retrospectively investigated outcomes of 232 patients with locally advanced or lymph node metastatic PCa treated by LRP plus ePLND.

Materials and methods

Patients' selection

This retrospective study was conducted in accordance with the guidelines of the Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University. From June 2004 to March 2014, of the total 1018 patients treated by LRP in our hospital, 232 diagnosed with pathological advanced PCa (pT3-4N0-1M0) who received immediate ADT after LRP plus ePLND were included in our study. Their clinical and pathological characteristics were summarized in Table 1. The CAPRA-S score was performed (Table 2) as a straightforward tool for improved prediction of outcomes after

LRP[9]. In all these cases, including 160 lymph node negative and 72 lymph node positive PCa, a pelvic CT or MRI scan was performed before operation to measure lymph node metastasis and clinical stage. The preoperative PSA >10 ng/ml, biopsy Gleason score ≥ 7 or T stage >T2b was the indication for PLND[10].

LRP plus ePLND and ADT

Before extra-fascia LRP, ePLND was performed through transperitoneal approach. The dissected lymph node clusters included external iliac artery, common iliac artery, obturator fossa, internal iliac, and presacral lymph nodes. Each lymph node was dissected en bloc for histopathological analysis to evaluate the metastatic status. Following the ePLND, LRP comprises the following steps in turn: 1) bladder and anterior mobilization; 2) ligation of the dorsal venous complex; 3) dissection of the anterior and posterior bladder neck; 4) detachment of the seminal vesicles; 5) mobilization of prostate; 6) vesicourethral anastomosis[11,12]. Rectal injury and positive surgical margin (PSM) should be avoided during the operation[13].

ADT that oral nonsteroidal antiandrogen drugs such as bicalutamide (50 mg) once a day and gonadotropin-releasing hormone analogue (GnRH-a) such as subcutaneous goserelin (3.6 mg) or triptorelin (3.75 mg) monthly lasted 9 months for every patient after 3 months of surgery.

Assessment and follow-up

Biochemical progression (recurrence) was defined as a serum PSA level ≥ 0.2 ng/ml on two consecutive measurements in 3 months during or after ADT[14]. Systemic disease progression was defined as an imaging-identified systemic metastasis lesions or a biopsy-proven local recurrence. Cancer-specific mortality was defined as a death resulting from PCa or PCa-related events.

Postoperative follow-up for enrolled patients was performed quarterly in the first year, semiannually for the second year, and annually thereafter by clinical evaluation, PSA, and others as indicated. Hemoglobin, aminophorase and creatinine were measured annually during ADT. Chest X-ray and bone scan (ECT) were conducted annually after surgery.

Statistical analysis

Biochemical relapse-free survival rate, cancer-specific survival, and overall survival rate were analyzed using Kaplan–Meier method with the log-rank test for significance. Significance was defined by $P < 0.05$. The data were analyzed using IBM Statistical Package for the Social Science (SPSS Inc, Chicago, Illinois, USA) version 19.0.

Results

Complications and functional results

LRP plus ePLND was successfully performed for all the 232 cases. The mean operation time was 230 min and intra-operative bleeding was 105 ml. Catheter was removed within 2 weeks for most cases. Rectal and Ureter injury was observed in 3 and 1 cases, respectively. Urine leak, urinary retention, and vesicourethral anastomotic stricture after surgery occurred in 3, 1, and 11 cases, respectively. Urinary tract infection after decatheterization was found in 9 cases. PSM rate was 17.7 %. Urine incontinence occurred in only 11 (4.7 %) patients. Complications and functional results were summarized in Table 3.

Biochemical recurrence

After 12–124 months of follow-up, we found 122 biochemical recurrence cases. The overall biochemical relapse-free survival rate was 46.7 % (Fig. 1A). The 5- and 8-year biochemical relapse-free survival rates were 47.3 and 46.7 %, respectively. The survival analysis showed that biochemical relapse-free survival rates were significantly lower for patients with higher pathologic Gleason score (77.3 vs. 39.6 vs. 30.8 %, $P = 0.003$ log rank, Fig. 1C), higher T stage (55.7 vs. 41.4 vs. 21.4 %, $P = 0.039$ log rank, Fig. 1D), positive surgical margin (51.1 vs. 29.3 %, $P = 0.000$ log rank, Fig. 1E) and higher CAPRA-S score (68.6 vs. 35.0 vs. 29.2 %, $P = 0.000$ log rank, Fig. 1G). However, biochemical relapse-free survival rates of patients with different preoperative PSA levels (40.3 vs. 61.4 vs. 39.1, $P = 0.788$ log rank, Fig. 1B) and postoperative lymph node status (49.3 vs. 40.9 %, $P = 0.286$ log rank, Fig. 1F) showed no significant differences.

Survival

Thirty deaths were observed, including 14 died of PCa, 15 died of concomitant diseases (e.g., myocardial infarction, diabetes), and 1 died of misadventure (Table 4). The median survival time

for the 30 dead patients was 35 months (range 13–72 months). In our cohort of 232 patients, the overall survival and cancer-specific survival rates were 80.1 and 90.6 %, respectively (Fig. 2A, B). The 5- and 8-year overall survival rates were 81.2 and 80.1 %, respectively, and the 5- and 8-year cancer-specific survival rates were both 90.6%.

Outcomes of positive and negative lymph node PCa

Biochemical recurrences were observed in 80 patients with negative lymph node and 42 patients with positive lymph node and no significant difference between the two groups (49.3 vs. 40.9 %, $P = 0.286$ log rank, Fig. 1F). There were 18 of 160 cases with negative lymph node and 12 of 72 cases with positive lymph node who died in the follow-up phase. The overall survival rates of negative and positive lymph node PCa were 81.9 and 75.6 % ($P = 0.398$ log rank Fig. 3A), respectively. The cancer-specific survival rates of patients with negative and positive lymph node were 87.3 and 92.1 % ($P = 0.284$, log rank, Fig. 3B), respectively.

Discussion

Radiotherapy or conservative ADT alone or a combination therapy has become well-established treatment strategy for patients with locally advanced or pelvic lymph node metastatic PCa [1,15,16]. Though, a randomized control study by Warde et al. [16] for a total of 1057 patients with locally advanced PCa showed that the 7-year overall survival was significantly higher in cases treated by radiation than by ADT alone (74 % VS 65%), nearly a third of the patients manifested local progression as the first reported recurrence type in their study. Moreover, a report by Crook et al. [17] of high incidence of positive biopsy (10–91 %) after single radiotherapy also indicates that local control for locally advanced PCa treated by radiotherapy is still a great challenge for us, and for a better local control of locally advanced PCa, a development of more remedial modality should be necessary. RP is a golden standard modality for organ-confined PCa, while it was frequently avoided in the past years because it may not be able to cure most advanced non-extra node metastatic PCa with the potential of systemic progression [18,19]. However, some studies showed that RP became one of the modalities for advanced non-bone metastatic PCa with remarkable cancer-specific survival which is higher than endocrine ablation and as high as radiotherapy [4]. Also, a report by Casey et al. [20] showed that there was a comparable

continence rate between pT3 and localized PCa patients treated by robot-assisted LRP. More studies have also demonstrated LRP may benefit locally advanced PCa and lead to a better functional control compared with open radical prostatectomy [5,8]. In our study, LRP plus ePLND for non-extra node metastatic PCa resulted in 17.7 % of positive surgical margin, which was consistent with previously published range (14 to 61 %) for pT3 PCa treated by robot-assisted laparoscopic prostatectomy (RALP) [21,22]. We reported a higher continence rate of 94.8 % at 1 year postoperatively which was attributable to the modified prostate apex dissection in our operation [11]. Furthermore, as the surgical equipment and operation skills improved, the incidence of treatment-related complications decreased year by year [19,20]. In our study, the mean intra-operative bleeding was 105 ml, and of 232 patients, 4 cases were observed to have adjacent organ injury (3 rectal and 1 ureter), which also demonstrated that it can be safe for pathologically advanced PCa treated by LRP.

For patients with locally advanced PCa treated by RP, recent studies by Casey et al. [20] and Herrmann et al. [22] showed that the 5- and 10-year cancer-specific survivals were 85–95 % and 57–91.2 %, respectively. Here we reported the 5- and 8-year cancer-specific survivals were both 90.6 %, corresponding well with their reports. Moreover, the 5- and 8-year overall survivals in our study were 81.2 % and 80.1 %, respectively. However, of 232 patients, there were still 14 patients who died of local or systemic progressive PCa within 28–48 months, which may indicate that not all the patients with advanced PCa are suitable for LRP. RP is only recommended for patients with limited T3a, Gleason score 5–7, low PSA level, and a life expectancy of more than 10 years, which ensures a low risk of recurrence [23]. Previous studies have showed that Gleason score, pathological TNM stage, and surgical margin status were independent predictive factors for failure of treatment [24,25]. As a straightforward tool for improved prediction of outcomes after radical prostatectomy, the CAPRA-S score was first put forward by Cooperberg MR et al. By incorporating pathological information, CAPRA-S score has been used to predict disease recurrence after prostatectomy [9]. Here we reported that a higher CAPRA-S score predicted a lower biochemical relapse-free survival rate, which was consistent with Cooperberg MR's study. Still, we suggest that a patient with very high-risk PCa was not suitable for LRP.

Traditionally, standard PLND do not include presacral and internal iliac artery lymph nodes, which only totals a mean of 9 removed lymph nodes. However, previous studies have showed that

48%, 67%, and 48 % lymph node metastasis of PCa occurred in internal, external, and common iliac artery, respectively[26]. Moreover, some reports showed that an extended lymph node dissection could ensure a higher positive lymph node detection rate ranged from 23 to 26.2 % [18,27]. With a mean of 20 removed lymph nodes, the ePLND, including presacral, internal iliac artery and standard dissection area lymph nodes, should be performed in high-risk PCa with a very higher probability of lymph node invasion[28]. Later studies have also confirmed the importance of ePLND for advanced PCa and demonstrated the scope of the lymph node dissection should consist of internal iliac, external iliac, common iliac, presacral, and obturator fossa lymph nodes according to the lymph node drainage[5,27]. With all 232 patients received ePLND in our study, the mean removed lymph node was 20.35 and the lymph node positive rate was 31.0 %, which was higher than 7.3–11.2 % of standard PLND[26,29]. The ePLND can reduce the misdiagnosed positive nodes, and make sure of the maximum tumor-free state and accurate lymph node staging, which leads to a better local control and longer survival. A study by Van Baelen et al. [30] showed patients with 2 or fewer positive lymph nodes, who even not received adjuvant ADT after ePLND, could get a prolonged survival. In our study, the 8-year cancer-specific survival for 72 patients with lymph node metastasis was 87.3 %, as same as 92.1 % in statistics ($P = 0.284$) for 160 locally advanced PCa. Thus, we suggest that LRP plus ePLND is a feasible approach to patients with advanced PCa with or without lymph node metastasis as patients can get longer-term survival.

Conclusion

With very few complications, favorable functional outcomes, and competitive biochemical recurrence-free, overall and cancer-specific survival were reported, our study for 232 Chinese patients with locally advanced or lymph node metastatic PCa treated by LRP plus ePLND as primary therapy, which may suggest that LRP plus ePLND is a suitable intervention for pT3-4N0-1M0 PCa.

Clinical Practice Points

Previous study has showed that pathologically advanced PCa may benefit from LRP. Recently, CAPRA-S score has been used to predict disease recurrence after prostatectomy as a

straightforward tool for improved prediction of outcomes by incorporating pathological information. Here, a longer-term follow-up study firstly combined with CAPRA-S score was performed for confirming the effectiveness of LRP and the integrated assessment of clinical pathological parameters in long-time survival rate of patients with pT3-4N0-1M0PCa. CAPRA-S score may be useful in guidance for the choice of treatment on patients with advanced PCa.

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Tables

Table 1 Baseline characteristics of these 232 patients

Characteristic	Total	LN (-)	LN (+)	<i>P</i> value
No. of patients	232	160	72	
Preoperative PSA level (ng/ml)				0.137
<20	139 (59.9)	102 (63.8)	37 (51.4)	
20-50	70 (30.2)	46 (28.8)	25 (34.7)	
>50	23 (9.9)	12 (7.5)	10 (13.9)	
Clinical stage				0.447
T1c	40 (17.2)	26 (16.3)	14 (19.4)	
T2a	39 (16.8)	24 (15.0)	15 (20.8)	
T2b	62 (22.8)	47 (29.4)	15 (20.8)	
T2c	91 (39.2)	63 (39.4)	28 (38.9)	
Pathologic stage				0.056
T3a	107 (46.1)	82 (51.3)	25 (34.7)	
T3b	111 (47.8)	69 (43.1)	43 (59.7)	
T4	14 (6.0)	9 (5.6)	4 (5.6)	
Biopsy Gleason score				0.440
6	66 (28.4)	44 (27.5)	21 (29.2)	
7	113 (48.7)	82 (51.3)	31 (43.1)	
8-10	53 (22.8)	34 (21.3)	20 (27.8)	
Pathologic Gleason score				0.646
6	58 (25.0)	41 (25.6)	17 (23.6)	
7	96 (41.4)	63 (39.4)	33 (45.8)	
8-10	78 (33.6)	56 (35.0)	22 (30.6)	
PSM	41 (17.7)	24 (15.0)	18 (25.0)	0.067
Lymph node removed (mean)	9-38 (20.35)	9-30 (20.3)	11-38 (20.5)	0.103
Positive lymph node (mean)	0-25	0	1-25 (3.8)	<0.001
CAPRA-S score				
3-5	88 (37.9)			
6-7	96 (41.4)			
8-10	48 (20.7)			

Table 2 The characteristics of CAPRA-S for all 232 patients

Variable	Level	Points	N (%)
Preoperative PSA (ng/ml)	0-6	0	0 (0)
	6.01-10	1	2 (0.9)
	10.01-20	2	137 (59.1)
	>20	3	93 (40.1)
Surgical margins	Negative	0	191 (82.3)
	Positive	1	41 (17.7)
Seminal vesicle invasion	No	0	107 (46.1)
	Yes	1	125 (53.9)
Pathologic Gleason score	2-6	0	58 (25.0)
	3+4	1	41 (17.7)
	4+3	2	55 (23.7)
	8-10	3	78 (33.6)
Extracapsular extension	No	0	0 (0)
	Yes	1	232 (100)
Lymph node invasion	No	0	160 (69.0)
	Yes	1	72 (31.0)

Table 3 Complications and functional results for all 232 patients

Complication	N (%)
Rectal injury	3 (1.3)
Ureter injury	1 (0.4)
Urine leak	3 (1.3)
Urinary retention	1 (0.4)
Vesicourethral anastomotic stricture	11 (4.7)
Intraoperative hemorrhage	12 (5.2)
In-patient blood transfusion	16 (7.2)
Hernia	10 (6.9)
Infection after decatheterization	9 (3.9)
Lymphocele	2 (0.9)
Urethral stricture	12 (5.2)
Continence	
1 months	147 (63.4)
3 months	201 (86.7)
6 months	212 (91.4)
12 months	220 (94.8)

Table 4 Causes of death

Causes	N (%)
Local progression only	1 (3.3)
Distant progression only	8 (26.7)
Local and distant progression	5 (16.7)
Cerebrovascular events	2 (6.7)
Diabetes	5 (16.7)
Renal failure	1 (3.3)
Cardiac	7 (23.3)
Misadventure	1 (3.3)