Original Article

DOI: 10.6966/EDMJ.202206_9(2).0001

The Outcome of Laparoscopic Radical Prostatectomy in Prostate Cancer Patients with Preoperative Serum PSA Levels > 50 ng/mL: A Single Institution Experience

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Objectives: To assess the outcome of the patients diagnosed with prostate cancer with preoperative prostate-specific antigen (PSA) levels > 50 ng/mL who were treated with laparoscopic radical prostatectomy (LRP).

Methods: From January 2007 to December 2019, a total of 14 patients with an initial PSA level > 50 ng/mL who underwent LRP were included. All patients received pelvic lymph node dissection and eight of them underwent neurovascular bundle preservation. Perioperative parameters, pathologic features, functional outcomes, and survival rate data were collected and analyzed.

Results: For the 14 patients, the mean age was 69.4 ± 6.0 years and mean serum PSA level was 106.9 ± 86.1 ng/mL. Final pathology revealed that one patient was classified as stage pT2N0, one as pT2N1, two as pT3aN0, one as pT3aN1, five as pT3bN0, one as pT3bN1, two as pT4N0 and one as pT4N1. The positive surgical margin rate was 71%. Seven patients received long-term androgen-deprivation therapy (ADT) and five received radiation therapy plus adjuvant hormone therapy. A total of 93% of the patients achieved continence after an average recovery time of 71.5 days. Of the three patients who had fair erectile function pre-operatively, one remained potent after the operation. The cancer-specific survival, overall survival, and biochemical recurrence-free survival rates were 100%, 100%, and 93%, respectively.

Conclusions: Our experience showed that LRP can be considered to be the first step for patients with PSA > 50 ng/mL and can offer satisfactory disease control and functional outcomes. However, multimodal treatment such as hormone therapy or radiation therapy may be needed as adjuvant treatment.

Key words: prostate cancer, prostate-specific antigen, radical prostatectomy

Introduction

Prostate cancer is the second most common cancer in men in the western countries.[1]

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Received: August 24, 2020 Accepted: January 28, 2021

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With the increasing popularity of prostate cancer screening, the incidence of prostate cancer is also increasing in Asian countries.[2] Compared with western countries, a higher portion of prostate cancer seems to be detected at advanced stages in Asia, including Taiwan.[3] This may be due to differences in screening approach, treatment, lifestyle, and/or genetic factors.[2]

In clinical practice, patients diagnosed as having prostate cancer with very high prostate specific antigen (PSA) (> 50 ng/mL) levels are categorized as high-risk prostate cancer (HRPC). However, there is no optimal treatment for HRPC. External beam radiotherapy (EBRT) with androgen deprivation therapy (ADT), EBRT with brachytherapy with or without ADT, and radical prostatectomy (RP) with pelvic lymph node dissection are all available treatment options for high-risk patients. Although some research has emphasized comparable oncological outcomes between RP and EBRT plus ADT for patients with HRPC,[5] a review of contemporary published studies has revealed a higher number of patients receiving EBRT compared with RP.[4-6] One possible explanation may be surgeons' inclination to choose a conservative treatment approach for patients with serum PSA levels > 50 ng/mL who might be expected to have poor outcomes after attempted curative treatment.

The purpose of this study was to evaluate the efficacy of LRP as the first step of a multimodal treatment by a surgical team at a single institute through analyzing the outcomes of men with prostate cancer and very high (> 50 ng/mL) preoperative serum PSA levels.

Materials and Methods

Study design

From January 2007 to December 2019, a total of 1,645 patients were diagnosed with prostate cancer at a tertiary referral hospital (E-Da Hospital). Of those patients, 361 (21.9%) received radical prostatectomy performed by a dedicated surgical team.

Participants

Based on the National Comprehensive Cancer Network (NCCN) guideline (version 2020), EBRT is the Category 1 option for high- and very high-risk patients and should be performed on selective patients who are relatively young, of medium build as well as having a good performance status (ECOG:0-1) and a low Charlson Cormobidity Index without previous major abdominal operations except relatively minor procedures such as appendectomy or herniorrhaphy. Besides, the tumor must be resectable and not too close to the apex area to enable the preservation of enough urethra. Patients with distant metastasis [i.e., involvement of non-regional lymph nodes (LN), bone, or other distant sites] were excluded but not those with regional LN enlargement or locally advanced prostate cancer. Of all the eligible patients, 21 had initial PSA levels > 50 ng/mL. After excluding seven patients receiving robotic surgery and those with incomplete data or being lost to follow-up, 14 patients were finally enrolled. All 14 patients were treated by laparoscopic radical prostatectomy (LRP) which was conducted by a single surgical team. The demographic and perioperative data including age, body mass index, preoperative PSA level, biopsy Gleason sum, and clinical staging were collected and analyzed retrospectively. The protocol and procedures of the current study were reviewed and approved by the institutional review board (IRB) of E-Da Hospital and was registered at http://www.edah.org.tw/irb/ (IRB approval number: EMRP-102-093).

All 14 patients received preoperative magnetic resonance imaging or computed tomography plus an isotope bone scan for tumor staging. Pre-operative hormone therapy was not routinely used. Only four patients received few doses of pre-operative hormone therapy

from other hospital mainly because of the presence of regional pelvic LN lesion(s) on pre-operative imaging.

Operative procedures

LRP was performed using a four-port extra-peritoneal laparoscopic approach with pelvic lymphadenectomy as previously described.[7] Neurovascular bundle preservation was decided based on the patient's tumor location and the invasion depth. Urethrovesical anastomosis was performed by using 6 – 8 interrupted 2-0 Vicryl (RB-1 needle) with the placement of a 3-way 20 Fr. indwelling Foley catheter. No patient had undergone previous transurethral resection of the prostate. None of the patients required conversion to open surgery. The Foley catheter was removed on postoperative day 6 – 8. Cystography was not routinely performed except in patients with difficult reconstruction during their operation. The drain was removed if daily drainage amount was less than 50 mL. Postoperative hospital stay was calculated from the day of operation to the day of patient discharge.

Table 1. Baseline demography of patients with preoperative prostate-specific antigen (PSA) levels > 50 ng/mL who were treated with laparoscopic radical prostatectomy.

Baseline demographics	N = 14
Mean age, years ± SD	69.4 ± 6.0
BMI, kg/m^2 ± SD	24.3 ± 1.9
Clinical stage	
T1c	2
T2a	1
T2b	1
T2c	7
T3a	0
T3b	3
Image stage	
T2a	1
T2b	0
T2c	6
T3a	3
T3b	3
T4	1
N+	4
Biopsy Gleason score	
< 7	2
= 7	7
> 7	5
Mean PSA, ng/mL (range)	106.9 (50.7 – 372.5)
Pre-operation hormone therapy (%)	4 (29%)
Previous abdominal surgery (%)	2 (14%)

Study parameters and definitions

Perioperative complications were classified according to Clavien-Dindo grading.[8] Serum PSA concentrations were checked one month after the operation, followed by every three months for two years and every six months afterwards. Continence condition and erectile function were checked during each outpatient clinic follow-up. Continence was defined as 0 – 1 safety pad per day. Potency referred to having a morning erection or able to achieve vaginal penetration, which was represented by Erection Hardness Score 3 – 4, with or without phosphodiesterase type 5 (PDE 5) inhibitor. Biochemical recurrence was defined as two consecutive increasing postoperative serum PSA levels from PSA nadir or PSA > 0.2 ng/mL.

Statistical analysis

Analysis was performed with the SPSS statistical software package, version 22.0 (SPSS, Chicago, Illinois, USA).

Results

Patient demographics and disease status

The pre-operative general and demographic characteristics of the 14 patients are shown in Table 1. The mean age of the patients was 69.4 (range, 60 – 77) years and the mean body mass index was 24.3 (range, 21.4 – 28.2) kg/m^2. The median Charlson Comorbidity Index was three (range, 2 – 6). The average PSA level was 106.9 (range, 50.7 – 372.5) ng/mL. In terms of baseline demographics, nine (64%) patients were in clinical T2 stage and

seven (50%) patients had a Gleason score of 7. Imaging studies showed a tumor staging of T2, T3, and T4 in seven patients, six patients, and one patient, respectively. Four patients received pre-operative hormone therapy mainly because of the presence of regional pelvic LN lesion(s) on pre-operative imaging.

Operative procedures and treatment strategies

Perioperative parameters and pathological findings are presented in Table 2. Mean (range) operation time, intraoperative blood loss, specimen weight, postoperative hospital stays and catheterization days were 365.7 (250 – 495) minutes, 141.4 (50 – 400) mL, 56.5 (32.8 – 96.5) gm, 7.7 (6 – 15) days, and 8.4 (6 – 16) days respectively. About postoperative pathological stages, the 14 patients were classified into different stages according to the presence of LN metastasis, which was noted in one of the two patients at stage pT2, one of the three patients at stage pT3a, one of the six patients at stage pT3b, and one of the three patients at stage pT4 stage. The mean LN yield was 15.4 (5 – 33). Six (43%), three (21%), two (14%), and three (21%) patients had pathological Gleason scores of 3 + 4, 4 + 3, 4 + 4, 9 respectively. Upon pathological staging and grade correction, eight (67%) patients were up-staged from T1/2 to T3/4 and none was found to be down-staged. Besides, four (29%) were up-graded and four (29%) were down-graded. The overall positive surgical margin (PSM) rate was 71%. For the 10 patients with PSM, four was at the apex area, three were bilateral, one was on the left lateral side, one was on the right lateral side, and one was in the bladder neck region. Of the 14 patients, eight received neurovascular bundle preservation, including seven with bilateral preservation and one with unilateral preservation. Rhabdosphincter was repaired in eight patients. Four minor complications, which occurred during postoperative days 0 – 30, were categorized by using the Clavien-Dindo classification including contrast medium extravasation on cystogram in two patients and leg numbness in another two. No complications were noted during postoperative days 31 – 90. Adjuvant hormone therapy was used in patients with confirmed LN metastasis. Besides, because of high PSA level, micro-metastasis was considered in these patients and adjuvant hormone therapy was suggested even in the absence of pathologically proven metastasis. Although radiotherapy was encouraged for all the patients with PSM, not all the patients with this condition received radiation therapy. Finally, seven patients only received adjuvant hormone therapy and another five patients underwent adjuvant hormone therapy with ra-

Table 2. Perioperative parameters of patients with preoperative prostate-specific antigen (PSA) levels > 50 ng/mL who were treated with laparoscopic radical prostatectomy.

Perioperative parameters	N, (%)
Mean operation time, min ± SD	365.7 ± 69.9
Mean blood loss, mL ± SD	141.4 ± 117.1
Blood transfusion	0
Nerve sparing	
None	6 (43%)
Unilateral	1 (7%)
Bilateral	7 (50%)
Repair rhabdosphincter	8 (57%)
Converted to open surgery	0
Mean specimen weight, gm (range)	56.5 (32.8 – 96.5)
Mean LN count (range)	15.4 (5 – 33)
Complication	2 (14%, all grade I)
Pathological stage	
pT2	2 (14%)
pT3a	3 (21%)
pT3b	6 (43%)
pT4	3 (21%)
pN+	4 (29%)
Gleason score	
= 7	9 (64%)
> 7	5 (36%)
Positive surgical margin	10 (71%)
Pathological stage and grade correction	
Up staging (from T1/2 to T3/4)	8 (57%)
Down staging (from T3/4 to T1/2)	0 (0%)
Up grading	4 (29%)
Down grading	4 (29%)
Post operation stay, day (range)	7.7 (6 – 15)
Catheterization days, day (range)	8.4 (6 – 16)

diotherapy. Among the 10 patients with PSM, six only received adjuvant hormone therapy and three received adjuvant hormone therapy with radiotherapy. The PSA concentrations of two patients, whose initial PSA levels were 51.5 ng/mL and 62.8 ng/mL with pathological stages being pT2N0 and pT3aN0, respectively, returned to undetectable level without any adjuvant therapy. It took an average of 0.4 years to reach nadir PSA levels.

Follow-up and outcomes

In our study, the mean follow-up was 7.2 (3.8 – 13.0) years. Only one patient, who had a PSA concentration of 191.1 and a pathological stage of pT4N0, experienced a biochemical recurrence. This patient received adjuvant hormone therapy with radiotherapy and remained stable condition after a 17-month follow-up. Of the 14 patients, the overall continence rate was 93% and the average recovery time was 71.5 (7 – 303) days. Of the three patients who were potent preoperatively, only one recovered erectile function after six months of follow-up. This patient, who had an initial PSA level of 51.5 ng/mL, received bilateral neurovascular bundle preservation without adjuvant hormone therapy. During the follow-up period, the overall survival and cancer-specific survival rates were both 100%.

Discussion

For patients with HRPC, radiotherapy combined with hormonal therapy is highly recommended and RP is performed on a select group of patients. Currently, no randomized controlled trial was conducted to compare these two strategies and determine which was the preferred approach.[9] For patients receiving EBRT as their first treatment, local and systemic salvage therapy were performed less frequently than in RP patients. However, higher long-term complications, including minimally invasive urological procedures, admission of hospital, rectal-anal procedures, and open surgical procedures, than patients undergoing surgery were noted.[4,10] Some studies have shown that patients who underwent RP, followed by adjuvant radiotherapy, have benefitted from an increase in overall survival and PSA recurrence-free survival for T3 prostate cancer specifically.[11,12] Besides, RP not only can provide definitive stage and grade information but also has excellent local control and appears to reduce the risk of metastatic progression.[13,14] Recently, for the patients with regional LN enlargement/metastases or locally advanced prostate cancer, evidence for the benefit of RP for these patients has increased progressively and the results showed that RP can improve progression-free and overall survival.[15,16] Even in an entity of oligo-metastasis setting, local control has promising results.[17] Besides, salvage RP after RT is more difficult and challenging than primary RP. Worse functional outcomes and an increased risk of adverse effects can be expected compared with primary RP. Therefore, RP can be considered as one effective modality to cure the disease or as the first step of a multimodal treatment strategy and demonstrated favorable results in selected patients.

Of the clinical features that characterize prostate cancer, serum PSA is the most objective. Patients with preoperative serum PSA levels of > 50 ng/mL are classified as a high-risk group. However, the D'Amico criteria do not take pre-therapy PSA values of > 50 ng/mL as a cutoff value. Only a few studies try to evaluate the outcome of these high-risk patients. Because of a high PSA, a poorer prognosis could be considered compared with other high-risk group patients with prostate cancer. Therefore, more conservative treatments could be considered.

The incidence of PSA > 50 ng/mL in patients receiving radical prostatectomy was 5% in our hospital. The incidence reported by other groups ranged from 0.8% to 9.2%.[18]

This study demonstrates that patients with PSA values of > 50 ng/mL can be expected to present with Gleason grades ≥ 8 in 36%. More than 80% will have an extra-prostatic extension and 29% will have pelvic LN involvement. Partin et al. included 34 patients with preoperative PSA > 50 ng/mL showed 91% of extra-prostatic extension and 27% of LN metastasis.[19] Another dataset with a total of 234 patients from Inman et al. showed 25% of Gleason score ≥ 8, 83% of extra-prostatic extension, and 37% had pelvic LN involvement in this group.[13]

PSM is considered to be an adverse feature that will influence the early PSA recurrence-free survival rate and may require additional local therapy.[20,21] Thus, PSM rate plays an important role in oncologic outcomes of patients with HRPC. For the PSM rate, it was 71% in our study. It seems quite high compared with other published articles treating patients with HRPC, where the range of PSM was from 26 to 43%.[9,22] However, when focusing on patients with PSA > 50 ng/mL, Inman et al. reported a 79% PSM rate and Ou et al. reported 87%.[13,18] Therefore, our PSM rate is not higher than that in the previous report. Besides, if we want to reach a lower level of PSM rates, more extensive excision has to be done. This, in turn, means we may have to sacrifice more continence, erectile function or perirectal tissue to achieve this goal. After all, even with a high PSM rate, by using a multimodal treatment approach, we still are afforded satisfactory disease control and functional outcomes.

The concept of treating this kind of patients is that RP is not usually adequate as a monotherapy. A multimodal treatment (like ADT and radiotherapy) is often required to achieve long-term success rates. Therefore, most patients received adjuvant hormone therapy for fear of micro-metastasis. During the following period, seven (50%) received ADT and five (36%) received adjuvant radiotherapy plus ADT. Radiation therapy was suggested to all patients with a PSM, but some refused due to fear of its side effects. Only two patients achieved nadir PSA without adjuvant hormone therapy and their initial PSA levels were 51.5 and 62.8.

In this study, we defined continence as "0 – 1 safety pad per day" and potency as "having morning erection or able to achieve vaginal penetration, which was represented by Erection Hardness Score 3 – 4, with or without PDE 5 inhibitor". The results showed 93% patients achieved continence and 33% patients recovered their potency. In the report by Pompe et al., the 1-year continence and potency rates were 81.9% and 45.2%, respectively, in the high-risk group of 1,369 patients.[23] Pierorazio et al. reported continence and potency rates of 93% and 69.6%, respectively, in 47 HRPC cases with at least one year of follow-up.[24] However, there is no available published data showing the functional outcomes for patients with an initial PSA of > 50 ng/mL who received RP as their primary treatment.

It seems we have an acceptable continence rate compared with other large series but a lower potency rate. Interestingly, more than one-fifth of the patients used pharmacotherapy to assist erections in the Pompe et al. report.[23] On the contrary, none of our patients used phosphodiesterase type 5 inhibitors or intracavernous injection therapy to assist erections.

Our biochemical free survival rate is 93% which is much higher than Inman et al. and Ou et al. reported, which was 51% at five years and 10.1% at eight years respectively.[13,18] The result seems to be quite encouraging and promising, but this may be due to different therapeutic protocols, lack of tracking time, and the insufficient number of samples.

When discussing metastasis-free survival and cancer-specific survival, the study of Inman et al. showed patients with PSA values between 50 and 99 ng/mL experienced 10-year metastasis-free and cancer-specific survival rates of 83% and 90%, respectively.[13] Ou et

al. showed a 91.3% cancer-specific survival.[18] Though our cancer-specific survival rate was 100% and no metastasis was found, our mean follow-up time is limited.

Other limitations of this study were the mean follow up time and obvious small sample size. As the follow-up increased, the need for additional therapy might occur. Further large-scale studies with long-term follow-up are needed to verify our findings. Besides, we did not compare the outcomes between patients receiving radiotherapy and patients receiving RP as their first treatment at the same time point. Although this study has some clear limitation, we did successfully demonstrate that receiving LRP plus the use of a multimodality treatment approach for selected patients with PSA level > 50 ng/mL may not be as bad as our previous expectations.

Conclusions

Patients with prostate cancer and pre-operative serum PSA level of > 50 ng/mL are more likely to be pathologically advanced. Although the realization of the probability of worse outcomes compared with other patients of prostate cancer in an early stage, disease control and functional outcome of these high-risk group patients remain excellent and support the aggressive management style of these cases. Therefore, LRP can be considered a viable option in select patients with very elevated PSA level in an endoscopic center of excellence.

Conflicts of Interest

The authors report no conflict of interest.

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