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ORIGINAL ARTICLE

Salvage treatments for prostate-specific antigen relapse of $cT_3N_0M_0$ prostatic adenocarcinoma after radical prostatectomy combined with neoadjuvant androgen deprivation

Lufang Zhang[1], Dongliang Pan[2] (✉), Ludong Liu[1], Yunjiang Zang[1], Ningchen Li[2]

[1] Department of Urology, Weifang People's Hospital, Shandong 261000, China
[2] Department of Urology, Peking University Shougang Hospital; Wujieping Urology Medical Center of Peking University, Beijing 100144, China

Abstract

Objective The aim of the study was to evaluate the efficiency of salvage treatments for prostate specific antigen (PSA) relapse of $cT_3N_0M_0$ prostatic adenocarcinoma (PCa) after radical prostatectomy (RP) combined with neoadjuvant androgen deprivation (ADT).

Methods A total of 332 patients with $cT_3N_0M_0$ PCa were enrolled in the prospective study and received RP and pelvic lymph node dissection with neoadjuvant ADT for 3 months. All patients with PSA relapse were treated with salvage external beam radiation therapy (RT) and ADT for 6 months.

Results The 5-year postoperative PSA relapse rate was 40.96% (136/332). The patients have been divided into the PSA relapse and PSA relapse-free groups in order to compare patient characteristics. The ratio of patients with Gleason score ≥ 8 and positive surgical margin in the PSA relapse group were significantly higher than those of in the PSA relapse-free group (P = 0.01). The mean duration between the start of operative treatment and PSA relapse was 31 months. Salvage treatment to all 136 PSA relapse patients led to favorable outcomes. PSA relapse was not observed after salvage treatment by the end of follow-up. The 5-year overall survival rates of the PSA relapse and PSA relapse-free groups were 94.9% and 93.9%, respectively.

Conclusion In pursuit of curative treatment, our study showed that RP combined with neoadjuvant ADT is an aggressive multimodality strategy associated with lower PSA relapse and better survival outcomes for stage $cT_3N_0M_0$ PCa patients. Patients with PSA relapse after RP may benefit from early aggressive salvage RT combined with short-term ADT.

Key words: prostatic adenocarcinoma (PCa); radical prostatectomy (RP); neoadjuvant androgen deprivation (ADT); external beam radiation therapy; salvage treatment; prostate specific antigen (PSA) relapse

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$T_3N_0M_0$ prostatic adenocarcinoma (PCa) is a locally advanced disease characterized by tumors having various properties, with some exhibiting remarkably malignant behavior. To date, no standard treatment for the disease can be defined in the absence of level 1 evidence. A multimodal therapy comprising local treatment combined with a systemic one provides the best outcome, provided the patient is ready and fit enough to receive both. Nevertheless, the optimal local treatment is still a matter of debate.

There are many local treatment opinions as well as discussions about the use of operative procedures and radiation; however, most curative procedures are based on multidisciplinary strategies combined with androgen deprivation therapy (ADT). Surgery for locally advanced PCa as part of a multimodal therapy has been reported [1–3]. A prospective phase III RCT (SPCG-15) comparing radical prostatectomy (RP) with or without adjuvant

✉ Correspondence to: Dongliang Pan. Email: dongliangpan@hotmail.com

or salvage external beam radiation therapy (EBRT) against primary EBRT and ADT among patients with T_3 PCa is currently recruiting [4], and RP and laparoscopic techniques are continuously developing [5]. However, the comparative oncological effectiveness of RP as part of a multimodality treatment strategy versus upfront EBRT with ADT for T_3 PCa remains unknown.

We treated T_3 PCa patients with RP combined with neoadjuvant ADT from 2005 to 2014. When prostate-specific antigen (PSA) relapse occurred, these patients were treated with salvage EBRT and ADT. Outcomes for $T_3N_0M_0$ PCa patients from two hospitals were reported.

Patients and methods

Patients

A total of 332 patients with $cT_3N_0M_0$ PCa were diagnosed and treated at two investigative hospitals in China between 2005 and 2014. All patients had been initially diagnosed as having PCa and had not received any prior Gn-RH analogue or hormonal treatment. Their outcomes were documented in the present study after obtaining their informed consent and ethical approval of hospitals. Records of patient outcomes were completed by the end of 2019. The classification of stages was performed according to the National Comprehensive Cancer Network guidelines [6]. Pretreatment biopsy consisted of 12 cores that were performed via the perineal route, and the pathological findings were classified using the Gleason grading system with the ISUP 2005 modification [7]. Ultrasonography, magnetic resonance imaging, computed tomography, and whole-body bone scan were performed in all patients. Their mean age was 73.2 years (range: 61–80 years) and their total PSA values were 12.15–28.53 ng/mL.

Methods

Open or laparoscopic retropubic RP and pelvic lymph node dissection were performed with neoadjuvant ADT for 3 months. ADT consisted of a luteinizing hormone-releasing hormone analog with daily dose of 50 mg bicalutamide. Total PSA was measured every month after RP and then every 3 months from the second year. PSA relapse was defined as a linear increase in PSA of more than 0.1 ng/mL. Before the PSA level rose to > 0.5 ng/mL, all PSA relapse patients were treated with salvage EBRT and ADT for 6 months. EBRT was performed with total doses of 66–78 Gy. The clinical target volume was defined as the surgical bed of the entire prostate. After EBRT, total PSA was monitored similarly as during postoperative monitoring.

Statistical analyses

The SPSS statistical computer program (IBM SPSS V26.0; USA) was used to calculate PSA relapse and overall survival rate. The Cox proportional hazard model and multivariate analysis were used to evaluate the difference among clinical factors and outcomes. P values of ≤ 0.05 were considered significant. The follow-up time was calculated from the start date of treatment initiation up to the end of 2019.

Results

The 5-year postoperative PSA relapse rate in all patients was 40.96% (136/332). All 332 patients had been assigned into either the PSA relapse group or PSA relapse-free group in order to compare patient characteristics.

Some patient characteristics, such as the age, preoperative PSA value, and ratio of stage T_{3a} and T_{3b}, were similar between the two groups (Table 1). The ratio of patients with a Gleason score ≥ 8 was significantly higher in the PSA relapse group (42.0%) than in the PSA relapse-free group (32.7%; P = 0.01). However, there were no significant difference in the ratios of patients with Gleason scores ≤ 6 and 7 between these two groups.

According to the histological examination of operative specimens, cancerous tissues were found at the edge of the cutting surfaces in 7 patients of the PSA relapse group, whereas no patients in the PSA relapse-free group exhibited positive surgical margins (P = 0.001). No metastases were detected in regional lymph nodes. The

Table 1 Patient characteristics and outcomes [*n* (%)]

Characteristic	PSA relapse (*n* = 136)	PSA relapse-free (*n* = 196)
Age (year)	72.4 (61–79)	74 (61–80)
PSA (ng/mL)	24.6 (12.8–28.53)	21.13 (12.15–27.2)
Stage		
T_{3a}	113 (83.0%)	167 (85.2%)
T_{3b}	23 (17.0%)	29 (14.8%)
Gleason score		
≤ 6	56 (41.1%)	89 (45.4%)
= 7	23 (16.9%)	43 (21.9%)
≥ 8	47 (42.0%)	64 (32.7%)
Positive surgical margin	7	0
Positive lymph node	0	0
Postoperative PSA relapse	136 (40.9%)	0
Duration* (month)	31 (9–37)	–
Salvage treatment	136	–
PSA relapse after salvage treatment	0	–
Death		
Prostate Ca	0	0
Other	7 (5.1%)	12 (6.1%)

Note: Statistical significance of PSA relapse vs no relapse-positive surgical margin: P = 0.001; Gleason score ≥ 8: P = 0.01; * Start of relapse

extension of tumors through the prostate capsule was considered low in most of the patients, thus no adjuvant treatments were immediately scheduled.

The mean duration between the start of operative treatment and PSA relapse was 31 months. After relapse, good treatment compliance was observed and the salvage treatment in all 136 patients led to favorable outcomes. After the salvage treatment, no PSA relapse was observed until the end of follow-up.

The 5-year overall survival rates of the PSA relapse and PSA relapse-free groups were 94.9% and 93.9%, respectively. Deaths that occurred during the follow-up were not directly from prostate cancer. No detectable adverse effects were observed in the patients who underwent salvage treatment.

Discussion

Irrespective of the pT stage, between 27% and 53% of all PCa patients undergoing RP or RT increasingly develop PSA relapse. Moreover, between 5% and 20% continue to have detectable or persistent PSA after RP [8–9]. PSA relapse has been reported to occur in 60% of patients with stage T_3 PCa, 5 years after the start of treatment, which suggests a mortality rate of 70%–80% thereafter. ISUP score > 2 or patients classified as pT_3 pN_0 after RP due to positive margins, capsule rupture, and/or invasion of the seminal vesicles are at high risk of relapse; this risk can be as high as 50% after five years [10]. In another study, patients with stage T_3 PCa have been surgically examined to confirm negative regional lymph glands, then treated with RT; 64% of these patients experienced PSA relapse [11]. These findings indicate that RP or RT alone did not completely suppress subsequent disease progression. Therefore, numerous multimodality strategies are already being discussed to improve the survival of stage T_3 PCa patients.

RP with neoadjuvant ADT have been performed for several months in some studies [12–13], resulting in a decrease in the stage and a reduction of marginal invasion observed in the prostate specimen. Moreover, histological changes resulting from ADT have already been confirmed [14]. However, these improvements did not continue according to longer-term observations [15–17]. Some stage T_3 PCa patients exhibit postoperative PSA relapse, with the histological findings on the cancer tissues exhibiting a high Gleason pattern [18]. In our study, a similar pattern was also observed. The ratio of patients with Gleason score ≥ 8 in the PSA relapse group was significantly higher (42.0%) than in the PSA relapse-free group (32.7%; $P = 0.01$).

PSA relapse after RP may result from persistent local disease, pre-existing metastases, or residual benign prostate tissue. On the other hand, persistent PSA after RP is associated with more advanced disease (such as positive surgical margins, pathologic stage > T_{3a}, positive nodal status, and/or pathologic ISUP grade > 3). However, not all patients with persistent PSA after RP experience disease recurrence. Xiang *et al* showed a 50% 5-year biochemical relapse-free survival for patients who had persistent PSA level > 0.1 ng/mL, but < 0.2 ng/mL at 6–8 weeks after RP [19].

The timing and treatment modality for PSA-only relapse after RP remain controversial because of limited evidence. Active surveillance is the first choice for patients when their PSA levels are > 0.1 ng/mL but < 0.2 ng/mL. Salvage RT (SRT) is usually decided on the basis of biochemical relapse without histological proof of local recurrence, but only when the PSA level is < 0.5 ng/mL. Nevertheless, more than 60% of patients who have been treated before the PSA level rises to > 0.5 ng/mL achieved an undetectable PSA level [20–23], corresponding to an 80% chance of being progression-free five years later [24].

Early SRT provides the possibility of cure for patients with an increasing PSA after RP. Boorjian *et al* [25] reported a 75% reduced risk of systemic progression with SRT, when comparing 856 SRT patients with 1801 non-SRT patients. Wiegel *et al* [26] showed that following SRT to the prostate bed, patients with a detectable PSA after RP had significantly worse oncological outcomes when compared with those who achieved an undetectable PSA. Their 10-year metastasis-free survival was 67% *vs.* 83%, and their overall survival was 68% *vs.* 84%, respectively. Recent data from Preisser *et al* [27] also compared oncological outcomes in patients with persistent PSA who received SRT versus those who did not. In the subgroup of patients with persistent PSA, after 1:1 propensity score matching between patients with SRT *vs.* no RT, the 10-year overall survival rates after RP were 86.6% *vs.* 72.6% in the entire cohort ($P < 0.01$), 86.3% *vs.* 60.0% in patients with positive surgical margin ($P = 0.02$), 77.8% *vs.* 49.0% in pT_{3b} disease ($P < 0.001$), 79.3% *vs.* 55.8% in ISUP grade 1 disease ($P < 0.01$), and 87.4% *vs.* 50.5% in pN_1 disease ($P < 0.01$), for SRT and no RT, respectively. Moreover, the 10-year CSS rates after RP were 93.7% *vs.* 81.6% in the entire cohort ($P < 0.01$), 90.8% *vs.* 69.7% in patients with positive surgical margin ($P = 0.04$), 82.7% *vs.* 55.3% in pT_{3b} disease ($P < 0.01$), 85.4% *vs.* 69.7% in ISUP grade 1 disease ($P < 0.01$), and 96.2% *vs.* 55.8% in pN_1 disease ($P < 0.01$), for SRT and no RT, respectively. In multivariable models, after 1:1 propensity score matching, SRT was associated with a lower risk of death (HR: 0.42, $P = 0.02$) and lower cancer-specific death (HR: 0.29, $P = 0.03$). These survival outcomes for patients with persistent PSA who underwent SRT suggest that they benefit from the treatment; however, outcomes are still worse for patients experiencing biochemical relapse. Choo *et al* report that the addition of 2-year ADT to immediate RT in the prostate bed of patients with pathologic T_3

disease and/or positive surgical margins after RP may improve progression-free survival [28]. The GETUG-22 trial comparing RT with RT plus short-term ADT for post-RP PSA persistence (0.2–2.0 ng/mL) also reported good tolerability of the combined treatment; however, their oncological end-points are yet to be published [29]. In our present study, we reported that SRT and 6 months of ADT was associated with favorable results. Our findings suggest that patients with PSA relapse after RP may benefit from early aggressive multi-modality treatment such as SRT combined with short-term ADT.

Conclusion

In the pursuit of curative treatment for stage $cT_3N_0M_0$ healthy PCa patients, our findings show that RP combined with neoadjuvant ADT is one of the aggressive multimodality strategies associated with lower PSA relapse and better survival outcomes. Patients with PSA relapse after RP may benefit from early aggressive SRT combined with short-term ADT.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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