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ORIGINAL ARTICLE

Small-volume lymph node involvement and biochemical recurrence after robot-assisted radical prostatectomy with extended lymph node dissection in prostate cancer

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Abstract

Background We investigated prognostic factors for biochemical recurrence (BCR) after robot-assisted radical prostatectomy (RARP) with extended pelvic lymph node (LN) dissection.

Methods We included 173 patients who underwent RARP with extended pelvic LN dissection without neoadjuvant therapy at our hospital between October 2010 and April 2018. BCR was defined as prostate serum antigen (PSA) levels ≥ 0.2 ng/mL; BCR-free survival rates were determined using Kaplan–Meier analysis. We used Cox regression analysis to evaluate effects of PSA and pathologic variables on BCR.

Results Median follow-up was 27.9 (range 6.1–86.9) months. Five-year BCR-free survival was 89.5%. In multivariate analysis, positive LNs (HR 7.117; 95% CI 2.826–17.925; $P < 0.001$) and Gleason score (GS) ≥ 8 (HR 2.612; 95% CI 1.051–6.489; $P = 0.039$) were significant predictors of BCR. Patients with 1 or 2 positive LNs ($n = 10$) had significantly higher BCR-free survival rates than patients with ≥ 3 positive LNs ($n = 5$). We, therefore, stratified the patients as low-risk (GS < 8 and no positive LNs), intermediate-risk: (either GS ≥ 8 or positive LNs) and high-risk (both GS ≥ 8 and positive LNs). Their 1-year BCR-free survival rates were low-risk: 94.6%, intermediate-risk: 88.5%, and high-risk: 33.3% ($P < 0.05$).

Conclusions Patients with 1–2 positive LNs and GS < 8 have low risk for BCR; close observation without immediate adjuvant hormonal therapy can be considered for these patients.

Keywords Lymph node dissection · Radical prostatectomy · Robotics · Prostate cancer · Biochemical recurrence

Introduction

Robot-assisted radical prostatectomy (RARP) is widely used to treat clinically localized prostate cancer (PCa). The 5-year biochemical recurrence (BCR)-free survival rate after RARP is reportedly 74–87%; prostate-specific antigen (PSA) level, pathologic Gleason score (GS), pathologic T stage, positive surgical margin (PSM), and lymphovascular invasion are all reported to be independent predictors of BCR [1]. Novara et al. reported that PSM rates ranged from 6.5 to 32% among contemporary patients who had undergone radical prostatectomies, and PSM rates were similar following RARP, retropubic radical prostatectomy, and laparoscopic radical prostatectomy [1]. In contrast, some recent studies have shown RARP to reduce risks of PSM and BCR compared with open radical prostatectomy [2, 3]. However, RARP has a long learning curve with inferior outcomes initially, but progressively superior pT2 and pT3 PSM outcomes as skill is acquired [4]. Furthermore, RARP with extended pelvic LN dissection (PLND) is considered a feasible option for very high-risk PCa in elderly patients with satisfactory oncologic outcomes as one of the multimodal treatment [5].

Although patients with PCa and pathologically positive lymph nodes (LNs) are considered to have poorer prognosis than those with negative LNs [6–8], pathologically positive LNs are reportedly not predictive of BCR after radical prostatectomy, including RARP, in patients with locally advanced PCa [9–11]. However, although extended PLND

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is recommended for patients with higher-risk PCa according to several guidelines on PCa in the current robotic era [12, 13], the therapeutic benefit of PLND remains debatable, and no consistent conclusions have been reached. Nevertheless, some urologists have seen PCa patients with pathologically positive LNs, after radical prostatectomies from the open surgery era, and without additional adjuvant therapies, who had no BCR. Some authors report that PCa patients with a few pathologically positive LNs have low risk of BCR, or of poor cancer-specific survival (CSS) [14–17]. The number of urologists who perform extended PLND has increased in Japan and other countries as the use of, and expertise in, RARP has expanded [11, 18]. In the present study, we evaluated factors that predict BCR in PCa patients after RARP, including numbers of pathologically positive LNs. We also developed a prognostic factor-based risk stratification model for BCR.

Patients and methods

We retrospectively analyzed 416 consecutive patients with PCa who underwent RARP from October 2010 to April 2018 at our hospital. All surgeries were performed using the da Vinci Surgical System (Intuitive Surgical, Sunnyvale, CA, USA). We excluded patients who had neoadjuvant hormonal treatment ($n=39$), no PLND ($n=38$), limited PLND ($n=163$), or follow-up < 6 months ($n=3$). The median number of removed LNs in the limited PLND cohort was 8.0 (range 0–23) and only one patient (0.61%) had pathologically positive LNs. Finally, we included 173 patients who underwent extended PLND. The research protocol was approved by the institutional review board of Tottori University Hospital (No. 2545). The patients were preoperatively evaluated by chest–pelvic computed tomography, pelvic magnetic resonance imaging, or whole-body bone scans, according to physicians' judgement.

The decision to perform PLND was based on risk of LN metastases according to the European Association of Urology guideline or National Comprehensive Cancer Network classification, as the physicians preferred [12, 19]. Limited PLND and extended PLND were defined according to Ploussard et al. [20]: limited PLND includes the area between the external iliac vein and above the obturator nerve, whereas extended PLND includes limited PLND plus the area below the obturator nerve and up to the internal iliac vessels, plus the proximal common iliac vessel area under the ureter. All LN specimens were serially sectioned, fixed in 10% neutral buffered formalin, embedded in paraffin blocks, and stained with hematoxylin and eosin. Pathologists at our institution diagnosed pathologically positive LNs after examining them microscopically for cancer cells.

No patients in this study received immediate adjuvant treatment (either androgen-deprivation therapy or radiotherapy) until BCR had been confirmed. Patients were followed-up with PSA tests every 3 months during the first 2 years after surgery, every 6 months during the second to fourth years, and annually thereafter. BCR was defined as PSA levels ≥ 0.2 ng/mL with second confirmatory increase at least 6 weeks after surgery. BCR-free survival rates were determined by Kaplan–Meier analysis. Cox regression analysis was used to investigate associations between BCR and PSA, GS, extraprostatic extension, seminal vesicle invasion, perineural invasion, lymphovascular invasion, PSM, and pathologically positive LNs. SPSS 25 for Windows (IBM SPSS Japan, Tokyo, Japan) was used for statistical analyses. $P<0.05$ (two sided) was considered significant.

Results

Table 1 shows patients' clinical characteristics in this study. Their median follow-up time was 27.9 months (range 6.1–86.9 months). Median age at surgery was 68 years (range 49–76 years). Of these 173 patients, 146 (84.4%) were classified as high risk by the National Comprehensive Cancer Network criteria [19]. Seven urologists at our hospital performed extended PLND in the same way, and this study included the initial cases for each surgeon. Among these, two surgeons performed > 20 extended PLNDs (A.T. performed 77 operations and S.M. performed 53 operations), and the others performed < 20 operations. In terms of the removed LNs, the two surgeons who performed > 20 operations removed a median of 18.8 LNs (range 6–40) LNs and the others removed 15.7 (range 5–28) LNs. There was a significant difference in the number of removed LNs due to the learning curve ($P=0.011$).

Table 2 shows patients' pathological characteristics after RARP. Their median number of removed LNs was 18.0 (range 5–40). Fifteen patients (8.7%) had pathologically positive LNs [≥ 3 pathologically positive LNs: $n=5$ (33.3%), 2 pathologically positive LNs: $n=2$ (13.3%), 1 pathologically positive LN: $n=8$ (53.3%)]. Of these 15 patients, 10 (66.7%) had locally advanced PCa, 9 (60.0%) had pathologic GS of ≥ 9, and 7 (46.7%) had seminal vesicle invasion. Additionally, 12 patients (80.0%) only had positive LNs in the obturator/internal iliac region including the periprostatic fat tissue, and three patients (20.0%) had positive LNs in both the obturator/internal iliac and external/common iliac regions. We removed 33 positive LNs from these patients in this study. In terms of the locations of the removed positive LNs, 26 positive LNs (78.8%) were removed from the obturator/internal iliac region, five (15.2%) from the external/common iliac region, and two (6.1%) from the periprostatic fat tissue. Notably, all the patients with positive LNs in

Table 1 Clinical characteristics of total cohort and patients with pN1 after robot-assisted radical prostatectomy

		Total cohort, $n=173$		pN1 patients, $n=15$	
Age, year, median (range)		68	(49–76)	69	(53–75)
Prostate serum antigen, ng/ml, median (range)		9.3	(2.4–39.2)	10.4	(5.5–39.2)
Biopsy Gleason score, *n* (%)	6	5	(2.9)	0	(0)
	7	54	(31.2)	2	(13.3)
	8	78	(45.1)	7	(46.7)
	9	34	(19.7)	6	(40.0)
	10	2	(1.2)	0	(0)
Clinical T statge, *n* (%)	T1c	15	(8.7)	0	(0)
	T2a	58	(33.5)	0	(0)
	T2b	7	(4.0)	0	(0)
	T2c	47	(27.2)	6	(40.0)
	T3a	44	(25.4)	8	(53.3)
	T3b	2	(1.2)	1	(6.7)
NCCN risk classification, *n* (%)	Low	0	(0)	0	(0)
	Intermediate	27	(15.6)	0	(0)
	High	146	(84.4)	15	(100)

NCCN National Comprehensive Cancer Network

Table 2 Pathological outcomes of total cohort and patients with pN1 after robot-assisted radical prostatectomy

		Total cohort, $n=173$		pN1 patients, $n=15$	
Pathologic T stage, *n* (%)	T2a	17	(9.8)	0	(0)
	T2b	8	(4.6)	0	(0)
	T2c	116	(67.1)	5	(33.3)
	T3a	18	(10.4)	2	(13.3)
	T3b	13	(7.5)	7	(46.7)
	T4	1	(0.6)	1	(6.7)
Pathologic Gleason score, n, (%)	6	2	(1.2)	0	(0)
	7	116	(67.1)	6	(40.0)
	8	19	(11.0)	0	(0)
	9	36	(20.8)	9	(60.0)
	10	0	(0)	0	(0)
Extraprostatic extension, *n* (%)		22	(12.7)	6	(40.0)
Perineural invasion, *n* (%)		136	(78.6)	13	(86.7)
Vascular invasion, *n* (%)		44	(25.4)	8	(53.3)
Lymph vessel invasion, *n* (%)		89	(51.4)	14	(93.3)
Seminal vesicle invasion, *n* (%)		13	(7.5)	7	(46.7)
Positive surgical margin, *n* (%)		29	(16.8)	7	(46.7)
Lymph nodes removed, median (range)		18	(5–40)	18	(11–35)
Number of positive lymph node, median (range)		0	(0)	1	(1–6)

both the external/common iliac and obturator/internal iliac regions were confirmed as BCR after RARP.

We confirmed that 21 patients (12.1%) had BCR after RARP during the follow up period, and the 5-year BCR-free survival rate was 84.9% in this study. Table 3 shows the results of univariate and multivariate analyses for associations between perioperative factors and BCR. In univariate analysis, GS, lymph vessel invasion, seminal vesicle invasion, PSM, and pathologically positive LNs were significantly associated with BCR. In multivariable regression analysis, pathologically positive LNs (HR 7.117; 95% CI 2.826–17.925; $P<0.001$) and GS ≥ 8 (HR 2.612; 95% CI 1.051–6.489; $P=0.039$) were significant predictors of worse BCR-free survival. Figure 1 shows Kaplan–Meier curves for BCR-free survival by GS and by pathologically positive LNs. We found that respective 6- and 12-month BCR-free survival rates by number of pathologically positive LNs were 0 pathologically positive LN: 96.2 and 93.6%; 1–2 pathologically positive LNs: 70.0 and 60.0%; and ≥ 3 pathologically positive LNs: 20.0 and 20.0% (Fig. 2a). Among the 15 patients with pathologically positive LNs, 7 patients had no confirmed BCR after RARP during the follow up period,

Table 3 Univariate and multivariate analyses for biochemical recurrence

Variable		Univariate	Multivariate		
		p value	HR	95% CI	*p* value
Prostate serum antigen (ng/ml)	≥ 20 vs. < 20	0.413			
Pathologic T stage	≥ T3a vs. < T3a	0.054			
Pathologic Gleason score	≥ 8 vs. < 8	0.003	2.612	1.051–6.489	0.039
Extraprostatic extension	1 vs. 0	0.110			
Perineural invasion	1 vs. 0	0.191			
Vascular invasion	1 vs. 0	0.133			
Lymph vessel invasion	1 vs. 0	0.009			
Seminal vesicle invasion	1 vs. 0	< 0.001			
Positive surgical margin	1 vs. 0	0.019			
Positive lymph nodes	1 vs. 0	< 0.001	7.117	2.826–17.925	< 0.001

HR hazard ratio, CI confidence interval

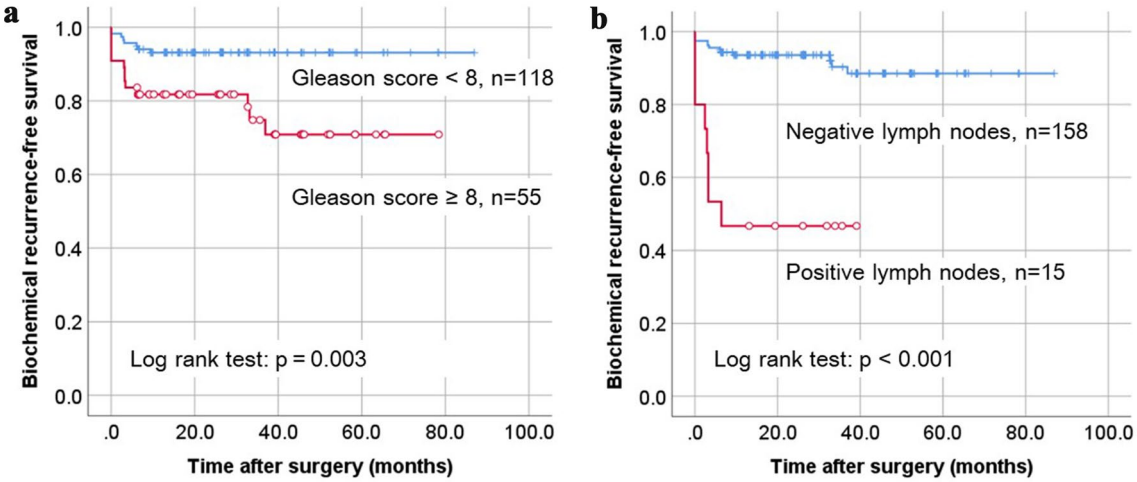

Fig. 1 Kaplan–Meier curves for biochemical recurrence-free survival by **a** Gleason score, and **b** pathologically positive lymph nodes

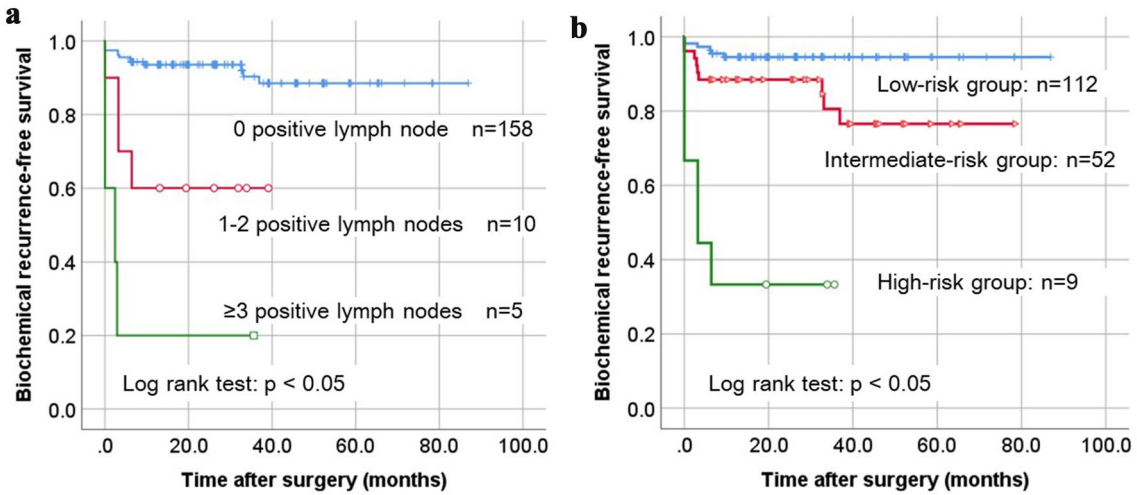

Fig. 2 Kaplan–Meier curves for biochemical recurrence-free survival according to **a** number of pathologically positive lymph nodes and **b** risk stratification model based on Gleason score and presence of pathologically positive lymph nodes. Low-risk group: Gleason score < 8 and 0 positive lymph node; Intermediate-risk group: either Gleason score ≥ 8 or positive lymph nodes; High-risk group: both Gleason score ≥ 8 and positive lymph nodes

despite not receiving adjuvant therapy. Of these 7 patients, 6 (85.7%) had only 1 or 2 pathologically positive LNs, and 4 (57.1%) had GS < 8. We, therefore, stratified the entire cohort by GS (< or ≥ 8) and number of pathologically positive LNs into 3 groups (low-risk: GS < 8 and 0 positive LN; intermediate-risk: either GS ≥ 8 or positive LNs; high-risk: both GS ≥ 8 and positive LNs). Their 1-year BCR-free survival rates were low-risk: 94.6%, intermediate-risk: 88.5% and high-risk: 33.3% (Fig. 2b).

Discussion

This was the first study of the therapeutic value of extended PLND during radical prostatectomy during the robotic surgery era in Japan. Age at surgery, PSA at diagnosis, GS ≥ 8, advanced T stage, PSM, lymphovascular invasion, and positive LNs have been recognized as independent predictors of BCR after radical prostatectomy [1, 15, 16, 21, 22]. Several recent reports have focused on seminal vesicle invasion and prostate cancer prognosis [23–25]. Tosco et al. reported that pathologic high-risk features (pT3b-4 and GS ≥ 8, and pN1) were associated with mortality after radical prostatectomy with PLND. They retrospectively evaluated 2823 patients with high-risk prostate cancer treated with surgery in a multimodal setting, of whom 1019 patients (36.1%) had pT3b-4 disease. However, although seminal vesicle invasion is considered to be a strong predictor for prostate cancer prognosis, only 13 patients (7.5%) in the current study had pT3b-4 disease, and this was not identified as a significant prognostic factor for BCR in multivariate regression analysis.

In our RARP series, pathologically positive LNs and GS ≥ 8 were significant predictors of BCR-free survival in multivariable regression analysis. Among the patients with pathologically positive LNs, those with 1–2 positive LNs had significantly higher BCR-free survival rates than those with ≥ 3 positive LNs, especially within the first year after RARP. Interestingly, although patients with pathologically positive LNs tended to develop confirmed BCR within 12 months after surgery, patients who did not develop BCR within 12 months after surgery tended to remain BCR-free afterwards.

Several studies have assessed the risk of omitting postsurgical adjuvant treatment for PCa patients with pathologically positive LNs. Boorjian et al. reported that 10-year CSS and BCR-free survival rates for PCa patients with pathologically positive LNs were 85.8% and 56%, respectively; they concluded that immediate adjuvant hormone therapy (AHT) is best [6]. Messing et al. showed that early initiation of androgen-deprivation therapy confers a survival benefit, compared with those who receive deferred treatment [26]. However, Touijer et al. reported that a considerable subset of PCa patients with pathologically positive LNs remained free of disease 10 yearss after radical prostatectomy with extended PLND alone, and concluded that PCa patients with GS < 8 and low nodal metastatic burden were a favorable group [16]. Seiler et al. reported that PCa patients with 1 positive LN have a good 10-year CSS probability, and a 20% chance of remaining BCR-free after a median follow-up of 15.6 years, even without immediate AHT [27]. Furthermore, Schumacher et al. reported that patients with low metastatic burden already have favorable prognoses and may not need immediate systemic AHT [28].

Although this study had a short observation period, our PCa patients with pathologically positive LNs tended to develop confirmed BCR within 12 months after surgery; however, patients with pathologically positive LNs who did not develop BCR within 12 months after surgery tended to remain BCR-free thereafter. The clinical course of PCa with positive LNs is heterogeneous; it is not all lethal, and it can be associated with no clinical progression even in the absence of adjuvant treatment [14]. Some patients with small-volume LN involvement can be cured by extended PLND during RARP; we, therefore, recommend that close observation without immediate AHT for the 12 months after surgery be considered for these patients. As redundant immediate AHT may produce adverse effects such as hot flashes, osteoporosis, and hepatic dysfunction, and incur unnecessary medical costs, we do not recommend immediate AHT except for patients with ≥ 3 pathologically positive LNs.

According to our risk stratification model, the high-risk group (patients with both pathologically positive LNs and GS ≥ 8) had a significantly lower 1-year BCR-free survival rate than other patients (low-risk group: 94.6%, intermediate-risk group: 88.5%, high-risk group: 33.3%). Touijer et al. conjectured that high GS reflects more aggressive tumor behavior: pathologically positive LNs indicate that the cancer has gained the molecular alterations needed for metastasis and proliferation outside the primary organ [16]. This reasoning implies that PCa patients with pathologically positive LNs and GS ≥ 8 should receive immediate AHT after RARP with extended PLND. RARP with extended PLND should be considered as a first step in a multimodal approach for these high-risk patients, and is recommended for patients with high-risk and locally advanced PCa, according to the European Association of Urology Guidelines [13]. These guidelines also indicate that improving local control with pelvic radiation therapy combined with androgen-deprivation therapy is beneficial in PCa patients with pathologically positive LNs treated with extended PLND.

Although removing higher numbers of LNs during radical prostatectomy is reportedly associated with better CSS rates [29], the therapeutic benefit of extended PLND remains debatable. Neither imaging techniques nor lymphoscintigraphy can replace PLND for PCa because of their low sensitivity [27].

Extended PLND for PCa patients with potential of positive LNs also improves pathological diagnostic accuracy. Extended PLND with at least 20 LNs reportedly provides correct LN staging in 90% of cases, regardless of tumor characteristics [30]. However, according to the multimodality mapping study, only 75% of LNs in the pelvis are located along the common iliac vessels to the ureteric crossing, the external and internal iliac vessels, and in the obturator fossa [31]. Therefore, nearly, 25% of all prostate primary lymphatic landing sites are passed over in an extended PLND during RARP. As some patients with node-negative disease have micrometastatic disease, they may benefit from PLND [7]. Similarly, we consider that some patients with 1 or 2 positive LNs will benefit from extended PLND, as extended PLND during RARP improves tumor control by decreasing risk of micrometastasis.

However, lymph vessel invasion was significantly associated with BCR in univariate analysis, but was not a significant predictor of poorer BCR-free survival in multivariate analysis in this study. Although we confirmed a strong correlation between lymph vessel invasion and pN1 ($P < 0.001$), lymph vessel invasion was not significantly associated with BCR among pN0 patients according to Kaplan–Meier analysis ($P = 0.064$, data not shown). Wilczak et al. reported that the status of lymphatic invasion provided comparable prognostic information in patients with prostate cancer, and suggested that most patients with lymph vessel invasion may have nodal metastases at the time of surgery [32]. It might thus be important to consider the tumor's potential for lymphatic dissemination during the follow-up period in PCa patients with lymph vessel invasion, even in the absence of pN1.

Our study has some limitations. First, it is a single-institution retrospective study, and contains selection biases towards patients who underwent RARP with extended PLND. Second, although all radical prostatectomy specimens were evaluated by pathologists at our hospital, no central pathology review was performed. Third, our median follow-up period (27.9 months) was too short to assess the long-term BCR rate, or to analyze overall survival. Furthermore, our sample population was too small and the low incidence of pN1 might have affected the statistical results. However, we confirmed 6-month BCR-free survival rates by numbers of pathologically positive LNs (0: 95.6%, 1 or 2: 70.0%, ≥ 3: 20.0%); they imply that PCa patients with ≥ 3 pathologically positive LNs should receive immediate AHT after RARP with extended PLND.

Conclusions

As some patients with 1–2 pathologically positive LNs can be cured by extended pelvic LN dissection during RARP, close observation without immediate AHT can be considered in these patients. However, immediate AHT is strongly recommended for PCa patients with ≥ 3 pathologically positive LNs and GS ≥ 8 after extended PLND during RARP.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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