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ORIGINAL ARTICLE – UROLOGIC ONCOLOGY

Prognostic Importance of Lymphovascular Invasion for Specific Subgroup of Patients with Prostate Cancer After Robot-Assisted Radical Prostatectomy (The MSUG94 Group)

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ABSTRACT

Objective. This study aimed to investigate whether lymphovascular invasion (LVI) was associated with oncological outcomes in patients with prostate cancer (PCa) undergoing robotic-assisted radical prostatectomy (RARP).

Methods. This retrospective multicenter cohort study was conducted on 3195 patients with PCa who underwent RARP in nine institutions in Japan. The primary endpoints were the associations between biochemical recurrence (BCR) and LVI and between BCR and clinicopathological covariates, while the secondary endpoints were the association between LVI and the site of clinical recurrence and metastasis-free survival (MFS).

Results. In total, 2608 patients met the inclusion criteria. At the end of the follow-up period, 311 patients (11.9%) were diagnosed with BCR and none died of PCa. In patients with pathological stage T2 (pT2) + negative resection margins (RM−), and pT3+ positive RM (RM+), LVI significantly worsened BCR-free survival (BRFS). For patients with PCa who had pT3 and RM+, the 2-year BRFS rate in those with LVI was significantly worse than in those without LVI. Patients with LVI had significantly worse MFS than those without LVI with respect to pT3, RM+, and pathological Gleason grade (pGG). In multivariate analysis, LVI was significantly associated with BRFS in patients with pT3 PCa, and with worse MFS in PCa patients with pT3, RM+, and pGG ≥ 4.

Conclusions. LVI was an independent prognostic factor for recurrence and metastasis after RARP, particularly in patients with pT3 and RM+ PCa. Locally advanced PCa with positive LVI and RM+ requires careful follow-up because of the high likelihood of recurrence.

Keywords Prostate cancer · Lymphovascular invasion · Robot-assisted radical prostatectomy · Locally advanced prostate cancer

Localized prostate cancer (PCa) typically has slow progression; however, locally advanced PCa has higher rates of biochemical recurrence (BCR) or clinical recurrence, a higher likelihood of progression to castration-resistant PCa

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(CRPC), and higher PCa mortality after definitive therapy; thus, it requires a strategy combining various treatment modalities.[1,2] Furthermore, the biological characteristics of advanced PCa in different patients vary, and what treatment should be selected for such cases remains controversial.[3] Although locally advanced PCa can be treated with robotic-assisted radical prostatectomy (RARP) because of relatively favorable cancer control and oncologic outcomes, the therapeutic efficacy of surgery as a part of primary or multimodal treatment for high-risk PCa has been limited.[3] Recent studies on RARP for locally advanced PCa showed high BCR rates of 18.5–28.6%, and 5-, 10-, and 15-year metastasis-free survival (MFS) rates of 87.4%, 72.2%, and 61.7%, respectively.[3,4] Conversely, the 5-, 10-, and 15-year cancer-specific survival rates in locally advanced PCa were 94.0–94.8%, 84.0–85.0%, and 75.5–76.0%, respectively, showing relatively favorable prognosis.[4,5] Similarly, in our previous study, patients with pathological stage T (pT) 3/4 had significantly lower 2-year BCR-free survival (BRFS) than those with pT2 (75.3% vs. 93.4%); for those with PCa and pT3b, the 1- and 3-year BRFS rates were 76.4 and 50.8%, respectively, suggesting that RARP alone may not be sufficient to achieve cancer control in locally advanced PCa.[6,7]

In the RARP era, various clinicopathological covariates, including prostate-specific antigen (PSA), pT, Gleason grade, and resection margin (RM) status, have been reported as factors predicting BRFS after surgery.[8,9] Our previous study also showed that pT, pathological Gleason grade (pGG), and positive RM (RM+) were significantly correlated with BCR after RARP.[4] Conversely, lymphovascular invasion (LVI) is recognized as a detrimental pathological feature; however, its positive rate varies widely, ranging from 5.1 to 46.3%.[9] Moreover, no consensus has been established on the association between LVI and BCR, and our previous report also did not show any significant association between LVI and BCR.[4,8,10,11] LVI, defined as the presence of tumor cells within endothelium-covered structures (lymph or blood vessels), is a possible step in the metastatic cascade and is likely to be associated with recurrence and distant metastasis in PCa.[11,12] LVI has been reported to significantly correlate with BRFS in locally advanced PCa, although pT2 showed no significant association with BRFS.[8]

Therefore, this study aimed to identify the association between oncologic outcomes and LVI and clinicopathologic factors that predict them in patients with PCa who underwent RARP.

METHODS

Patients

We conducted this study with the approval of the Institutional Review Board of Gifu University (Approval No. 2021-A050) and the Institutional Review Boards of the participating institutions. The requirement for informed consent was waived because of the retrospective nature of this study. In accordance with the provisions of the Japanese Ethics Committee and Ethics Guidelines, retrospective and observational studies do not require written consent to release research information using existing materials and other sources. Information used in this study, which is available only in Japanese, is available at https://www.med.gifu-u.ac.jp/visitors/disclosure/docs/2021-B039.pdf.

This retrospective multicenter cohort study used data of patients with PCa who underwent RARP between September 2012 and August 2021 in nine institutions in Japan. We collected information on the following preoperative clinical covariates: patient age, height, weight, body mass index (BMI), Eastern Cooperative Oncology Group performance status (ECOG-PS),[13] preoperative serum PSA level, prostate volume (PV), biopsy Gleason grade group (bGG), clinical stage, National Comprehensive Cancer Network (NCCN) risk stratification,[14] and neoadjuvant or adjuvant therapy. Tumor staging in all patients was determined based on the 8th edition of the American Joint Committee on Cancer Staging Manual.[15] The following pathological features were recorded: T and N stages of the surgical specimen, pGG, states of LVI, extraprostatic extension (EPE), seminal vesicle invasion, and RM. Locally advanced PCa was defined as pathological T stage ≥ 3a, and the choice regarding whether to perform pelvic lymph node dissection (PLND), extent of PLND, and presence or absence of nerve preservation was based on patients' request, surgeons' preference, or the policies of each institution.

Follow-Up Schedule

The enrolled patients were evaluated for serum PSA levels at 3-month intervals after RARP. BCR was diagnosed when the postoperative serum PSA levels exceeded 0.2 ng/mL. If the postoperative PSA level did not decrease to <0.2 ng/mL, the BCR was defined as the date of RARP.[16]

Pathological Analysis

All prostatectomy specimens were evaluated using whole-layer staining according to the 2005 guidelines of the International Society of Urologic Pathology.[17] The apex of the prostate was sectioned perpendicular to the prostatic urethra, and the edge of the bladder neck was cut conically from the specimen and perpendicularly sectioned. The remaining prostatic tissue was cut completely along a plane perpendicular to the urethral axis at 3 or 5 mm intervals.

Statistical Analysis

The primary endpoints were the association between BCR and LVI, and between BCR and pre- and postoperative covariates, whereas the secondary endpoints were the association between LVI and the site of clinical recurrence and MFS. The enrolled patients were divided into two groups based on their LVI status: patients without LVI (Group I) and patients with LVI (Group II). In each group, patients were further subdivided according to their pT, pGG, and RM statuses. The JMP Pro 17 software (SAS Institute Inc., Cary, NC, USA) was used for data analysis. The Mann–Whitney U test or Kruskal–Wallis test were used to compare continuous variables between the two groups. The follow-up duration was defined as the time from the date of RARP to the last follow-up. BRFS and MFS were defined as the times from RARP to BCR or metastasis diagnosis, respectively. The Kaplan–Meier method was used to assess oncological outcomes, and the log-rank test was used to investigate differences in clinical variables. Multivariate analysis was performed using the Cox proportional hazards model to examine the postoperative pathological factors affecting oncological outcomes. Statistical significance was defined as a two-sided p-value <0.05.

RESULTS

Patients and Characteristics

The clinicopathological covariates of the enrolled patients are listed in Table 1. Of the 3195 patients, those with pT4, pathologically detected lymph node metastases (pN) or unknown LVI, and who received neoadjuvant or adjuvant therapy were excluded from the study. Consequently, 2608 patients were included in the analysis.

Oncologic Outcome

At the end of the follow-up period, 311 (11.9%) patients had BCR, 29 (1.1%) were diagnosed with radiological recurrence, and 11 (0.4%) developed CRPC, although none of the patients died of PCa. The 2-year BRFS rate in the enrolled patients was 89.6%. According to the NCCN risk stratification, the 2-year BRFS rates in low-, intermediate-, and high-risk patients with PCa were 96.8%, 87.4%, and 60.7%, respectively ($p<0.001$).

Groups I and II were further subdivided by pT3, RM status, and pGG, resulting in eight subgroups, and BRFS was compared among the subgroups (Fig. 1). For patients with pT2, we found a significant difference in BCR according to RM status, regardless of pGG. In patients with pT2 and RM+, no significant difference was observed between Groups I and II (Fig. 1b, d), whereas in patients with pT2 and RM−, Group II showed a significantly worse BCR than Group I (Fig. 1a, c). The 2-year BRFS for those with pGG ≤ 3 and RM− was 97.7% in Group I and 94.0% in Group II ($p<0.001$) (Fig. 1a). The 2-year BRFS for those with pGG ≥ 4 and RM− was 89.5% in Group I and 82.7% in Group II ($p=0.036$) (Fig. 1c). Similarly, for patients with pT3, we found a significant difference in BCR depending on the RM status, regardless of pGG. A significant difference was also observed in BCR among pT3 patients according to their RM status, regardless of their pGG. Although there was no significant difference between Groups I and II in patients with RM− status and pT3 (Fig. 1e, g), Group I showed significantly better BRFS than Group II in patients with RM+ status and pT3 (Fig. 1f, h). The 2-year BRFS for patients with pGG ≤ 3 and RM+ was 90.4% in Group I and 71.4% in Group II ($p<0.001$) (Fig. 1f). The 2-year BRFS for patients with pGG ≥ 4 and RM+ was 71.7% in Group I and 43.5% in Group II ($p=0.019$) (Fig. 1h).

In a multivariate analysis of patients with pT2, initial PSA, pGG, and RM+ were independent prognostic predictors of BRFS (Table 2). Conversely, pGG, RM+, and LVI+ were identified in multivariate analysis as predicting factors of BRFS for patients with pT3 (Table 3).

Metastasis After Robot-Assisted Radical Prostatectomy

According to pT3, the 2-year MFS rates were 99.7% in Group I and 96.4% in Group II ($p<0.001$) (Fig. 2a). Regarding RM+, the 2-year MFS rates in Groups I and II were 99.8% and 96.4%, respectively ($p<0.001$) (Fig. 2b). Based on pGG ≥ 4, the 2-year MFS rate was 100% in Group I and 95.0% in Group II ($p<0.001$) (Fig. 2c).

Figure 3 shows the distribution of metastatic sites in the groups divided according to the pT, RM, and LVI status. The most common sites of metastasis were lymph nodes and bones in 13 patients. Metastases were most frequently observed in pT3 patients, with RM+ and LVI+ being the most common, followed by RM− and LVI+.

DISCUSSION

In this study, LVI was significantly correlated with BRFS after RARP in patients with pT2 and RM−, or pT3 and RM+. In patients with pT2, RM+ was significantly associated with BCR; however, the difference was not significant for LVI. Contrastingly, in patients with pT3, both LVI+ and RM+ were significantly correlated with BCR. In pT2, even if LVI is identified, the biological malignant potential is not high and the ability to extend outside the PCa might be low. Therefore, residual cancer may be more significant in BCR than in the invasion of PCa into LVI. Thus, prevention of RM+ may be more important in localized PCa. In contrast, locally advanced PCa with LVI may have a higher biological

TABLE 1 Patient characteristics

	LVI− [*n* = 1838]	LVI+ [*n* = 770]	*p*-Value[a]
Age, years [median (IQR)]	68 (64–72)	69 (65–73)	0.004
BMI [median (IQR)]	23.6 (21.7–25.6)	23.5 (21.8–25.4)	0.427
ECOG PS [*n* (%)]			
0	1788 (97.3)	744 (96.6)	0.536
1	48 (2.6)	24 (3.1)	
2	2 (0.1)	2 (0.3)	
Initial PSA, ng/mL [median (IQR)]	7.2 (5.4–10.4)	8.7 (5.9–13.1)	< 0.001
Prostate volume, mL [median, IQR)]	30 (23–40)	28 (21–37)	< 0.001
bGG [*n* (%)]			
1	469 (25.5)	110 (14.3)	< 0.001
2	628 (34.2)	208 (27.0)	
3	362 (19.7)	180 (23.4)	
4	305 (16.6)	198 (25.7)	
5	74 (4.0)	74 (9.6)	
Clinical T stage [*n* (%)]			
1	406 (22.1)	123 (16.0)	< 0.001
2	1350 (73.5)	560 (72.8)	
3	81 (4.4)	86 (11.2)	
NCCN risk classification [*n* (%)]			
Low	289 (15.7)	57 (7.4)	< 0.001
Favorable intermediate	620 (33.7)	178 (23.1)	
Unfavorable intermediate	455 (24.8)	207 (26.9)	
High	451 (24.5)	293 (38.1)	
Very high	23 (1.3)	35 (4.6)	
pGG [*n* (%)]			
1	192 (10.5)	12 (1.6)	< 0.001
2	813 (31.7)	244 (31.7)	
3	541 (38.1)	293 (38.1)	
4	162 (14.9)	115 (14.9)	
5	124 (6.7)	106 (13.8)	
Pathological T stage [*n* (%)]			
2	1454 (79.1)	441 (57.3)	< 0.001
3a	321 (17.5)	214 (27.8)	
3b	63 (3.4)	115 (14.9)	
PLND [*n* (%)]			
Not performed	633 (34.4)	222 (28.8)	0.015
Performed	1205 (65.6)	548 (71.2)	
Nerve-spare [*n* (%)]			
Not performed	1224 (66.6)	583 (75.7)	< 0.001
Unilateral	442 (24.1)	168 (21.8)	
Bilateral	170 (9.3)	19 (2.5)	
RM status [*n* (%)]			
Negative	1350 (73.5)	501 (65.1)	< 0.001
Positive	488 (26.6)	269 (34.9)	
With pT2	279 (19.2)	98 (22.2)	
With pT3a	170 (53.0)	98 (45.8)	
With pT3b	39 (61.9)	73 (63.5)	
BCR [*n* (%)]	152 (8.3)	159 (20.7)	< 0.001
Metastasis [*n* (%)]	6 (0.3)	23 (3.0)	< 0.001
Follow-up period, months [median (IQR)]	23.5 (11.3–46.7)	29.4 (13.3–53.1)	< 0.001

LVI− negative lymphovascular invasion, *LVI+* positive lymphovascular invasion, *IQR* interquartile range, *BMI* body mass index, *ECOG PS* Eastern Cooperative Oncology Group performance status, *PSA* prostate-specific antigen, *bGG* biopsy Gleason grade group, *NCCN* National Comprehensive Cancer Network, *pGG* pathological Gleason grade group, *PLND* pelvic lymph node dissection, *RM* resection margins, *BCR* biochemical recurrence

[a]Statistical significance was defined as a two-sided p-value < 0.05

invasive potential and be more advanced than expected at diagnosis. Therefore, if both LVI and RM are positive after RARP, the PCa may have a higher biological malignancy and consequently be more prone to BCR and metastasis. This study suggests that Group II patients with RM+ are more likely to develop distant metastasis. Although performing surgery to avoid RM+ at the time of RARP is important, considering adjuvant therapy may be necessary, especially because PCa with LVI has a poor prognosis and is more likely to be aggressive with distant metastasis.

Previous studies remain equivocal regarding the usefulness of LVI for predicting BCR in localized or locally advanced PCa.[18–20,21] Several reports have shown LVI as a significant risk factor for BCR;[18–20] however, other studies showed that LVI is not an important prognostic predictor of BCR.[21] With respect to the presence or absence of LVI, the 2- and 5-year BRFS in patients with PCa after surgery were 91% versus. 94% and 76% versus. 84%, respectively.[18] In a multivariate analysis of this study, LVI was an independent predictor of BCR, particularly in patients with high-grade pathology.[18] Conversely, for patients with PCa who were diagnosed with pT3N0, LVI has been reported as a significant independent predictor of disease progression or BRFS.[19,20] Shariat et al. [21] reported that LVI is not associated with the risk of developing BCR after surgery in a multivariate analysis but was associated with metastasis to regional lymph nodes. These results suggest that further investigation is required to determine the role of LVI+ in postoperative BCR, local invasion, and metastasis of PCa.

Similar to the present study, many studies have shown that LVI is an important prognostic factor, especially for patients with PCa who have high-grade pathologic features.[11,18,23–25] LVI was a strong independent prognostic factor for BCR in patients with PCa who had high-grade pathologic features such as EPE, seminal vesicle invasion, and pGG ≥3, although LVI did not correlate with BCR in patients with relatively low-grade PCa such as pT2 and pGG 1.[18] Kang et al.[22] reported a higher risk of BCR when both LVI and perineural invasion are detected compared with when either one is present. A study examining the association between p53 protein expression and LVI to predict PCa metastasis suggested that LVI and high p53 expression levels were significantly associated with MFS.[23] Jamil et al.[24] reported that LVI was not associated with overall survival (OS) in pT2 PCa; however, all-cause mortality was 1.2- to 1.4-fold higher in patients with pT3 PCa LVI than in those without LVI. A study on the malignancy of cancer-associated fibroblasts in the reactive stroma showed that patients with LVI and high malignancy of the reactive stroma are at a particularly high risk of death from PCa.[11] When the morphological pattern, frequency, and spatial distribution of LVI foci were examined, most specimens with LVI showed a cribriform pattern and/or intraductal carcinoma. Furthermore, patients with such morphologies have a high correlation with the risk of bone metastases.[26] For patients with PCa who have high-grade pathogenesis, such as those in our study, LVI may play an important role in the progression of PCa.

There are a few reports on metastatic sites, MFS, and OS after RARP. In a study on clinical recurrence sites in high- and very high-risk PCa after open and laparoscopic RP, local recurrence was observed in 67% of high-risk cases and bone or visceral metastases in 65% of clinical progression in very high-risk cases.[27] Among them, those with pT3 and LVI+ were especially at a higher risk of developing distant metastases.[27] Regarding metastasis, the 5-year MFS was 80% for patients with LVI+ and 94% for those with LVI−.[24] For patients with LVI+ and LVI−, 5-year OS was 94% vs. 95% for those with pT2, 92% vs. 95% for those with pT3a, and 86% vs. 92% for those with pT3b.[25] Similarly, the 5-year OS for patients with LVI+ vs. LVI− according to pN was 93.1% vs. 96.5% for those with pN0 and 86.6% vs. 93.3% for those with pN1.[25] Furthermore, the combination of LVI+ with pT3, RM+, and pGG ≥4 particularly worsened MFS; thus, LVI may play a significant role in its progression in high-grade PCa.[25] The widespread use of next-generation imaging allows for earlier and more accurate identification of metastatic sites after RARP, potentially clarifying the role of LVI in disease progression.[28]

Several limitations are present in this study. First, this was a multicenter retrospective cohort study and thus had a potential for bias among participating centers owing to differences in the diagnosis of PCa and RARP procedures. Second, the relatively short follow-up period did not allow us to investigate OS or cancer-specific survival. Third, one urologic pathologist did not re-evaluate all prostate biopsies and surgical specimens in this study. However, based on a report by Ghadjar et al.[29] there is likely little bias in the diagnosis of prostate specimens. Finally, the true role of positive LVI in PCa progression remains unclear. Therefore, the results of the present study should be interpreted with caution.

CONCLUSION

This study demonstrated that LVI might be a potential prognostic predictor in localized PCa with RM− and locally advanced PCa with RM+ after RARP. Regarding BRFS, RM was a stronger prognostic predictor than LVI in patients with localized PCa, whereas LVI was predictive of RM in patients with locally advanced PCa. Furthermore, we suggest that a combination of LVI and RM may predict BCR. These results suggest that LVI in locally advanced PCa may be significantly associated with recurrence and distant metastasis. Therefore, locally advanced PCa with both LVI+ and RM+ require careful follow-up. Prospective studies with long-term

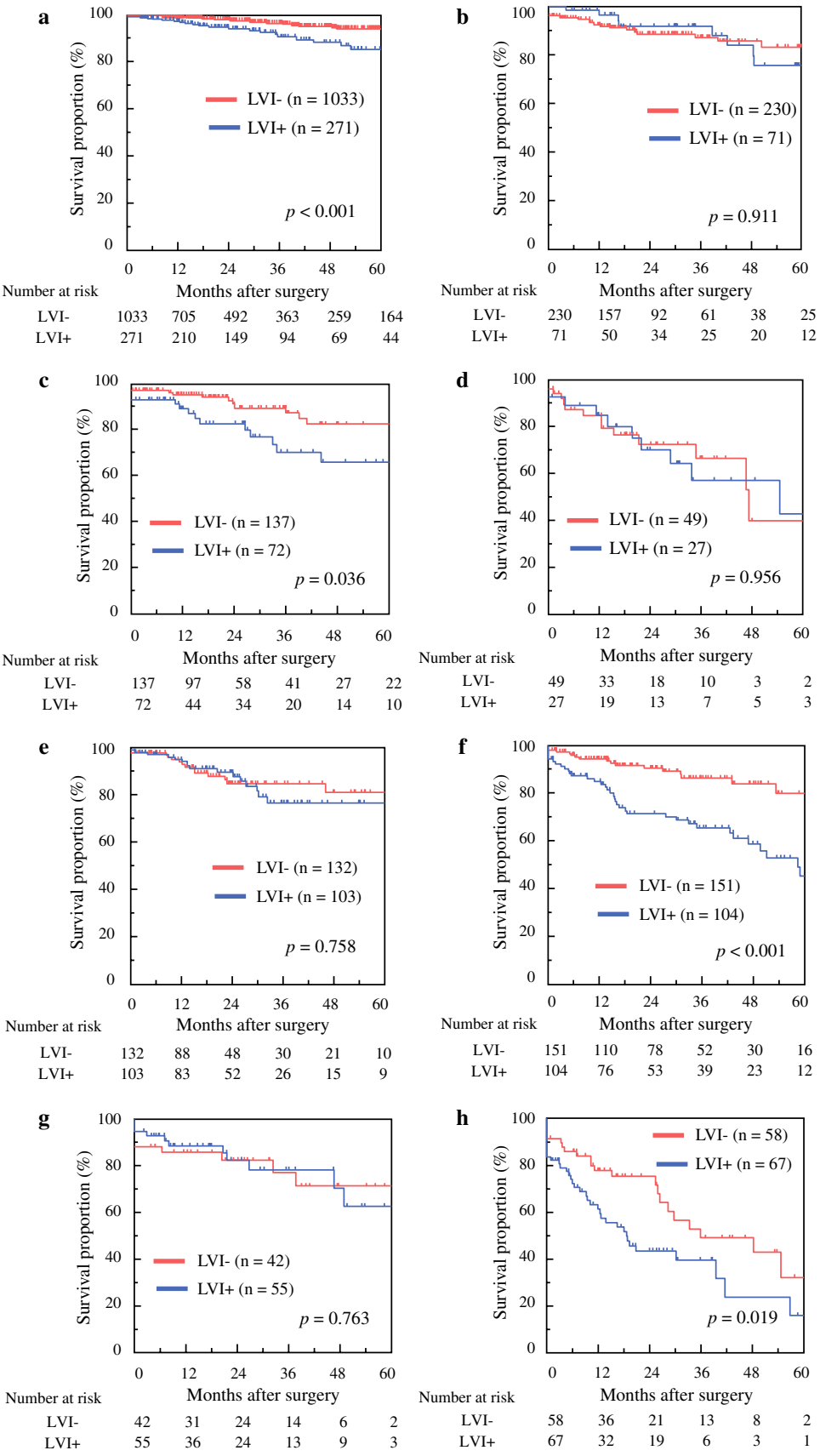

FIG. 1 Kaplan–Meier estimates of BRFS according to LVI stratified by pT 2 or 3, pGG group ≤3 or ≥4, and RM+ or RM− in patients with PCa. In patients with PCa and pT2/pGG ≤3/RM−, the 2-year BRFS rate was 97.7% in those without LVI (LVI−) and 94.0% in those with LVI (LVI+) [$p < 0.001$] (**a**). In patients with PCa and pT2/pGG ≤3/RM+, the 2-year BRFS rate was 88.6% in those with LVI− and 91.7% in those with LVI+ ($p = 0.911$) (**b**). In patients with PCa and pT2/pGG ≥4/RM−, the 2-year BRFS rate was 89.5% in those with LVI− and 82.7% in those with LVI+ ($p = 0.036$) (**c**). In patients with PCa and pT2/pGG ≥4/RM+, the 2-year BRFS rate was 72.3% in those with LVI− and 70.0% in those with LVI+ ($p = 0.956$) (**d**). In patients with PCa and pT3/pGG ≤3/RM−, the 2-year BRFS rate was 84.7% in those with LVI− and 89.5% in those with LVI+ ($p = 0.758$) (**e**). In patients with PCa and pT3/pGG ≤3/RM+, the 2-year BRFS rate was 90.4% in those with LVI− and 71.4% in those with LVI+ ($p < 0.001$) (**f**). In patients with PCa and pT3/pGG ≥4/RM−, the 2-year BRFS rate was 82.3% in those with LVI− and 82.3% in those with LVI+ ($p = 0.763$) (**g**). In patients with PCa and pT3/pGG ≥4/RM+, the 2-year BRFS rate was 71.7% in those with LVI− and 43.5% in those with LVI+ ($p = 0.019$) (**h**). *BRFS* biochemical recurrence-free survival, *LVI* lymphovascular invasion, *pT* pathological T stage, *pGG* pathological Gleason grade, *RM+* resection margin-positive, *RM−* resection margin-negative, *PCa* prostate cancer

TABLE 2 Multivariable Cox proportional hazard regression analyses for biochemical recurrence in patients with pathological T2

Variable	Univariate		Multivariate	
	[HR (95% CI)]	*p*-Value	[HR (95% CI)]	*p*-Value
Age (continuous)	1.020 (0.993–1.048)	0.151	1.012 (0.985–1.039)	0.386
Initial PSA (continuous)	1.035 (1.019–1.048)	< 0.001	1.026 (1.008–1.045)	0.010
pGG (continuous)	1.982 (1.720–2.282)	< 0.001	1.878 (1.621–2.176)	< 0.001
RM+ (vs. none)	3.412 (2.456–4.742)	< 0.001	2.788 (1.994–3.898)	< 0.001
LVI (vs. none)	2.034 (1.460–2.835)	< 0.001	1.405 (1.002–1.970)	0.052

HR hazard ratio, *CI* confidence interval, *PSA* prostate-specific antigen, *pGG* pathological Gleason grade group, *RM+* positive resection margin, *LVI* lymphovascular invasion

TABLE 3 Multivariable Cox proportional hazard regression analyses for biochemical recurrence in patients with pathological T3

Variable	Univariate		Multivariate	
	[HR (95% CI)]	*p*-Value	[HR (95% CI)]	*p*-Value
Age (continuous)	0.995 (0.969-1.021)	0.677	0.986 (0.962–1.011)	0.275
Initial PSA (continuous)	1.029 (1.014–1.043)	< 0.001	1.016 (0.999–1.030)	0.063
pGG (continuous)	1.635 (1.422–1.879)	< 0.001	1.632 (1.415–1.882)	< 0.001
RM+ (vs. none)	1.966 (1.413–2.736)	< 0.001	2.126 (1.522–2.970)	< 0.001
LVI (vs. none)	1.876 (1.372–2.566)	< 0.001	1.767 (1.285–2.429)	< 0.001

HR hazard ratio, *CI* confidence interval, *PSA* prostate-specific antigen, *pGG* pathological Gleason grade group, RM+, positive resection margin, *LVI* lymphovascular invasion

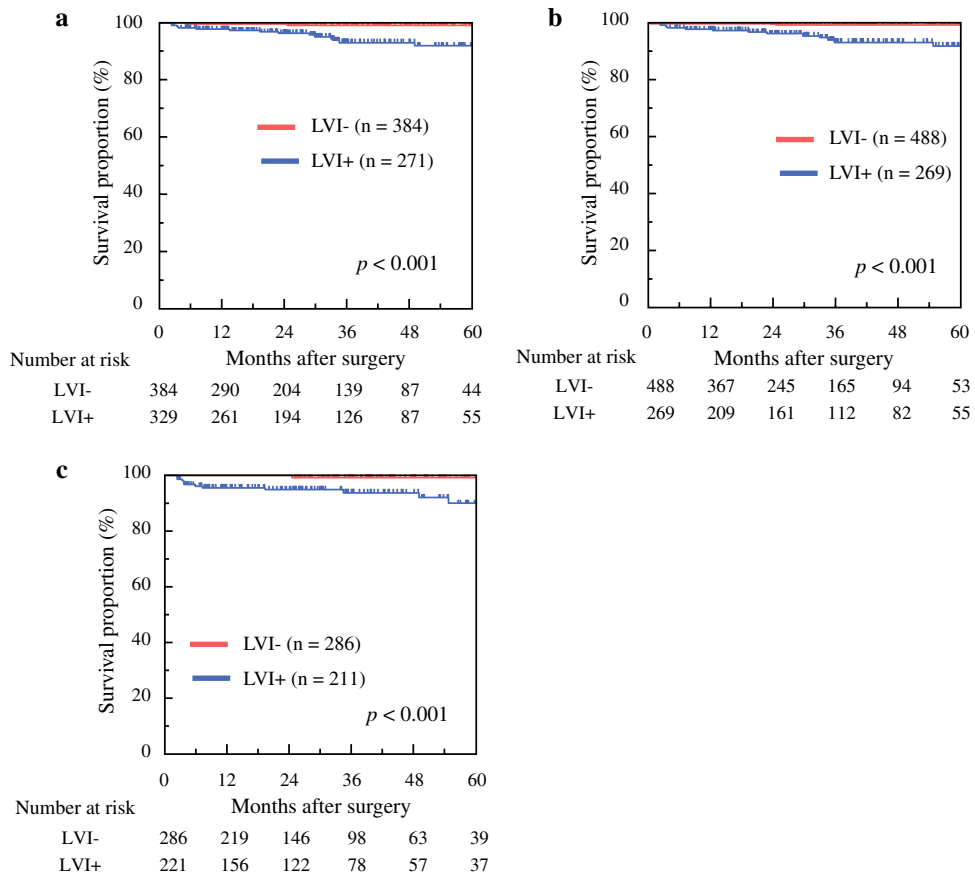

FIG. 2 Kaplan–Meier estimates of MFS according to LVI status. The 2-year MFS rate of patients with pathological T stage 3 was 99.7% in those without LVI (LVI−) and 96.4% in those with LVI (LVI+) ($p < 0.001$) (**a**). The 2-year MFS rate of patients with positive surgical margin was 99.8% in those with LVI− and 96.4% in those with LVI+ ($p < 0.001$) (**b**). The 2-year MFS rate of patients with pathological Gleason grade group ≥ 4 was 100% in those with LVI− and 95.0% in those with LVI+ ($p = 0.036$) (**c**). *MFS* metastasis-free survival, *LVI* lymphovascular invasion

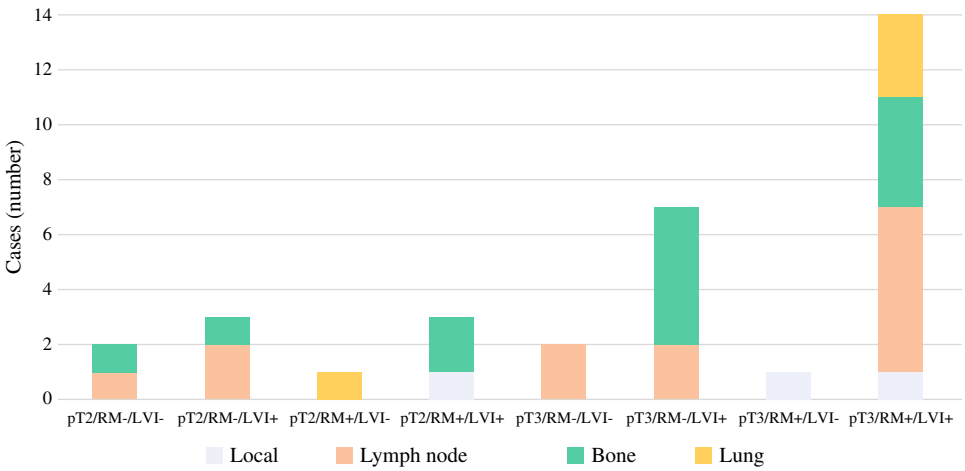

FIG. 3 Distribution of clinical relapse sites by eight subgroups stratified by pT 2 or 3, RM+ or RM−, and without LVI (LVI−) or with LVI (LVI+). The most common sites of metastasis were lymph nodes and bone in 13 patients. Metastases were most frequently observed in patients with pT3, with RM+ and LVI+ cases being the most common, followed by RM− and LVI+ cases. *pT* pathological T stage, *RM+* resection margin-positive, *RM−*resection margin-negative, *LVI* lymphovascular invasion

follow-up are required to evaluate the relationship between LVI and survival.

AUTHOR CONTRIBUTIONS Conceptualization: MK and TK conceived the presented idea. Data collection, formal analysis and investigation: MK, SE, TT, TS, YI, AN, MT, TY, KS and JT. Methodology: TK, KM, HK, KS, FK, SU. Writing – original draft preparation: MK and TK. Writing – review and editing: TI, FK and TK. Data analysis: MK. All authors discussed the results and contributed to the manuscript, and read and approved the final version.

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ETHICS APPROVAL Approval of the research protocol by an Institutional Reviewer Board: 2021-B039.

INFORMED CONSENT Given the data are anonymous, and patients privacy are fully protected, the Ethics Committee waived this retrospective study to obtain written informed consent from patients, referring to the Council for International Organizations of Medical Sciences (CIOMS) guidelines.

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