



Review

Lymphovascular invasion as a prognostic value in small rectal neuroendocrine tumor treated by local excision: A systematic review and meta-analysis



Ho Suk Kang^a, Mi Jung Kwon^{b,*}, Tae-Hwan Kim^c, Junhee Han^d, Young-Su Ju^e

^a Division of Gastroenterology, Department of Internal Medicine, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Anyang, Gyeonggi-do, Republic of Korea

^b Department of Pathology, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Anyang, Gyeonggi-do, Republic of Korea

^c Department of Orthopaedic Surgery, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Anyang, Gyeonggi-do, Republic of Korea

^d Department of Statistics, Hallym University, Chuncheon, Republic of Korea

^e Department of Occupational and Environmental Medicine, Hallym University Sacred Heart Hospital, Anyang, Gyeonggi-do, Republic of Korea

ARTICLE INFO

Keywords:

Carcinoid
Neuroendocrine
Endoscopic resection
Lymphovascular invasion
Lymph node metastasis
Prognosis
Meta-analysis

ABSTRACT

Because rectal neuroendocrine tumors (NETs) are usually small-sized despite of malignant potential, endoscopic resection techniques are recommended. It is unclear whether the lymphovascular invasion (LVI) in the endoscopic resected specimens of small rectal NETs should be indicated for completion surgery. We performed a systematic review and meta-analysis for the incidence of LVI in small rectal NETs (≤ 20 mm) treated by endoscopic resection and its prognostic impacts.

We searched the relevant literature published before January 2019. A total of 21 publications including 1816 patients were enrolled.

Overall prevalence of LVI in small rectal NETs was 21.8%. Immunohistochemical method significantly increased the detection rate of LVI up to 35.8% compared than H&E staining only (13.2%). Tumor size more than 5 mm was a risk factor for LVI in small rectal NET, whereas tumor grade did not influence the risk. The LVI in the endoscopic resected specimens was a risk factor for subsequent lymph node metastasis. Separately analyzed in detail, the vascular invasion had a stronger impact on lymph node metastasis than the lymphatic invasion. The prognosis of endoscopically treated rectal NET with LVI was excellent with only 0.3% of recurrence rate during the 5-year follow-up period.

LVI is highly prevalent and a risk factor for lymph node metastasis in the small rectal NETs. Endoscopically treated small rectal NETs had excellent short-term prognoses despite of LVI. Immediate completion radical surgery is not absolutely necessary for the LVI-positive small rectal NETs. However, long-term follow-up is recommended for any delayed recurrence.

1. Introduction

Rectal neuroendocrine tumors (NETs) are rare and usually small in size, but they are potentially malignant [31]. Thus, its clinical implication is highly debated because the prognosis varies widely based on grade, size, invasion depth, and lymphovascular invasion (LVI) [2,4,35,37]. In Asia, the rectum is the most common primary location, accounting for 60%–89% of all gastroenteropancreatic NETs [7,10]. The worldwide incidence of rectal NETs has been rapidly increasing [28]; particularly, a nine-fold increase in incidence was recorded in

Korea [7]. Because the majority (66%–80%) of rectal NETs are small in size (i.e., < 10 mm) and are found incidentally during screening colonoscopy [11,28,32], local excision including endoscopic resection techniques and trans-anal excision are recommended for NETs confined to the mucosal or submucosal layer and without LVI [2,11,12,25]. However, although patients with tumors measuring ≤ 10 mm and 11–20 mm still have a 2%–3% and 10%–15% risk of metastasis, respectively even in tumors [31], it is still unclear whether the presence of LVI in the endoscopic resected specimens of small rectal NETs is a necessary requisite for further radical resection. The optimal treatment

* Corresponding author at: Department of Pathology, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, 22, Gwanpyeong-ro 170beon-gil, Dongan-gu, Anyang-si, Gyeonggi-do, 14068, Republic of Korea.

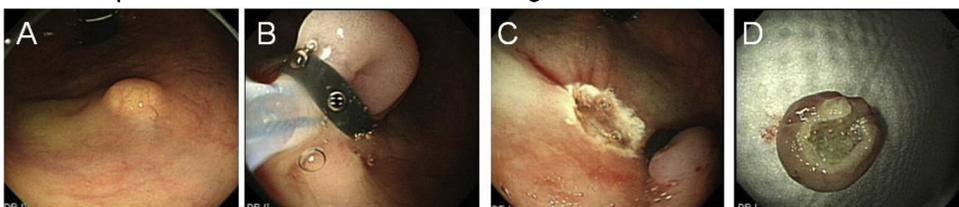
E-mail addresses: mulank99@hallym.or.kr, mulank@hanmail.net (M.J. Kwon).

<https://doi.org/10.1016/j.prp.2019.152642>

Received 28 July 2019; Received in revised form 26 August 2019; Accepted 15 September 2019

0344-0338/© 2019 The Authors. Published by Elsevier GmbH. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

Endoscopic submucosal resection with a ligation



Endoscopic submucosal dissection

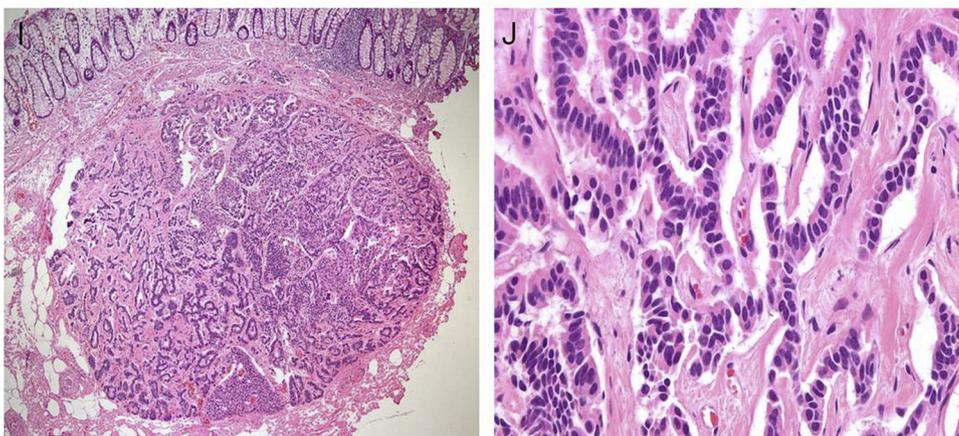
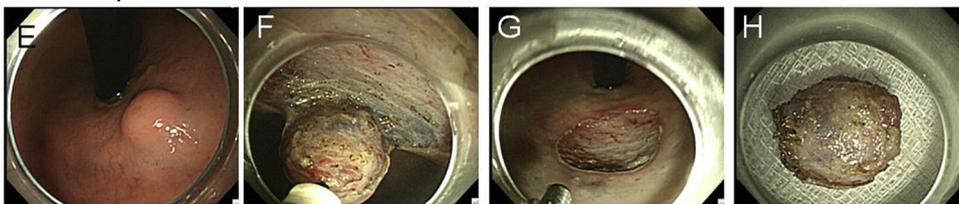


Fig. 1. (A–D) Endoscopic submucosal resection with a ligation. Small neuroendocrine tumor measuring 0.7 cm is elevated at 2 cm from anal verge. (B) Aspiration of the lesion into the ligator device and deployment of the elastic band. (C) Snare resection below the band. (D) En bloc specimen. (E–H) Endoscopic submucosal dissection. (E) Small rectal neuroendocrine tumor measuring 1 cm is elevated at 2 cm from anal verge. (F) Dissection with Dual Knife. (G) Submucosal dissection base. (H) En bloc specimen. (I) Magnified scans of H & E slide shows a well-demarcated submucosal tumor with clear resection margins. (J) Neuroendocrine tumors consisting of well-demarcated islands and trabeculae of uniform tumor cells show marked tumor retraction from the surrounding fibrotic stroma within tumor mimicking lymphovascular invasion. (Footnotes: Fig. 1A–H have been published previously [18] and the authors permitted from the original authors of the figures).

modality for such LVI-positive small rectal NETs is currently debated. Because there is no consensus on the relevant clinical impact of LVI for lymph node metastasis or recurrences of small rectal NETs, there are no clear guidelines for treatment or follow-up plans of LVI-positive small rectal NETs. Therefore, a meta-analysis to pool study results and clarify the prognostic value of the presence of LVI in the endoscopically-resected small rectal NETs are crucial to validate the safety of endoscopic treatment.

LVI is defined as the presence of tumor cells in blood vessels and/or lymphatic channels, and it plays an important role in lymph node metastasis and the spread of cancer cells [8]. Further, LVIs are thought to increase the risk of micrometastasis in loco-regional cancer [8]. Because rectal NETs are highly vascular tumors [36], LVI can be a potentially high risk factor for metastasis, and thus precise histological evaluation of LVI in the resected specimens is clinically important. Nevertheless, identifying true LVI on routine hematoxylin and eosin (H & E)-stained slides is often challenging due to the marked tumor retraction from the surrounding fibrotic stroma within NETs [27]. Accordingly, the detection rates for LVI vary depending on the diagnostic modality, which includes either standard H&E staining method or additional immunohistochemical (IHC) staining methods [18,23,29,33]. Further, data on the incidence of LVI are limited in rectal NETs.

This meta-analysis aimed to systematically review and investigate the incidence, risk factors, and prognostic impacts of LVI in the endoscopically-resected, small rectal NETs measuring less than 20 mm to help determine the appropriate management and follow-up strategies for these patients.

2. Materials and methods

2.1. Search strategy

This study was carried out in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [22]. To identify the potentially relevant publications, MEDLINE, EMBASE and the Cochrane Library were searched for articles published up to January 2019 using the following keywords: ('rectum' or 'rectal') and ('carcinoid' OR 'neuroendocrine') and ('lymphovascular' or 'lymphatic' or 'vascular' or 'LVI'). We also manually checked the citations of the included publications.

2.2. Study selection and data extraction

Studies were considered eligible if they included patients with rectal NETs measuring ≤ 20 mm in size who also had LVI (population). Those treated with local or radical resection (intervention) were compared with patients without LVI (comparator) to investigate the risk factors, lymph node metastasis, and prognosis (outcomes) in published observational studies (study design). Two reviewers (KMJ and KHS) selected the studies, analyzed the manuscripts, and independently extracted data. Discrepancies were resolved through consensus.

2.3. Quality assessment

The quality of the included studies was independently assessed by two authors (KMJ and KHS) using the Newcastle-Ottawa Scale (NOS; range, 0–9) [34]. Studies with a cumulative score of ≥ 7 were considered to be of high quality; 6, moderate quality; and < 6 stars, low

quality.

2.4. Statistical analysis

This meta-analysis was performed using the Review Manager (RevMan) software, version 5.3. (The Nordic Cochrane Centre, Copenhagen, Denmark). All dichotomous variables were analyzed using estimation of odds ratios (OR) with 95% confidence interval (CI). Random-effect models were chosen for calculation of pooled odd ratios. The heterogeneity of the pooled OR with 95% CI was tested via Cochrane's Q test (Chi-squared test) and I^2 metric ($I^2 < 25\%$: no heterogeneity; $I^2 = 25\%$ – 50% : mild heterogeneity; $I^2 = 50\%$ – 75% : moderate heterogeneity; $I^2 > 75\%$: extreme heterogeneity). Publication bias was analyzed by using visual inspection of funnel plots. Additionally, Begg–Mazumdar test and Harbord–Egger test were performed in R (version 1.1.463). A P -value ≤ 0.05 was considered a statistically significant publication bias.

3. Results

3.1. Characteristics of the included studies

The search strategy and study selection flowchart is shown in Supplementary Fig. 1. A total of 493 potentially relevant studies were identified through systematic literature search. After title and/or abstract screening, 347 studies were excluded because they were duplicates, reviews, or case reports or the association between LVI and lymph node metastasis or survival was not evaluated. After reviewing the 72 remaining studies, 38 were further excluded because they included non-rectal NETs or had missing data of LVI. Finally, 21 retrospective studies involving 1816 patients were included in the study.

The main characteristics and clinicopathological outcomes in the included studies are summarized in Tables 1 and 2. All studies were published between 2007 and 2019, of which 20 studies were predominantly conducted in Asia (6 in Korea and 14 in Japan) and 1 in the United States. The treatment modalities were endoscopic resection ($n = 1486$), trans-anal excision or trans-anal micro-invasive surgery ($n = 82$), and subsequently radical surgery after endoscopic resection ($n = 248$) (Fig. 1). The median follow-up of patients ranged from 24 to 67.5 months. Tumor depth was investigated in 1588 cases; of these, 1542 (97.1%) cases had tumors confined to the submucosa. Tumor grade was recorded in 599 cases; of these, 93.2% (559/599) were grade 1 and 6.6% (40/599) were grade 2.

With respect to the diagnostic modality for LVI (Fig. 2A–D), 6 studies used IHC, while 15 studies used H&E staining. The overall incidence of LVI after excision was 21.8% (396/1816) and ranged from 0% to 66.6%. The frequency of LVI in tumors measuring < 10 mm was 26.4% (169/639). The detection rate of LVI was higher in using IHC method (35.8%, 149/1127) than in using H&E staining method only (13.2%, 247/689).

3.2. Association between LVI and tumor size in small rectal NETs after local excision

In total, 10 studies reported on tumor size dichotomized according to the following two criteria: diameter less than 10 mm [16,18,19,21,33,35] and 10–20 mm [5,6,19,21,30]. The correlation of LVI according to tumor size [> 5 mm vs. ≤ 5 mm (Fig. 3A) or > 1 cm vs. ≤ 1 cm (Fig. 3B)] was investigated independently. A meta-analysis of the pooled data demonstrated that larger tumor size (> 5 mm) was associated with a higher frequency of LVI than smaller tumor size (≤ 5 mm) (OR 2.17; 95% CI 1.40–3.36, $P = 0.00005$). Similarly, the pooled data revealed that larger tumor size (> 10 mm) was also associated with a higher detection rate of LVI (OR 2.94; 95% CI 1.12–7.12, $P = 0.03$). Both had low heterogeneity ($P = 0.74$, $I^2 = 0\%$; $P = 0.18$, $I^2 = 34\%$, respectively). Collectively, these results indicated that larger

tumor size might increase the risk of LVI regardless of the criteria for size (OR 2.38; 95% CI 1.57–3.61, $P = 0.0001$) (Fig. 3C). The Cochrane Q test ($\chi^2 = 12.09$; $P = 0.36$) and I^2 test ($I^2 = 9\%$) did not show any significant heterogeneity.

For subgroup analysis on the staining method for detecting LVI, studies that investigated tumor size (> 1 cm) were excluded. Because IHC was performed only in the study by Lee et al [19], it was not analyzed separately. The results showed that the LVI detection rate is higher in IHC than that in H&E (OR 2.21; 95% CI 1.42–3.44, $P = 0.0005$ vs. OR 1.23; 95% CI 0.09–16.48, $P = 0.87$).

3.3. Association between LVI and tumor grade in small rectal NETs after local excision

Tumor grade was investigated in 3 studies [16,18,21] (Fig. 3D). Yamagishi et al [35] examined the Ki-67 index only, we classified tumors with Ki-67 index $> 2\%$ as grade 2, and included in the meta-analysis (Fig. 2E–F). The pooled data suggested that tumor grade did not influence the increased risk of LVI (OR 1.70; 95% CI 0.40–7.26, $P = 0.47$). Medium heterogeneity was significant ($I^2 = 65\%$, $P = 0.04$).

3.4. Association of LVI, lymphatic invasion, or vascular invasion with post-excision lymph node metastasis in small rectal NETs

Histologically confirmed data on LVI and lymph node metastasis and their association in rectal NETs were available in five studies [6,17,19,21,35], while one study [19] evaluated LVI and lymph node metastasis using both histologic evaluation and imaging findings. In two studies [6,17], both lymphatic invasion and vascular invasion were independently investigated.

Of the 5 studies [6,17,19,21,35], the pooled data indicated that LVI showed statistically significant correlation with increased risk of lymph node metastasis of locally resected small rectal NETs (OR 4.98; 95% CI 1.13–21.95, $P = 0.03$) (Fig. 4A). The Cochrane Q test ($\chi^2 = 14.87$; $P = 0.005$) and I^2 test ($I^2 = 73\%$) showed medium heterogeneity.

Further, subgroup analysis was also performed on 4 studies [6,17,21,35], which lymph node metastasis were evaluated by histological method. Tumors with LVI also exhibited a significantly higher risk for lymph node metastasis than those without LVI (OR 3.51; 95% CI 1.91–6.45, $P < 0.0001$), of which studies did not exhibit significant heterogeneity ($P = 0.72$, $I^2 = 0\%$).

The relationships between lymphatic invasion or vascular invasion and lymph node metastasis were analyzed separately (Fig. 4B). The pooled data demonstrated that tumors with vascular invasion had a significantly higher risk for lymph node metastasis than those without vascular invasion (OR 3.84; 95% CI 2.01–7.31, $P < 0.0001$). By contrast, the presence of lymphatic invasion in small rectal NETs did not influence the risk of lymph node metastasis after excision (OR 6.02; 95% CI 0.7–51.17, $P = 0.100$).

3.5. Association of LVI in endoscopic resection specimens with disease recurrence

Fifteen studies that included 1213 patients provided sufficient data to evaluate the prognostic impact of LVI on disease recurrence (Table 2). In total, 1022/1213 (84.2%) cases were followed up. Because of the heterogeneity of the data, a meta-analysis could not be performed. Two cases (0.3%, 4/1022) of recurrence during follow-up were recorded. In total, 109 patients in 3 studies did not undergo an additional operation, although LVI was identified in the endoscopic resection specimens. None of those 109 cases recurred during the follow-up period (median, 30–76 months). By contrast, 31 patients underwent additional radical surgery after endoscopic resection, of which lymph node metastasis was identified on 21.7% (5/23).

Table 1

Characteristics of the included studies with small rectal neuroendocrine tumors less than 20 mm treated by local excision including endoscopic resection and trans-anal excision.

Author	Period	Country	Multi-center	No. of cases	Median size (range, mm)	Grade 2 (%)	Resection methods			IHC	LVI (%)	NOS score	
							ER (CR)	TAE	RS				
Takita [33] (2019)	2002-2017	Japan	No	181	4.7 (2-10)	0 ^c	181(99.4%)			Yes	37	7	
Matsuhashi [21] (2017)	2005-2013	Japan	No	12	7.4 (3-15)	33.3				12	No	66.60	5
Choi [3] (2017)	2008-2015	Korea	No	134	5.5 (< 10)	0	134(85.8%)			No	0.70	7	
Okubo [24] (2016)	1996-2015	Japan	No	42 ^a	5 (1-10)	19	42			Yes ^b	23.8(LI), 30.9(VI)	7	
Nakamura [23] (2016)	2001-2012	Japan	Yes	170	5 (2-13)	2.4	170(85.9%)			Yes	22.30	6	
Kwon [18] (2016)	2005-2015	Korea	No	104	5 (1.2-10)	26.0 ^f	104(84.6%)			Yes	27.80	7	
Kojima [17] (2016)	2001-2011	Japan	Yes	200	< 20	12.0				200	No	26.5(LI), 34.5(VI)	6
Kitagawa [16] (2016)	2001-2011	Japan	No	102	5 (1-10)	8.80	102(71.6%)			Yes	56.80	7	
Sekiguchi [29] (2015)	1997-2011	Japan	No	90	5.0 (2-13)	0	90(96.7%)			Yes	46.60	7	
Mitsuhashi [21] (2015)	2007-2014	Japan	No	56	6.2 ± 2.5 ^b	0	56			No	23.20	6	
Shigeta [30] (2014)	1990-2010	Japan	No	74	6 (5-8) ^c		65	9		No	25.60	7	
Kim, J [13] (2014)	2009-2013	Korea	No	76	4.65(1-10)		76			No	1.30	6	
Lee [19] (2013)	2008-2010	Korea	Yes	281	6.0 ± 3.5 ^{a,d}		243	28	10	No	4.9(LI)	6	
Yamagishi [35] (2012)	2000-2011	Japan	No	14	12.85(5-20)				14	No	50.00	6	
Kim, H [12] (2012)	2001-2010	Korea	Yes	100	3-12		100(95%)			No	0	6	
Fujii [5] (2011)	1991-2009	Japan	No	18	≤15			18		No	16.6	5	
Fujimoto [6] (2010)	2005-2007	Japan	Yes	12	10.5 (6-18)				12	No	66.60	6	
Baek [1] (2010)	2004-2009	Korea	No	12	10.6 (5-13)		12(100%)			No	0	4	
Mashimo [20] (2008)	1999-2008	Japan	No	63	6.4 (2-12)		63(95.2%)			No	0	4	
Kinoshita [15] (2007)	1994-2006	Japan	No	27	9.1 (5-13)			27		No	0	4	
Fahy [4] (2007)	1957-2004	USA	No	48	≤20	16.3 ^g	48			12	No	12.5	6

ER, Endoscopic resection; CR, complete resection rate; TAE, trans-anal excision; RS, radical surgery; IHC, immunohistochemical staining; NOS, Newcastle Ottawa scale; LVI, lymphovascular invasion; LI, lymphatic invasion; VI, vascular invasion.

^a 1 case of sigmoid neuroendocrine tumor is included in the study.

^b Mean ± SD or Mean.

^c Inter-quartile range.

^d Average size that includes the 3 cases of > 20 mm tumor.

^e Grade 2/3 was excluded from the original study design.

^f Ki-67 index was re-evaluated using a cut-off of < 2%.

^g Mitosis was used to evaluate tumor grade.

^h Only D2-40 staining was used for immunohistochemical staining.

Table 2

Clinical outcomes in small rectal neuroendocrine tumor with lymphovascular invasion.

Case	ER only	Size (mm)	LVI (%)	Follow-up			
				Case	Duration (mo, median)	Recurrence (%)	
Takita [33]	181	Yes	4.7(2-10)	37	136	26-61 ^a	0
Choi [3]	134	Yes	5.5 (< 10)	0.70	134	27.8 ± 16.7 ^a	0
Okubo [24]	42	Yes	5 (1-10)	30.9	22	5-191 ^c	0
Nakamura [23]	170	Yes	5 (2-13)	22.3	170	49	0
Kwon [18]	104	Yes	5 (1.2-10)	27.8	68	26.9	0
Kitagawa [16]	102	Yes	5 (1-10)	56.8	95	51.7	0
Sekiguchi [29]	90	Yes	5.0 (2-13)	46.6	90	67.5	0
Mitsuhashi [21]	56	Yes	6.2 ± 2.5 ^a	23.2	56	2007-2014 ^d	0
Shigeta [30]	74	No	6 (5-8) ^b	25.6	74	31	1 (1.3) ^f
Kim, J [13]	76	Yes	4.65 (1-10)	1.30	28	16 ± 10 ^a	0
Yamagishi [35]	14	No	12.85 (5-20)	50.0	14	67.1 ^a	1 (7.1) ^g
Baek [1]	12	Yes	10.6 (5-3)	0	12	28 ^a	0
Mashimo [20]	61	Yes	6.4 (2-12)	0	61	24	0
Kinoshita [15]	27	No	9.1 (5-13)	0	14	70.6 ^a	0
Fahy [4]	70	No	< 20	12.5	48	14.5-17.0 ^e	2 (4.2) ^h

ER, endoscopically resected; Recur, recurrence; LVI, lymphovascular invasion; OP, Operation; LN+: lymph node metastasis.

^a Mean ± SD or mean.

^b Inter-quartile range.

^c Follow-up month range.

^d Follow-up was done during the study period.(2007-2014).

^e 14.5 months (size < 10 mm) and 17.0 months of follow up (size.10-19 mm).

^f 20-mm sized tumor with lymphovascular invasion recurred after 18 months.

^g 15-mm sized tumor with distant metastasis at initial diagnosis.

^h 8 mm- and 10 mm-sized tumor without lymphovascular invasion recurred after 14 and 18 months, respectively.

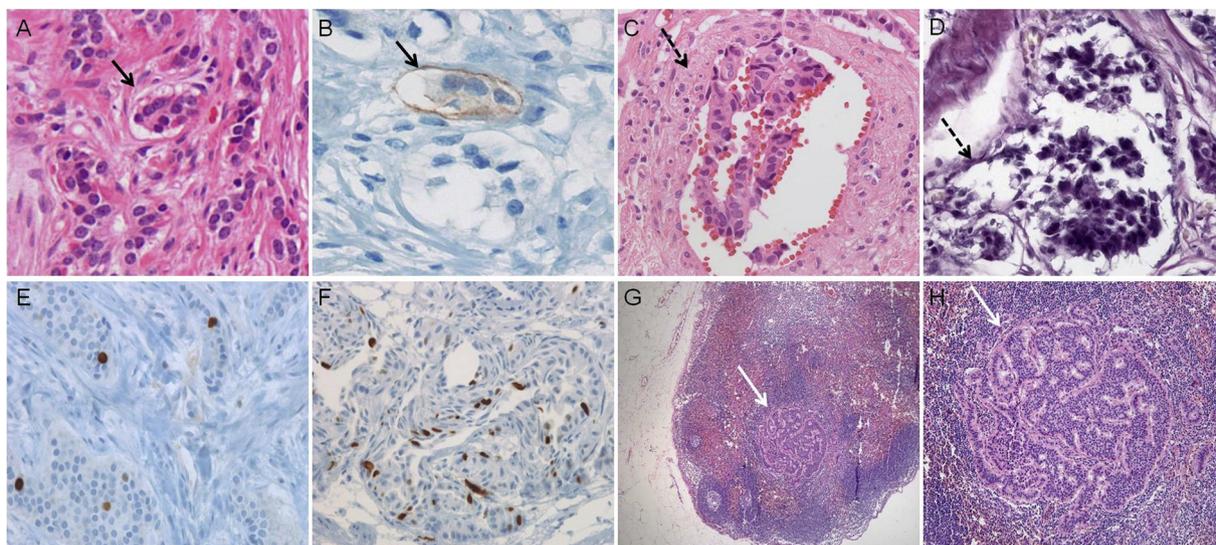


Fig. 2. Ancillary staining methods assessed for lymphatic or vascular invasion and Ki-67 index in rectal neuroendocrine tumors. (A) Lymphatic invasion with thin endothelial cell lining is observed on H&E (arrow). (B) The tumor emboli in D2-40-stained lymphatic vessels reveal the recognition of lymphatic invasion (arrow). (C) Vascular invasion in H&E (dotted arrow). (D) Elastica van Gieson stain identifies vascular invasion of tumor cells (dotted arrow). (E) Grade 1 tumor with 0.6% Ki-67 index. (F) Grade 2 tumor with 4.7% Ki-67 index. (G–H) Magnified scan of H&E slide shows lymph node metastasis (white arrow) from grade 1 rectal neuroendocrine tumor measuring 0.5 × 0.4 cm. The tumor was completely excised by endoscopic submucosal dissection. However, because lymphatic invasion was identified in the specimen of endoscopic submucosal dissection, the subsequently radical resection was performed and the synchronous lymph node metastasis was observed. (Footnotes: Figs. 2C–2D have been published previously [18] and the authors permitted from the original authors of the figures).

3.6. Publication bias

The funnel plots of the relevant factors on the risk of LVI including tumor size (> 5 mm vs. ≤ 5 mm and > 10 mm vs. ≤ 10 mm) and tumor grade as well as LVI as a predictor of lymph node metastasis in this meta-analysis is shown in Supplementary Fig. 2. Visual inspection of the funnel plots revealed no obvious publication bias for the predictors studied. Begg's test and Egger's test suggested no significant publication bias for the included studies (tumor size > 5 mm vs. ≤ 5 mm, $P = 0.851$ and $P = 0.939$; tumor size > 10 mm vs. ≤ 10 mm, $P = 0.573$ and $P = 0.254$; tumor grade, $P = 1.000$ and $P = 0.798$; LVI as a predictor of lymph node metastasis, $P = 0.624$ and $P = 0.871$).

4. Discussion

This systematic review and meta-analysis assessed the risk factors for the LVI, lymph node metastasis, or recurrence after endoscopic resection in patients with small rectal NETs. We have shown that tumor size proved to be a risk factor for LVI. LVI itself was proved as a risk factor for subsequent lymph node metastasis in small rectal NETs, independent of tumor grade. In fact, we authors have previously experienced a synchronous lymph node metastasis from endoscopically resected, grade 1 small rectal NET in size of 0.5 × 0.4 cm (Fig. 2G–H). In this meta-analysis, the overall prevalence of LVI in small rectal NETs less than 2 cm was relatively common in small rectal NETs, with 21.8% exhibiting LVI. Notably, this rate was not markedly different from the 29.4% in small rectal NET patients who developed recurrence and the 26.4% rate in patients with tumors measuring < 10 mm. Therefore, grade 1 rectal NET with LVI also needs to be radiologically examined to rule out the synchronous or metachronous lymph node metastasis.

Our meta-analysis also demonstrated that the detection rate of LVI was approximately three-fold higher in using IHC method (35.8%) than in using H&E staining method only (13.2%). Because the detection rate for LVI using routine H&E staining is low (1.1%–10.2%) due to the marked tumor retraction [23,27,29], additional ancillary IHC staining (D2-40, CD34, CD31, and Elastica van Gieson) has increased the sensitivity and the specificity for detecting LVI in small rectal NETs, up to the detection rate of 22.4%–46.7% [18,23,29,33]. These results

emphasize that adding IHC to the diagnostic method yields more reliable findings of LVI in the endoscopic resected specimens.

Despite of the common presence of LVI, the prognosis of small rectal NET with LVI was favorable, with only 0.3% of recurrence in the 1022 patients. In comparisons, the patients with rectal NETs measuring < 20 mm have a favorable prognosis without lymph node metastasis after endoscopic resection only, with a 3-year survival rate of up to 100% [25]. In the era of IHC staining, 3 additional studies reported no metastasis or recurrence over a median follow-up period of 5 years in patients with small rectal NETs who had LVI in the endoscopic resection specimens but did not undergo additional surgery [16,18,33]. By contrast, lymph node metastasis was observed in 5 of 23 (21.7%) cases that additionally underwent a radical operation because of the presence of the LVI in the endoscopic resection specimens [3,16,18,24,33]. Although LVI-positive small rectal NETs were at high risk of post-excised lymph node metastasis, the prognosis of LVI-positive small rectal NETs appears to be complex and not proportional to the presence of LVI. Otherwise, the process of LVI to lymph node metastasis can be as extremely slow as the nodal metastatic size has remained unchanged during a 7-year follow-up [14]. A delayed recurrence is developed 23 years after the endoscopic resection of a 4-mm, grade 1, rectal NET [9]. Although the intra-lymphovascular NET cells may gain access to the lymphatics as one of the earliest events in lymph node metastasis, they may need further complex factors to reach the lymph node [26]. Vascular invasion might aid to lymphatic invasion in the setting of lymph node metastasis, because the presence of vascular invasion had a stronger impact on subsequent lymph node metastasis (OR 3.94) rather than lymphatic invasion in small rectal NETs. Rectal NETs are truly highly vascular tumors [36]. The vascular invasion has also been demonstrated as a risk factor of lymph node metastasis (OR 6.26) in a previous meta-analysis of radically resected rectal NETs [37]. Recent study using next-generation sequencing failed to demonstrate the specific genetic mutations statistically related to LVI, lymph node metastasis, or recurrence in rectal NETs, although rectal NETs commonly carry pathogenic/likely-pathogenic mutations [26]. These inconclusive facts still underline the clinical difficulty with precise prediction for the recurrences of rectal NETs. Based on our study, completion radical surgery would not be absolutely necessary for LVI-positive small rectal

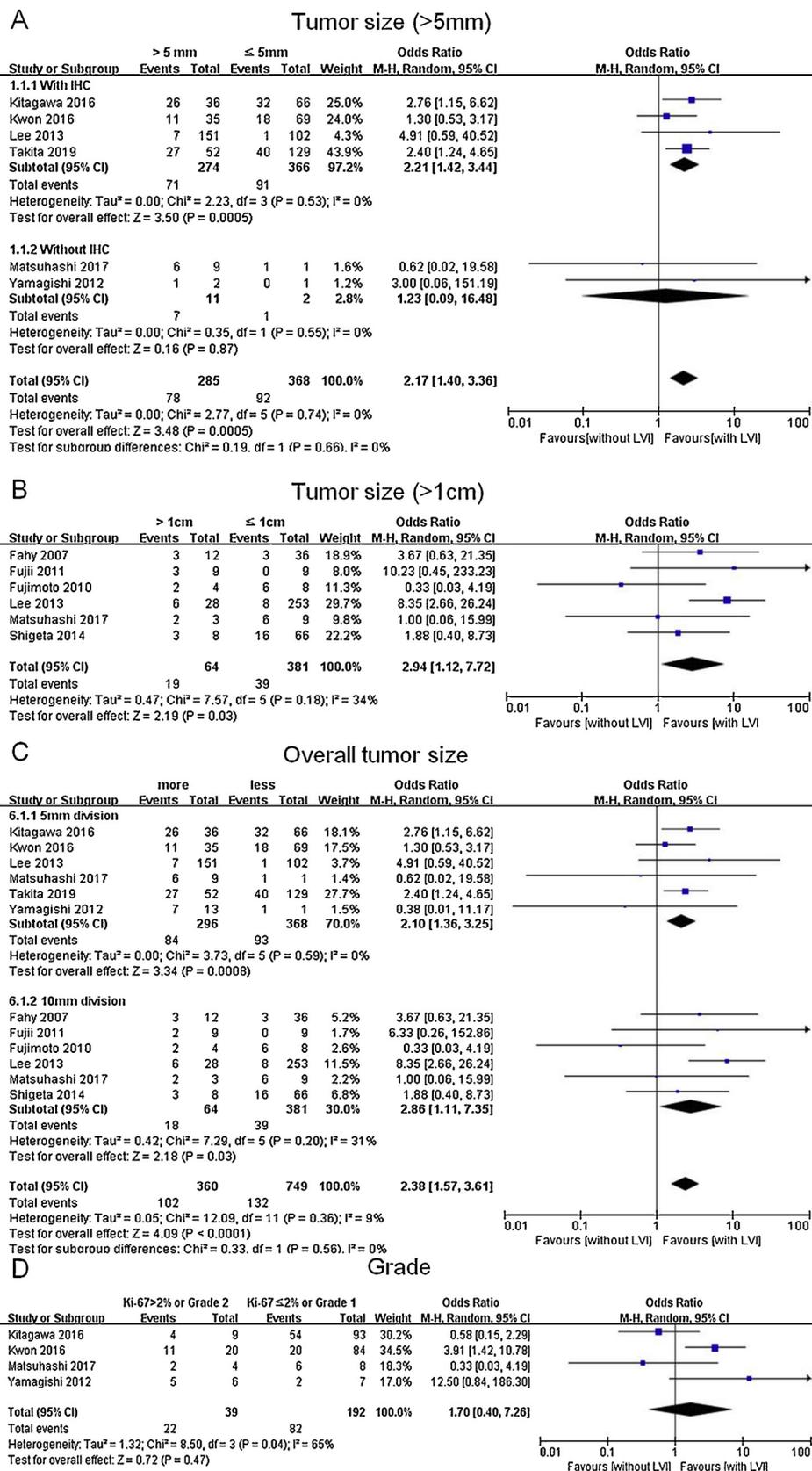
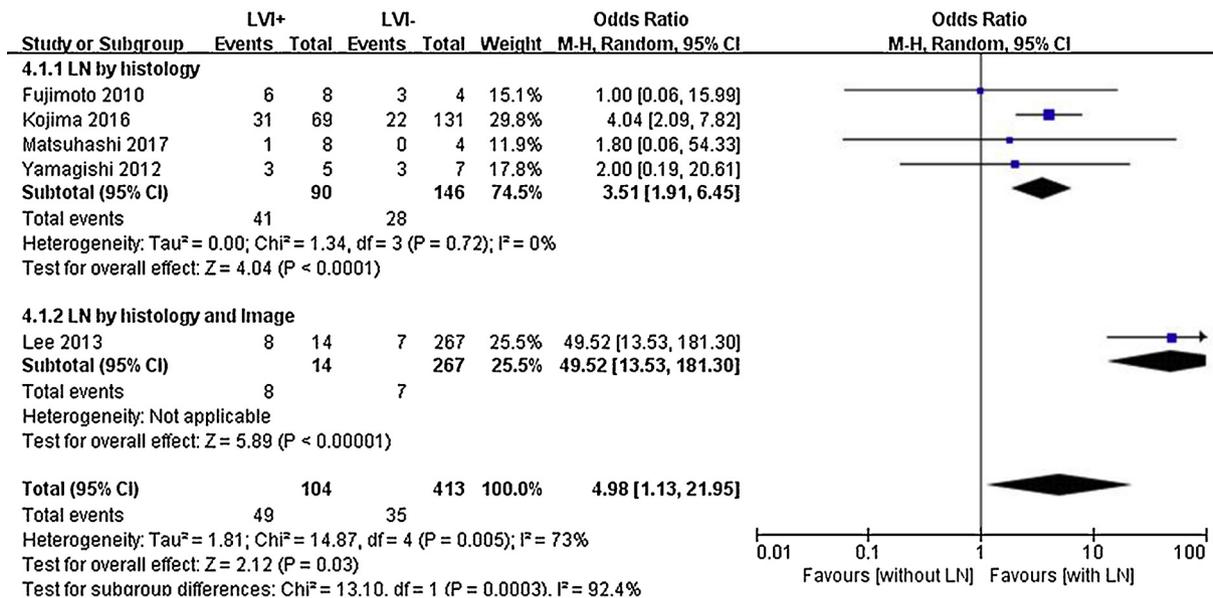


Fig. 3. Forest plots of the association between lymphovascular invasion and relevant factors in rectal neuroendocrine tumors. (A) Tumor size > 5 mm. (B) Tumor size > 1 cm. (C) Overall tumor size. (D) Grade.

(Abbreviations: With IHC, lymphovascular invasion (LVI) was evaluated via immunohistochemical staining; Without IHC, LVI was evaluated via H&E staining).

A

Lymphovascular invasion



B

Lymphatic or vascular invasion

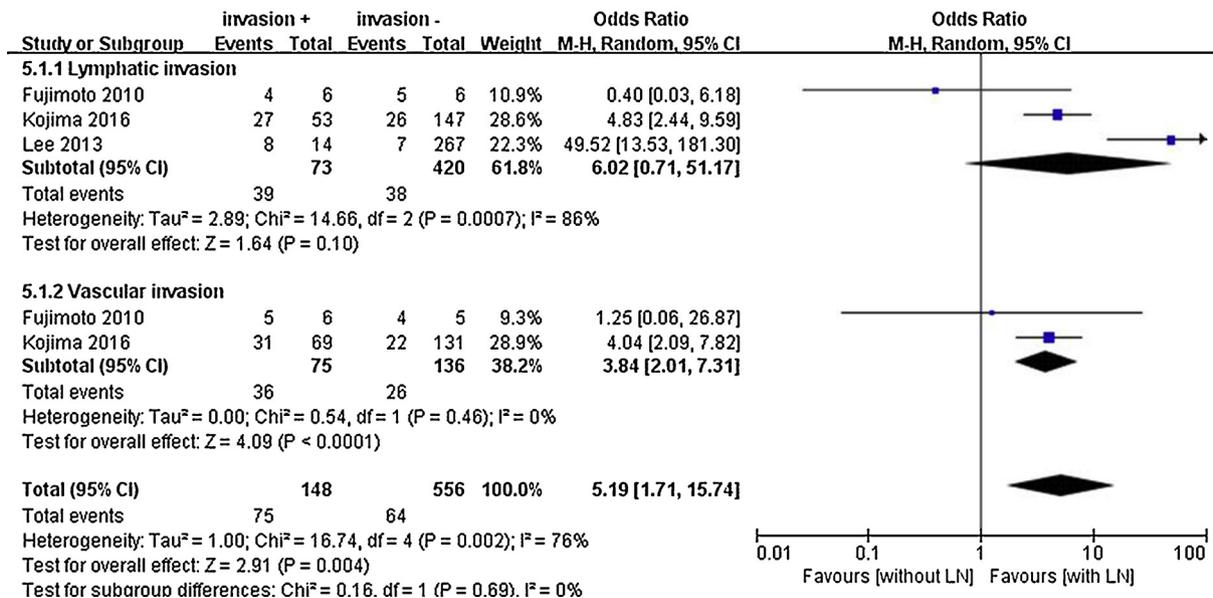


Fig. 4. Forest plots of meta-analyses of lymphovascular invasion (A) and lymphatic or vascular invasion (B) as predictors of lymph node metastasis. (Abbreviations: LN by pathology, lymph node metastasis was evaluated via pathologic evaluation; LN by pathology and imaging, lymph node metastasis was evaluated via pathologic evaluation or radiologic imaging).

NETs treated with endoscopic resection. However, because of the clear evidence of LVI associated with lymph node metastasis, LVI-positive rectal NET patients who do not undergo additional operation should undergo long-term follow-up of 10–20 years.

The limitations in this meta-analysis are the small numbers of available studies due to the disease rarity and the possible selection bias only enrolling locally excised small tumors. Although uniform criteria were used to select eligible studies, inherent differences among the studies still existed. Substantial heterogeneity was observed in the meta-analysis, and this was probably caused by the differences in study factors including additional radical surgery, follow-up duration, and limited data of tumor depth due to endoscopic resection. Nevertheless,

some messages emerged from our results. LVI is frequent in small rectal NETs. LVI is a risk factor for the subsequent lymph node metastasis, but small rectal NET patients with LVI tend to have excellent short-term prognoses. Immediate completion radical surgery is not absolutely necessary for LVI-positive small rectal NETs. However, long-term follow-up of 10 to 20 years is recommended to assess for any delayed recurrence. The present meta-analysis helps improve understanding of the clinicopathological role of LVI in small rectal NET patients who are endoscopically treated only.

Declaration of Competing Interest

The authors declare that there are no conflicts of interests regarding the publication of this paper.

Acknowledgments

This research was supported by the Hallym University Research Fund (HURF-2018-46) to HS Kang, by the Basic Science Research Program through the National Research Foundation of Korea (NRF) grant funded by the Ministry of Science and ICT of Korea government (NRF- 2019R1C1C1004463), and Korea Evaluation Institute of Industrial Technology (KEIT) grant funded by the Korea government (MOTIE) (No. 10047831) to MJ Kwon.

The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.prp.2019.152642>.

References

- I.H. Baek, Endoscopic submucosal dissection or conventional endoscopic mucosal resection is an effective and safe treatment for rectal carcinoid tumors: a retrospective study, *J. Laparosc. Adv. Surg. Tech. Part A* 20 (2010) 329–331.
- M. Caplin, A. Sundin, O. Nilsson, R.P. Baum, K.J. Klöse, F. Kelestimur, U. Plockinger, M. Papotti, R. Salazar, A. Pascher, ENETS Consensus Guidelines for the management of patients with digestive neuroendocrine neoplasms: colorectal neuroendocrine neoplasms, *Neuroendocrinology* 95 (2012) 88–97.
- C.W. Choi, S.B. Park, D.H. Kang, H.W. Kim, S.J. Kim, H.S. Nam, D.G. Ryu, The clinical outcomes and risk factors associated with incomplete endoscopic resection of rectal carcinoid tumor, *Surg. Endosc.* 31 (2017) 5006–5011.
- B.N. Fahy, L.H. Tang, D. Klimstra, W.D. Wong, J.G. Guillem, P.B. Paty, L.K. Temple, J. Shia, M.R. Weiser, Carcinoid of the rectum risk stratification (CaRRs): a strategy for preoperative outcome assessment, *Ann. Surg. Oncol.* 14 (2007) 396–404.
- T. Fujii, Y. Tabe, R. Yajima, S. Tsutsumi, T. Asao, H. Kuwano, Transanal local excision in the treatment of rectal carcinoid: results and implications, *Hepatogastroenterology* 58 (2011) 1168–1170.
- Y. Fujimoto, M. Oya, H. Kuroyanagi, M. Ueno, T. Akiyoshi, T. Yamaguchi, T. Muto, Lymph-node metastases in rectal carcinoids, *Langenbecks Arch. Surg.* 395 (2010) 139–142.
- P. Gastrointestinal Pathology Study Group of Korean Society of, M.Y. Cho, J.M. Kim, J.H. Sohn, M.J. Kim, K.M. Kim, W.H. Kim, H. Kim, M.C. Kook, D.Y. Park, J.H. Lee, H. Chang, E.S. Jung, H.K. Kim, S.Y. Jin, J.H. Choi, M.J. Gu, S. Kim, M.S. Kang, C.H. Cho, M.I. Park, Y.K. Kang, Y.W. Kim, S.O. Yoon, H.I. Bae, M. Joo, W.S. Moon, D.Y. Kang, S.J. Chang, Current trends of the incidence and pathological diagnosis of gastroenteropancreatic neuroendocrine tumors (GEP-NETs) in Korea 2000–2009: multicenter study, *Cancer Res. Treat.* 44 (2012) 157–165.
- M. Ishii, M. Ota, S. Saito, Y. Kinugasa, S. Akamoto, I. Ito, Lymphatic vessel invasion detected by monoclonal antibody D2-40 as a predictor of lymph node metastasis in T1 colorectal cancer, *Int. J. Colorectal Dis.* 24 (2009) 1069–1074.
- S. Judd, S. Nangia, E. Levi, F. Antaki, Rectal carcinoid tumor: a delayed localized recurrence 23 years after endoscopic resection, *Endoscopy* 46 (Suppl. 1) (2014) E555–E556 UCTN.
- E.S. Jung, Y.K. Kang, M.Y. Cho, J.M. Kim, W.A. Lee, H.E. Lee, S. Park, J.H. Sohn, S.Y. Jin, Update on the proposal for creating a guideline for cancer registration of the gastrointestinal tumors (I-2), *Korean J. Pathol.* 46 (2012) 443–453.
- G.U. Kim, K.J. Kim, S.M. Hong, E.S. Yu, D.H. Yang, K.W. Jung, B.D. Ye, J.S. Byeon, S.J. Myung, S.K. Yang, J.H. Kim, Clinical outcomes of rectal neuroendocrine tumors $\leq 10\text{ mm}$ following endoscopic resection, *Endoscopy* 45 (2013) 1018–1023.
- H.H. Kim, S.J. Park, S.H. Lee, H.U. Park, C.S. Song, M.I. Park, W. Moon, Efficacy of endoscopic submucosal resection with a ligation device for removing small rectal carcinoid tumor compared with endoscopic mucosal resection: analysis of 100 cases, *Dig. Endosc.* 24 (2012) 159–163.
- J.H. Kim, W. Moon, S.J. Park, M.I. Park, S.E. Kim, K.H. Ku, G.W. Lee, Y.J. Choi, Clinical impact of endoscopic ultrasonography for small rectal neuroendocrine tumors, *Turk. J. Gastroenterol.* 25 (2014) 657–660.
- S.H. Kim, D.H. Yang, J.S. Lee, S. Park, H.S. Lee, H. Lee, S.H. Park, K.J. Kim, B.D. Ye, J.S. Byeon, S.J. Myung, S.K. Yang, J.H. Kim, C.W. Kim, J. Kim, Natural course of an untreated metastatic perirectal lymph node after the endoscopic resection of a rectal neuroendocrine tumor, *Intest. Res.* 13 (2015) 175–179.
- T. Kinoshita, E. Kanehira, K. Omura, T. Tomori, H. Yamada, Transanal endoscopic microsurgery in the treatment of rectal carcinoid tumor, *Surg. Endosc.* 21 (2007) 970–974.
- Y. Kitagawa, D. Ikebe, T. Hara, K. Kato, T. Komatsu, F. Kondo, R. Azemoto, F. Komoda, T. Tanaka, H. Saito, M. Itami, T. Yamaguchi, T. Suzuki, Enhanced detection of lymphovascular invasion in small rectal neuroendocrine tumors using D2-40 and Elastica van Gieson immunohistochemical analysis, *Cancer Med.* 5 (2016) 3121–3127.
- M. Kojima, K. Ikeda, N. Sakuyama, K. Koushi, S. Kawano, T. Watanabe, K. Sugihara, N. Saito, M. Ito, A. Ochiai, Colorectal neuroendocrine tumours in Japan: comprehensive-multi-institutional survey data, *Virchows Arch.* 469 (2016) S73–S74.
- M.J. Kwon, H.S. Kang, J.S. Soh, H. Lim, J.H. Kim, C.K. Park, H.R. Park, E.S. Nam, Lymphovascular invasion in more than one-quarter of small rectal neuroendocrine tumors, *World J. Gastroenterol.* 22 (2016) 9400–9410.
- S.H. Lee, B.C. Kim, H.J. Chang, D.K. Sohn, K.S. Han, C.W. Hong, E.J. Lee, J.B. Lee, D.S. Lee, I.T. Lee, E.G. Youk, Rectal neuroendocrine and L-cell tumors: diagnostic dilemma and therapeutic strategy, *Am. J. Surg. Pathol.* 37 (2013) 1044–1052.
- Y. Mashimo, T. Matsuda, T. Uraoka, Y. Saito, Y. Sano, K. Fu, T. Kozu, A. Ono, T. Fujii, D. Saito, Endoscopic submucosal resection with a ligation device is an effective and safe treatment for carcinoid tumors in the lower rectum, *J. Gastroenterol. Hepatol.* 23 (2008) 218–221.
- N. Matsushashi, T. Takahashi, H. Tomita, H. Araki, T. Ibuka, K. Tanaka, T. Tanahashi, S. Matsui, Y. Sasaki, Y. Tanaka, N. Okumura, K. Yamaguchi, S. Osada, K. Yoshida, Evaluation of treatment for rectal neuroendocrine tumors sized under 20 mm in comparison with the WHO 2010 guidelines, *Mol. Clin. Oncol.* 7 (2017) 476–480.
- D. Moher, L. Shamseer, M. Clarke, D. Ghersi, A. Liberati, M. Petticrew, P. Shekelle, L.A. Stewart, Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement, *Syst. Rev.* 4 (2015) 1.
- K. Nakamura, M. Osada, A. Goto, T. Iwasa, S. Takahashi, N. Takizawa, K. Akahoshi, T. Ochiai, N. Nakamura, H. Akiho, S. Itaba, N. Harada, M. Iju, M. Tanaka, H. Kubo, S. Somada, E. Ihara, Y. Oda, T. Ito, R. Takayanagi, Short- and long-term outcomes of endoscopic resection of rectal neuroendocrine tumours: analyses according to the WHO 2010 classification, *Scand. J. Gastroenterol.* 51 (2016) 448–455.
- Y. Okubo, O. Motohashi, N. Nakayama, K. Nishimura, R. Kasajima, Y. Miyagi, M. Shiozawa, E. Yoshioka, M. Suzuki, K. Washimi, K. Kawachi, M. Nito, Y. Kameda, T. Yokose, The clinicopathological significance of angiogenesis in hindgut neuroendocrine tumors obtained via an endoscopic procedure, *Diagn. Pathol.* 11 (2016) 128.
- C.H. Park, J.H. Cheon, J.O. Kim, J.E. Shin, B.I. Jang, S.J. Shin, Y.T. Jeon, S.H. Lee, J.S. Ji, D.S. Han, S.A. Jung, D.I. Park, I.H. Baek, S.H. Kim, D.K. Chang, Criteria for decision making after endoscopic resection of well-differentiated rectal carcinoids with regard to potential lymphatic spread, *Endoscopy* 43 (2011) 790–795.
- H.Y. Park, M.J. Kwon, H.S. Kang, Y.J. Kim, N.Y. Kim, M.J. Kim, K.W. Min, K.C. Choi, E.S. Nam, S.J. Cho, H.R. Park, S.K. Min, J. Seo, J.Y. Choe, H.K. Lee, Targeted next-generation sequencing of well-differentiated rectal, gastric, and appendiceal neuroendocrine tumors to identify potential targets, *Hum. Pathol.* (2019).
- R.H. Riddell, P.E. Petras, G.T. Williams, L.H. Sobin, Tumors of the intestines, in: J. Rosai (Ed.), *Atlas of Tumor Pathology*, Armed Forces Institute of Pathology, Washington, DC, 2003, pp. 279–321.
- H. Scherubl, Rectal carcinoids are on the rise: early detection by screening endoscopy, *Endoscopy* 41 (2009) 162–165.
- M. Sekiguchi, S. Sekine, T. Sakamoto, Y. Otake, T. Nakajima, T. Matsuda, H. Taniguchi, R. Kushima, Y. Ohe, Y. Saito, Excellent prognosis following endoscopic resection of patients with rectal neuroendocrine tumors despite the frequent presence of lymphovascular invasion, *J. Gastroenterol.* 50 (2015) 1184–1189.
- K. Shiget, K. Okabayashi, H. Hasegawa, Y. Ishii, H. Ochiai, M. Tsuruta, M. Mukai, K. Kameyama, T. Uraoka, N. Yahagi, Y. Kitagawa, Long-term outcome of patients with locally resected high- and low-risk rectal carcinoid tumors, *J. Gastrointest. Surg.* 18 (2014) 768–773.
- J. Soga, Carcinoids of the rectum: an evaluation of 1271 reported cases, *Surg. Today* 27 (1997) 112–119.
- S. Taghavi, S.N. Jayarajan, B.D. Powers, A. Davey, A.I. Willis, Examining rectal carcinoids in the era of screening colonoscopy: a surveillance, epidemiology, and end results analysis, *Dis. Colon Rectum* 56 (2013) 952–959.
- M. Takita, E. Sakai, T. Nakao, Y. Kimoto, R. Ishii, T. Konishi, S. Ueno, K. Kanda, R. Negishi, T. Muramoto, H. Hashimoto, T. Morikawa, N. Matsushashi, K. Ohata, Clinical outcomes of patients with small rectal neuroendocrine tumors treated using endoscopic submucosal resection with a ligation device, *Digestion* 99 (2019) 72–78.
- S.B. Wells, G. D. O'Connell, J. Peterson, V. Welch, M. Losos, P. Tugwell, The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses, Accessed on 2017-3-15 Available from: URL Ottawa Hospital Research Institute, Ottawa, 2013 http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
- D. Yamagishi, N. Matsubara, M. Noda, T. Yamano, K. Tsukamoto, T. Kuno, M. Hamanaka, M. Kobayashi, H. Ikeuchi, I. Matsuda, S. Hirota, N. Tomita, Clinicopathological characteristics of rectal carcinoid patients undergoing surgical resection, *Oncol. Lett.* 4 (2012) 910–914.
- S. Yazdani, A. Kasajima, K. Tamaki, Y. Nakamura, F. Fujishima, H. Ohtsuka, F. Matoi, M. Unno, M. Watanabe, Y. Sato, H. Sasano, Angiogenesis and vascular maturation in neuroendocrine tumors, *Hum. Pathol.* 45 (2014) 866–874.
- X. Zhou, H. Xie, L. Xie, J. Li, W. Fu, Factors associated with lymph node metastasis in radically resected rectal carcinoids: a systematic review and meta-analysis, *J. Gastrointest. Surg.* 17 (2013) 1689–1697.