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REVIEW ARTICLE

Factors Associated with Lymph Node Metastasis in Radically Resected Rectal Carcinoids: a Systematic Review and Meta-analysis

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Abstract
Background Although various guidelines regarding neuroendocrine tumors were released, treatment for rectal neuroendocrine tumors with size between 1 and 2 cm has not been explicitly elucidated. The determinant factor of the choice between endoscopic resection and radical surgery is whether lymph node involvement exists.
Aim This study aims to explore factors associated with lymph node involvement in rectal neuroendocrine tumors by conducting a meta-analysis.
Methods A broad literature research of Pubmed, Embase&Medline, and The Cochrane Library was performed, and systematic review and meta-analysis about factors associated with lymph node involvement were conducted.
Results Seven studies were included in this meta-analysis. Tumor size>1 cm (odds ratio (OR) 6.72, 95 % confidence interval (CI) [3.23, 14.02]), depth of invasion (OR 5.06, 95 % CI [2.30, 11.10]), venous invasion (OR 5.92, 95 % CI [2.21, 15.87]), and central depression (OR 3.00, 95 % CI [1.07, 8.43]) were significantly associated with lymph node involvement.
Conclusion The available clinical evidence suggests that tumor size>1 cm, invasion of muscularis properia, venous invasion, and central depression could be risk factors of lymph node involvement, while other factors reported by few studies need further research.

Keywords Neuroendocrine tumors · Lymph node metastasis · Rectal

Introduction

Since it was put forward by Oberndorfer in 1907, the term "carcinoid" has been used to denote a variety of neuroendocrine tumors.[1] The largest epidemiological data of neuroendocrine tumors came from the Surveillance, Epidemiology, and End Results (SEER) database; a rapidly increasing incidence of neuroendocrine tumors was observed during the period between 1937 and 2005 from 1.09 per 100,000 to 5.25 per 100,000, with the incidence of rectal neuroendocrine tumors being highest among colored races.[2] A recent survey from Japan indicated that the incidence of gastrointestinal neuroendocrine tumors was 3.45 per 100,000, of which 60 % were from hindgut.[3] Surgery is the only approach to cure neuroendocrine tumors,[4] including removal of primaries, lymph node metastases, and distant metastases. Currently, consensus has been reached about the endoscopic resection of tumors smaller than 1 cm and radical resection of tumors larger than 2 cm, but disputes still exist on the treatment of tumors between 1 and 2 cm.[4–7] The determinant factor of the choice between endoscopic resection and radical surgery is whether lymph node involvement exists. A variety of factors associated with metastatic characteristics of rectal neuroendocrine tumors were reported,

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such as size, depth of invasion, lymphatic invasion, atypical endoscopic features, mitotic rate, and Ki-67 index,[1,8–10] but all of them were based on relatively small cohorts and single-center experiences. To elucidate factors associated with lymphatic metastases of rectal neuroendocrine tumors, we conducted this systematic review and meta-analysis.

Materials and Methods

Search Strategy

A comprehensive search strategy was adopted to include as many relevant studies as possible. Pubmed, Embase&Medline Databases, and the Cochrane Library were searched for articles published from their introduction until November 2012. The search term combinations were Medical Subject Heading (MeSH) terms, text words, and word variants for neuroendcrione tumors, APUDoma, carcinoids, rectal, and lymph node metastasis (Appendix 1). Only studies published in English were included. The reference lists of all retrieved articles were searched manually for other possible studies.

Table 1 Inclusion and exclusion criteria for study selection

	Inclusion	Exclusion
Population	Studies investigating patients with rectal neuroendocrine tumors presenting with lymph node involvement who underwent radical resection	Studies in which (1) rectal and other neuroendocrine tumors were collectively studied and (2) mainly patients who underwent local resection were studied
Outcomes	Studies investigating lymph node involvement in patients with rectal neuroendocrine tumors	Studies (1) investigating recurrence or prognosis only and (2) in which lymph node metastases and distant metastases were studied together as metastatic diseases
Comparators	Studies allowing estimates of association between factors and lymph node involvement	Studies that fail to provide comparative data on factors and lymph node involvement
Study design	All observational studies, published and unpublished	Descriptive studies with no comparative data such as review articles or case reports

Table 2 Quality assessment of studies (points scored)

Participant selection
- Cases and controls drawn from the same population (1)
- Cases and controls drawn from different sources or the selection of groups was not described (0)

Comparability of groups
- No differences between the groups explicitly reported unless it was one of these variables that were under investigation or such differences were adjusted for (2)
- Differences between groups were not recorded (1)
- Groups differed (0)

Outcomes
- Lymph node involvement confirmed by pathological examination (2)
- Methods for diagnosis of lymph node involvement not explicated(1)
- Lymph node involvement indicated by imaging CT/MRI or EUS (0)

Size
- > 100 participants in each group (2)
- < 100 participants in each group (1)

Cohort design
- Prospective cohort design (2)
- Retrospective design/use of cancer registry or database (1)

Study Selection and Data Extraction

Two reviewers analyzed each title and abstract independently and then met to discuss any discrepancies. Then, selected studies were obtained and the full paper was

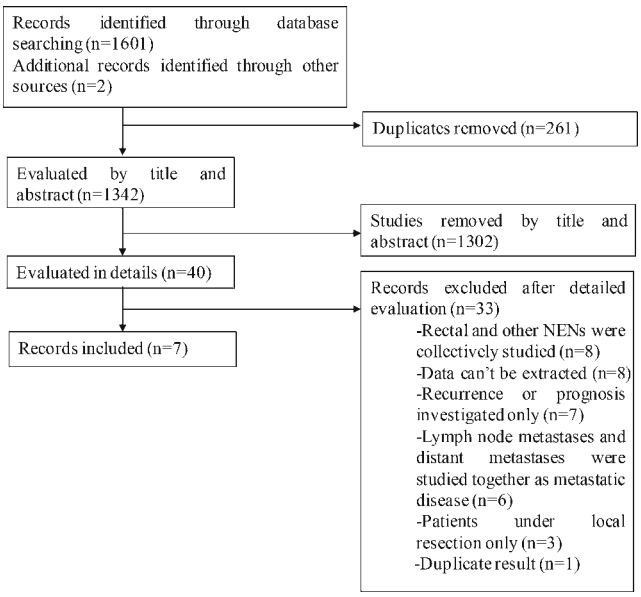

Fig. 1 Flow diagram demonstrating how the final articles were selected

Table 3 Characteristics of included studies

Study	Period	Country	Multi-center	Number of patients	Radically resected	Lymph node involvement
Yamagishi[16]	2000–2011	Japan	No	20	16	13
Kasuga[8]	1979–2009	Japan	No	229	60	24
Lee[15]	2006–2009	Korea	Yes	402	36	17
Shields[1]	1999–2010	Europe/American	Yes	202	100	34
Fujimoto[14]	2005–2007	Japan	No	17	17	12
Tsukamoto[13]	1973–2007	Japan	No	23	23	14
Konishi[12]	1984–1998	Japan	Yes	332	263	36

analyzed by the two reviewers in the same way. If the same data were published twice or more, either the one of higher quality or the latest publication was included. Study characteristics and outcome effects were extracted; only factors identified by more than one study were included in the final analysis (Table 1).

Quality Assessment

A criteria list with a total of nine points previously used by Duckitt and Harrington was adopted to assess the methodological quality of these studies, as outlined in Table 2, which was designed for quality assessment of observational studies and was used to assess the same components of methodological quality in their systematic review as ours.[11] Each component of the quality assessment was allocated a score between 0 and 2 following the descriptions as outlined in Table 2 by the two independent reviewers.

Statistical Analysis

This meta-analysis was performed using the Review Manager (RevMan) software, version 5.0. All dichotomous variables were analyzed using estimation of odds ratios (OR) with 95 % confidence interval (95 % CI). Heterogeneity was evaluated by χ^2 and I^2. Heterogeneity was considered to be present if $I^2>50$ %, and $P<0.05$ was considered as significant. Pooled effect was calculated using the random effects model if heterogeneity existed and fixed effects model if not.

Results

Characteristics of Included Studies

Seven studies involving 1,225 patients were included for analysis,[1,8,12–16] and a flow diagram for the above process is provided in Fig. 1. The study by Konishi et al. evaluated both patients with colon and rectal neuroendocrine tumors, but of the 332 patients evaluated, 304 originated from the rectum, and tumor site *was not* significantly associated with lymph node involvement in their study ($p=0.681$),[12] so their study was included. Of the 1,225 patients, 515 underwent radical resection and all 150 patients with lymph node involvement were confirmed by pathological investigation (Table 3). Outcomes of quality assessment for each study were listed in Table 4.

Table 4 Quality assessment of included studies (points scored: see protocol Table 2)

Included study	Selection	Comparability	Outcome	Size	Cohort design	Total
Yamagishi[16]	1	2	2	1	1	7
Kasuga[8]	1	2	2	1	1	7
Lee[15]	1	2	2	1	1	7
Shields[1]	1	2	2	2	1	8
Fujimoto[14]	1	2	2	1	1	7
Tsukamoto[13]	1	2	2	1	1	7
Konishi[12]	1	2	2	2	1	8

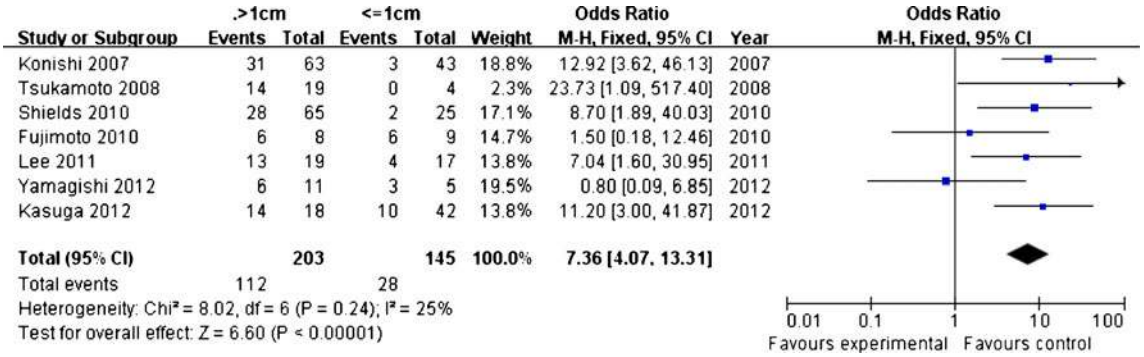

Fig. 2 Forest plot for tumor size

Meta-analysis Results

Tumor Size

A diameter of 1 cm was used in all seven studies as a division line.[1,8,12–16] Analysis of the pooled data revealed a significant difference in lymph node involvement between two groups (OR 6.72, 95 % CI [3.23, 14.02]) (Fig. 2).

Depth of Invasion

Invasion depth was studied in six studies;[1,8,12–14,16] analysis of the pooled data revealed a significant difference in lymph node involvement between two groups with and without muscularis properia invasion (OR 5.06, 95 % CI [2.30, 11.10]) (Fig. 3).

Venous Invasion

Venous invasion was studied in three studies;[8,12,14] analysis of the pooled data revealed a significant difference in lymph node involvement between two groups (OR 5.92, 95 % CI [2.21, 15.87]) (Fig. 4).

Lymphatic Invasion

Lymphatic invasion was studied in three studies;[8,12,14] analysis of the pooled data failed to reveal a significant difference in lymph node involvement between two groups (OR 4.51, 95 % CI [0.31, 65.72]) (Fig. 5).

Central Depression

Central depression was studied in two studies;[8,16] analysis of the pooled data revealed a significant difference in lymph node involvement between two groups (OR 3.00, 95 % CI [1.07, 8.43]) (Fig. 6).

Discussion

With the release of a new classification system of neuroendocrine neoplasms, which divided the neuroendocrine tumors into neuroendocrine tumor grade 1 (NET G1), neuroendocrine tumor grade 2 (NETG2), neuroendocrine carcinoma (NEC), and mixed adenoendocrine carcinoma (MANEC),[17] the word "carcinoid" should be discarded or incorporated into

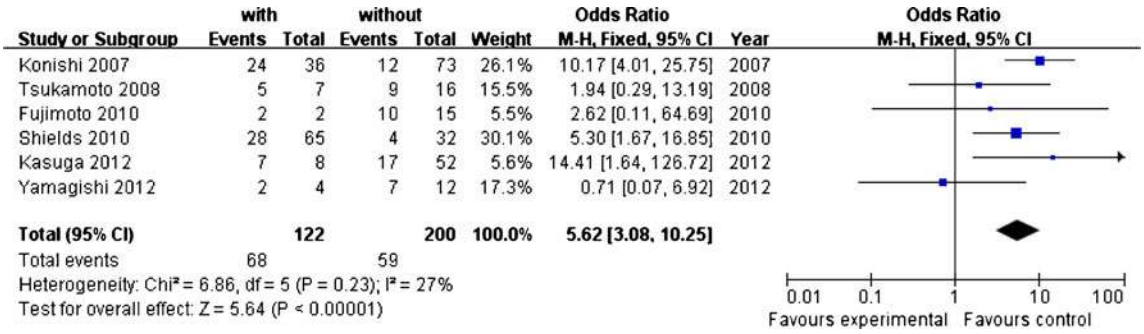

Fig. 3 Forest plot for muscularis properia invasion

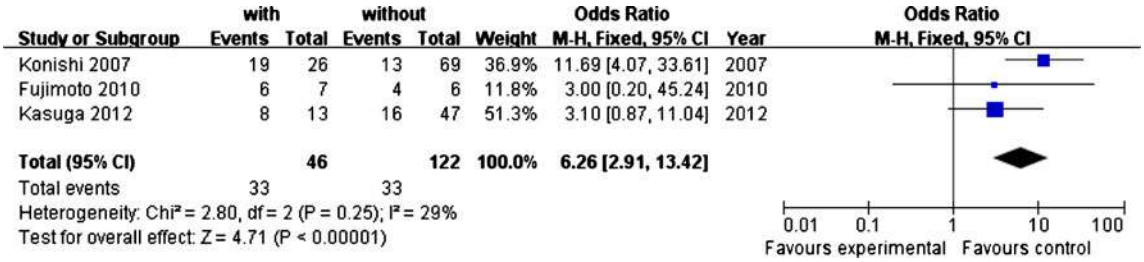

Fig. 4 Forest plot for venous invasion

the content of NET G1, meaning well-differentiated neuroendocrine tumors. In the ENETS 2011 Consensus Guidelines, lesions <1 cm in diameter were considered to have a low risk of metastatic disease and could be completely resected endoscopically or by other local transanal techniques, while rectal tumors>2 cm, T3 or T4 stage, with G3 grading, or rectal tumors with loco-regional lymph node involvement should be treated similarly to rectal adenocarcinoma, but for tumors between 1 and 2 cm, an ambiguous recommendation was given, while the metastatic risk is considered to be between 10 and 15 %.[4] The NANETS 2010 consensus guidelines gave a more vague guidance to classify tumors into <1–2 and>2-cm,[5] thus avoiding the dispute of optimal treatment for tumors between 1 and 2 cm. In order to gain more evidence to optimize treatment for these tumors, we conducted this systematic review and meta-analysis. To the best of our knowledge, this is the first comprehensive meta-analysis to study risk factors associated with lymph node metastasis in rectal neuroendocrine tumors.

In the meta-analysis conducted by Glasgow et al. about metastatic risk factors in rectal adenocarcinoma, statistically significant ORs were found in tumor stage, overall differentiation, tumor budding, vascular invasion, lymphatic invasion, and differentiation at the invasive front, while other common features such as tumor size, morphology (e.g., sessile vs. polypoid), and mucinous content failed to reach significance for predicting lymph node involvement[18]. Nevertheless, rectal neuroendocrine tumors, while in its early stage, possess rather different properties from adenocarcinoma. Also derived from the data on rectal adenocarcinoma, the sensitivity and specificity of EUS for detection of lymph node involvement were 67 % (95 % CI [60–73 %]) and 78 % (71–84 %)[19] and that of MRI were 77 % (69–84 %) and 71 % (59–81 %), respectively,[20] which indicated a relative uncertainty in the confirmation of lymph node involvement by imaging methods.

Tumor size is a main index in deciding treatment for neuroendocrine tumors in nearly all guidelines and studies, but it differs among all publications. Some believe that it is safe to resect tumors with a diameter smaller than 2 cm endoscopically or via a transanal procedure without the risk factors listed earlier,[5] while some assume that tumors larger than 1 cm should be resected radically.[1,21] In our study, there was a significant difference between tumors smaller than 1 cm and tumors between 1 and 2 cm with an OR of 5.36, which necessitated an aggressive approach or at least a thorough investigation and a close follow-up.

Invasion of muscularis properia was found to be significantly associated with lymph node involvement with an OR of 5.06 (2.30, 11.10). Shields et al. found in their study that tumor depth was an associated factor on univariable analysis, but not on regression analysis, which was thought to represent a weak association with tumor size.[1] In the meta-analysis for rectal adenocarcinoma by Glasgow et al., invasion depth was found to be less influential on lymph node status than several other factors, with an OR of only 2.6 (2.33, 2.9), which might be due to difficulty in accurately distinguishing advanced T1 (invasion nearly to the bottom of tunicae submucosa) from T2 tumors histologically.[18] Depth of invasion can be determined preoperatively by endoscopic ultrasonography (EUS) and magnetic resonance imaging (MRI) or postoperatively by pathological examinations of specimens from local resection. There have

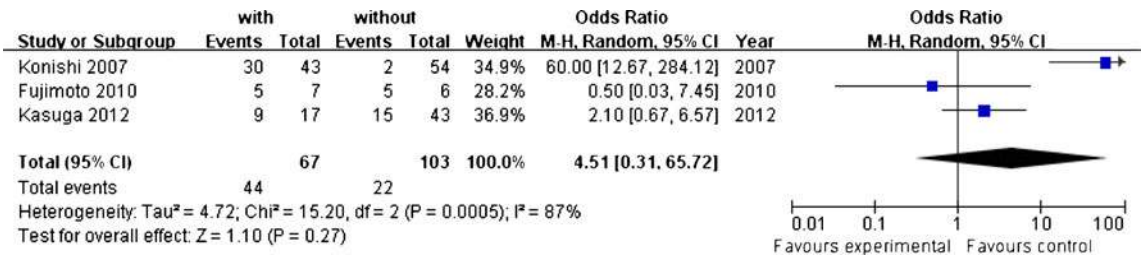

Fig. 5 Forest plot for lymphatic invasion

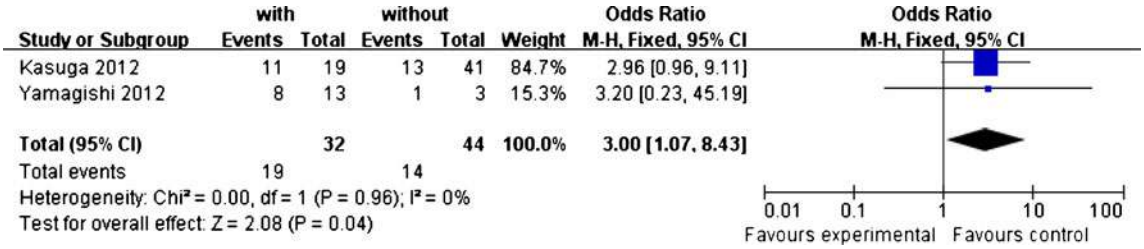

Fig. 6 Forest plot for central depression

been few studies concerning the specificity and sensitivity of imaging methods in the T staging for rectal neuroendocrine tumors. Ishii et al. reported in their study that the accuracy of the preoperative depth determination by EUS was 100 % in 22 patients with T1 tumor.[22] Data derived from rectal adenocarcinoma revealed that the sensitivity and specificity of EUS for muscularis properia invasion were 94 %(90–97 %) and 86 % (80– 90 %)[19] and that of MRI were 87 % (81–92 %) and 75 % (68–80 %), respectively.[20]

Venous invasion was considered in this study to be risk factors of lymph node involvement, while lymphatic invasion was not significantly associated. Shields et al. studied venous invasion and lymphatic invasion collectively as lymphovascular invasion in their study and found that it was significantly associated with lymph node involvement (OR 19.6, 95 % CI [12.3, 146.0]).[1] Confirmation of venous invasion and lymphatic invasion can be achieved by pathological examinations of specimens, so careful pathological investigation of acquired samples is needed for determining treatment decisions.

Central depression was a conspicuous feature under endoscope. Characteristic endoscopic findings include smooth, round, sessile elevations covered with normal-appearing or yellow-colored mucosa, while atypical endoscopic features include central depression, semipedunculated appearance, hyperemia, erosion, and ulceration.[23] Shim et al. reported in their study that tumor shape, surface change, and color were found to be associated with metastasis ($p<0.001$), and atypical endoscopic features occurred more frequently as the size of the tumor increased while surface change (depression/erosion) on

Table 5 Characteristics of tumors smaller than 1 cm with lymph node involvement

No.	Gender	Age (years)	Size (mm)	Invasion depth	Central depression	Lymphatic invasion	Venous invasion	Ki-67 index	Preoperative lymph node metastasis on CT
1	F	64	5	NG	−	−	+	<1	−
2	M	55	7	NG	−	−	−	<1	−
3	F	64	7	NG	−	−	+	<1	−
4	F	27	8	NG	−	+	−	<1	+
5	F	71	8	NG	+	−	−	<1	−
6	F	55	8	NG	−	−	+	<1	−
7	M	59	8	NG	−	+	+	<1	−
8	M	60	8	NG	−	+	+	<1	−
9	F	50	10	NG	+	+	+	<1	−
10	M	77	10	NG	−	−	−	<1	−
11	M	68	7	T1	−	NG	NG	NG	NG
12	M	65	7	T1	+	NG	NG	NG	NG
13	F	65	7	T1	+	−	−	1.4	NG
14	M	59	8	T1	NG	+	+	NG	+
15	M	53	8	T1	NG	−	−	NG	−
16	F	53	8	T1	NG	−	+	NG	−
17	M	76	10	T1	NG	−	−	NG	+
18	M	67	10	T1	NG	+	+	NG	−
19	F	64	10	T1	NG	−	+	NG	+

F female, *M* male, *NG* not given, *CT* computed tomography

Table 6 Search Strategies

Database	Search strategies	No. of records
Pubmed	#1 "Neuroendocrine Tumors"[MeSH] #2 "Carcinoid Tumor"[MeSH] #3 "Apudoma"[MeSH] #4 ((((((((((((((("neuroendocrine tumor*"[Text Word]) OR "neuroendocrine tumuor*"[Text Word]) OR "neuroendocrine cancer*"[Text Word]) OR "neuroendocrine carcinoma*"[Text Word]) OR "neuroendocrine malignan*"[Text Word]) OR "neuroendocrine neoplasm*"[Text Word]) OR carcinoid*[Text Word]) OR APUDoma*[Text Word]) OR "APUD tumor*"[Text Word]) OR "carcinoid tumor*"[Text Word]) OR "APUD cancer*"[Text Word]) OR "APUD carcinoma*"[Text Word]) OR "APUD malignan*"[Text Word]) OR "caricinoid malignan*"[Text Word]) OR "APUD neoplasm*"[Text Word]) OR "carcinoid neoplasm*"[Text Word] #5 #1 OR #2 OR #3 OR #4 #6 (((rectal*[Text Word]) OR rectum[Text Word]) OR colorectal*[Text Word]) OR hindgut[Text Word] #7 "Lymphatic Metastasis"[MeSH] #8 "Neoplasm Metastasis"[MeSH] #9 (metastas*[Text Word] OR "nod* involvement"[Text Word]) OR "lymphatic metastasis"[Text Word] #10 #7 OR #8 OR #9 #11 #5 AND #6 AND #10 #12 #11AND ("humans"[MeSH Terms] AND (Case Reports[ptyp] OR Review[ptyp] OR systematic[sb] OR Meta-Analysis[ptyp]) AND English[lang]) #13 #11 NOT #12	445
The Cochrane Central Register of Controlled Trials	#1 MeSH descriptor:[Neuroendocrine Tumors] explode all trees #2 MeSH descriptor:[Carcinoid Tumor] explode all trees #3 MeSH descriptor:[Apudoma] explode all trees #4 ((neuroendocrine near tumor*) or (neuroendocrine near tumour*) or (neuroendocrine near cancer*) or (neuroendocrine near carcinoma*) or (neuroendocrine near neoplas*) or (neuroendocrine near malignan*) or carcinoid* or (carcinoid near tumor*) or (carcinoid near tumour*) or (carcinoid near cancer*) or (carcinoid near carcinoma*) or (carcinoid near neoplasm*) or (carcinoid near malignan*) or APUDoma* or (APUD near tumor*) or (APUD near tumour*) or (APUD near cancer*) or (APUD near carcinoma*) or (APUD near neoplasm*) or (APUD near malignan*)):ti,ab,kw #5 #1 or #2 or #3 or #4 #6 (rectal* or rectum or colorectal* or hindgut): ti,ab,kw #7 #5 or #6 #8 MeSH descriptor: [Neoplasm Metastasis] explode all trees #9 ((lymphatic near metastas*) or (nod* near involvement) or metastas*): ti,ab,kw #10 #8 or #9	7

Table 6 (continued)

Database	Search strategies	No. of records
	#11 #7and #10	
Medline and Embase	#1 'neuroendocrine tumor'/exp #2 'carcinoid'/exp #3 'apudoma'/exp #4 (neuroendocrine NEAR/1 tumour*) OR (neuroendocrine NEAR/1 tumor*) OR (neuroendocrine NEAR/1 cancer*) OR (neuroendocrine NEAR/1 carcinoma*) OR (neuroendocrine NEAR/1 neoplasm*) OR (neuroendocrine NEAR/1 malignan*) OR carcinoid OR (carcinoid NEAR/1 tumour*) OR (carcinoid NEAR/1 tumor*) OR (carcinoid NEAR/1 cancer*) OR (carcinoid NEAR/1 carcinoma*) OR (carcinoid NEAR/1 neoplasm*) OR (carcinoid NEAR/1 malignan*) OR apudoma OR (apud NEAR/3 tumour*) OR (apud NEAR/3 tumor*) OR (apud NEAR/3 cancer*) OR (apud NEAR/3 carcinoma*) OR (apud NEAR/3 neoplasm*) OR (apud NEAR/3 malignan*):ab,ti #5 #1 OR #2 OR #3 OR #4 #6 rectal* #7 'rectum'/exp OR rectum #8 colorectal* #9 hindgut #10 #6 OR #7 OR #8 OR #9 #11 'metastasis'/exp #12 'lymph node metastasis'/exp #13 'lymph vessel metastasis'/exp #14 metastas*:ab,ti OR (lymphatic NEAR/1 metastasis):ab,ti OR (nod* NEAR/1 involvement):ab,ti #15 #11 OR #12 OR #13 OR #14 #16 'case report'/de OR 'nonhumans' OR 'systematic review'/de AND #5 AND #10 AND #15 #17 #5 AND #10 AND #15 NOT #16	1,149

tumors 10–19 mm in diameter was associated with metastasis (p=0.007)[9].

Although other risk factors of lymph node involvement such as elevated mitotic rate and Ki-67 index were reported to be associated with metastatic potential of rectal neuroendocrine tumors, lack of extractable data made us unable to conduct a meta-analysis about it. Shimizu et al. found in their research that Ki-67 index was significantly higher in lesions larger than 5 mm than in lesions smaller than 5 mm.[10] Hotta et al. found a high specificity (100 %) and positive predictive value (100 %) for metastases of both Ki-67 ratio (>1.5 %) plus tumor size (>10 mm) and Ki-67 ratio (>1.5 %) plus central depression (+).[24]

We also collected data of tumors smaller than 1 cm with lymph node involvement, as shown in Table 5.[8,14,16] As seen from the table, most of them possessed at least one of the aforementioned risk factors, and preoperative CT scan played an unfavorable role in identifying lymph node metastases.

The results of this meta-analysis should be applied with caution considering several limitations. First of all, there was apparent heterogeneity because it was impossible to match patient characteristics in all studies. We adopted a random-effect model when I^2>50 %, taking into consideration differences between studies, which might help to minimize this influence. Second, we only studied patients

who underwent radical resection, which might have caused a selection bias, but pathological investigation is the only gold standard to confirm the presence of lymph node involvement, and huge heterogeneity may exist in the diagnosis of nodal involvement by imaging approach. Third, the sample size was relatively smaller, with only 515 undergoing radical resection because we adopted a relatively strict inclusion standard to guarantee the homogeneity of included studies, and larger cohort studies are needed in the future to provide more vigorous proof. Lastly, the results of this review might be subject to publication bias because studies with positive and significant findings are more inclined to be accepted than those without even though we adopted a comprehensive search strategy to find as many relevant articles as possible.

Conclusion

Based on the current evidence, tumor size>1 cm, invasion of muscularis properia, venous invasion, and central depression were considered to be risk factors of lymph node involvement, while other factors reported by few studies need further research. Tumors with the aforementioned risk factors should be treated with caution; further examination with EUS and MRI, combined with pathological examination, are essential for decision-making.

References

1. Shields C J, Tiret E, Winter D C. Carcinoid tumors of the rectum: a multi-institutional international collaboration. Ann Surg, 2010, 252(5):750–755.
2. Tsikitis V L, Wertheim B C, Guerrero M A. Trends of incidence and survival of gastrointestinal neuroendocrine tumors in the United States: a seer analysis. J Cancer, 2012, 3:292–302.
3. Ito T, Sasano H, Tanaka M, et al. Epidemiological study of gastroenteropancreatic neuroendocrine tumors in Japan. J Gastroenterol, 2010, 45(2):234–243.
4. Caplin M, Sundin A, Nillson O, et al. ENETS consensus guidelines for the management of patients with digestive neuroendocrine neoplasms: colorectal neuroendocrine neoplasms. Neuroendocrinology, 2012, 95(2):88–97.
5. Anthony L B, Strosberg J R, Klimstra D S, et al. The NANETS consensus guidelines for the diagnosis and management of gastrointestinal neuroendocrine tumors (NETS): well-differentiated NETS of the distal colon and rectum. Pancreas, 2010, 39(6):767–774.
6. Ramage J K, Ahmed A, Ardill J, et al. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs). Gut, 2012, 61(1):6–32.
7. National Comprehensive Cancer Network (NCCN). NCCN practice guidelines for neuroendocrine tumors [EB/OL]. [2011-07-25] http://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf.
8. Kasuga A, Chino A, Uragami N, et al. Treatment strategy for rectal carcinoids: a clinicopathological analysis of 229 cases at a single cancer institution. J Gastroenterol Hepatol, 2012, 27(12):1801–1807.
9. Kim B N, Sohn D K, Hong C W, et al. Atypical endoscopic features can be associated with metastasis in rectal carcinoid tumors. Surg Endosc, 2008, 22(9):1992–1996.
10. Shimizu T, Tanaka S, Haruma K, et al. Growth characteristics of rectal carcinoid tumor. Oncology, 2000, 59(3):229–237.
11. Duckitt K, Harrington D. Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. BMJ, 2005, 330(7491):565.
12. Konishi T, Watanabe T, Kishimoto J, et al. Prognosis and risk factors of metastasis in colorectal carcinoids: results of a nationwide registry over 15 years. Gut, 2007, 56(6):863–868.
13. Tsukamoto S, Fujita S, Yamaguchi T, et al. Clinicopathological characteristics and prognosis of rectal well-differentiated neuroendocrine tumors. Int J Colorectal Dis, 2008, 23(11):1109–1113.
14. Fujimoto Y, Oya M, Kuroyanagi H, et al. Lymph-node metastases in rectal carcinoids. Langenbecks Arch Surg, 2010, 395(2):139–142.
15. Lee J B. Clinical characteristics of colorectal carcinoid tumors. Journal of the Korean Society of Coloproctology, 2011, 27(1):17–20.
16. Yamagishi D, Matsubara N, Noda M, et al. Clinicopathological characteristics of rectal carcinoid patients undergoing surgical resection. Oncology Letters, 2012, 4(5):910–914.
17. Bosman FT, Carneim F, Hruban RH, et al. WHO classification of tumours of the digestive system. Lyon: IARC. 2010.
18. Glasgow S C, Bleier J I, Burgart L J, et al. Meta-analysis of histopathological features of primary colorectal cancers that predict lymph node metastases. J Gastrointest Surg, 2012, 16(5):1019–1028.
19. Bipat S, Glas A S, Slors F J, et al. Rectal cancer: local staging and assessment of lymph node involvement with endoluminal US, CT, and MR imaging—a meta-analysis. Radiology, 2004, 232(3):773–783.
20. Al-Sukhni E, Milot L, Fruitman M, et al. Diagnostic accuracy of MRI for assessment of T category, lymph node metastases, and circumferential resection margin involvement in patients with rectal cancer: a systematic review and meta-analysis. Ann Surg Oncol, 2012, 19(7):2212–2223.
21. Modlin I M, Oberg K, Chung D C, et al. Gastroenteropancreatic neuroendocrine tumours. Lancet Oncol, 2008, 9(1):61–72.
22. Ishii N, Horiki N, Itoh T, et al. Endoscopic submucosal dissection and preoperative assessment with endoscopic ultrasonography for the treatment of rectal carcinoid tumors. Surg Endosc, 2010, 24(6):1413–1419.
23. Shim K N, Yang S K, Myung S J, et al. Atypical endoscopic features of rectal carcinoids. Endoscopy, 2004, 36(4):313–316.
24. Hotta K, Shimoda T, Nakanishi Y, et al. Usefulness of Ki-67 for predicting the metastatic potential of rectal carcinoids. Pathol Int, 2006, 56(10):591–596.