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REVIEWS

Rectal carcinoids: a systematic review

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Abstract
Background Rectal carcinoids are increasing in incidence worldwide. Frequently thought of as a relatively benign condition, there are limited data regarding optimal treatment strategies for both localized and more advanced disease. The aim of this study was to summarize published experiences with rectal carcinoids and to present the most current data.
Methods Following PRISMA guidelines, an electronic literature search performed of PubMed, Medline, Embase, and the Cochrane Library using the terms "rectum" or "rectal" AND "carcinoid" over a 20-year study period from January 1993 to May 2013. Non-English-language studies, animal studies, and studies of fewer than 100 patients were excluded. Study end points included demographic information, tumor features, intervention and outcomes. All included articles were quality assessed.
Results Using the search parameters and exclusions as outlined above, a total of 14 articles were identified for detailed analysis. The quality of articles was low/moderate for all included scoring 9 to 17 of 27. The articles included 4,575 patients diagnosed with a rectal carcinoid. Approximately 80 % of tumors were <10 mm, 15 % 11–20 mm, and 5 % >20 mm. Eight percent of patients presented with regional lymph node metastases, and 4 % presented with distant metastases. Tumor size >10 mm, and muscular and lymphovascular invasion are independently associated with an increased risk of metastases. The 5-year survival was 93 % in patients presenting with localized disease and 86 % overall.
Conclusions Small tumors up to 10 mm without any adverse features can be treated with endoscopic or local excision. The treatment of carcinoids between 10 and 20 mm is still contentious, but those up to 16 mm without adverse feature are suitable for local/endoscopic excision followed by careful histopathological assessment. Those >20 mm or with adverse features require radical surgery with mesorectal clearance in suitable patients.

Keywords Carcinoid · Outcomes · Prognostic factors · Rectal

Carcinoids were first described in 1867 [1] and defined histopathologically in 1888 [2]. The term carcinoid, which means "carcinoma-like," was coined in 1907 [3]. Rectal carcinoid tumors continue to be an elusive condition with unclear guidelines or best evidence for treatment modalities, and there is ongoing debate regarding the nomenclature of neuroendocrine tumors [4]. Despite being relatively uncommon compared to rectal adenocarcinoma, there is evidence that the incidence of rectal carcinoid is increasing [5–7], perhaps related to increased diagnostics with more access to endoscopy. Although rectal carcinoids often behave in a relatively indolent manner, they are malignant and can metastasize, as reflected in the American Joint Committee on Cancer classification [8]. In a large US series, the 5-year survival rate in patients for all carcinoids was 67 % and for

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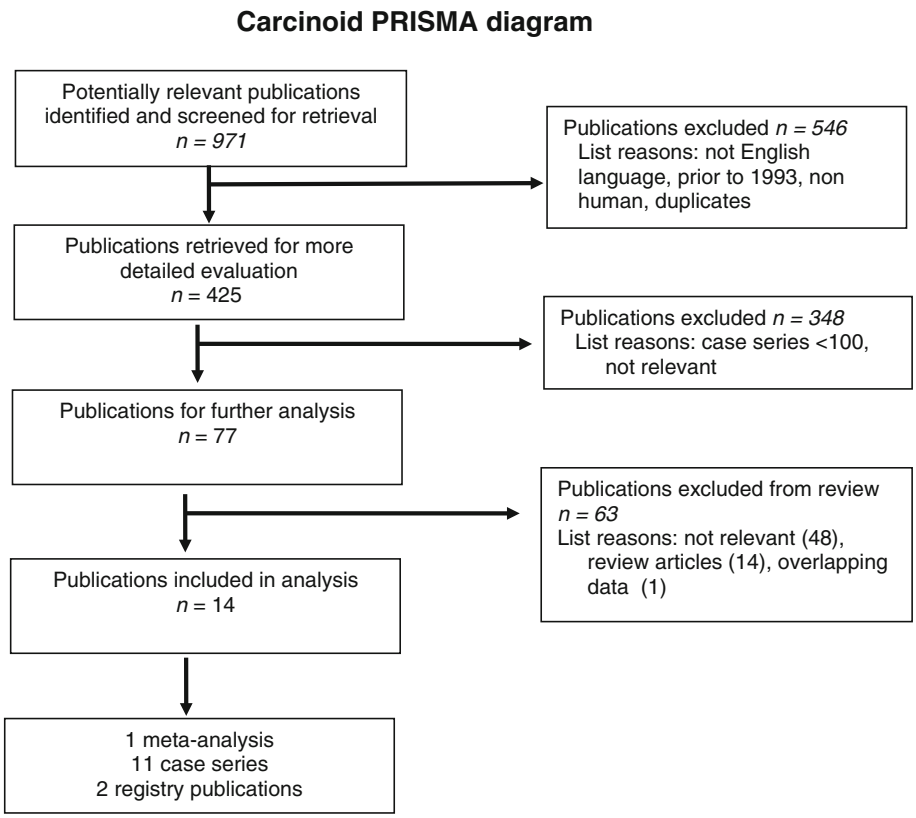
Fig. 1 PRISMA diagram [10]



rectal carcinoids was 88 %. Clearly this is not a benign condition; therefore, it must be appropriately managed and treated to reduce the risk of local and distant metastases.

There is a plethora of literature comparing different traditional and novel endoscopic treatments, but few articles provide robust data detailing their optimal treatment in terms of whether local excision, endoscopic treatment, or more radical surgery with mesorectal excision is appropriate.

The aim of this article was to systematically review the literature to present the most up-to-date information on this challenging condition.

Methods

Following PRISMA guidelines, an electronic literature search was performed of PubMed, Medline, Embase, and the Cochrane Library using the terms "rectum" or "rectal" and "carcinoid" over a 20-year study period from January 1993 to May 2013. Non-English-language studies, animal studies, and studies of fewer than 100 patients were excluded. Study end points included demographic information, tumor features, intervention, and outcomes. Further studies were identified from searches on Google Scholar, as well as manual searches through reference lists of the relevant studies found.

Because of the heterogeneity of data, a meta-analysis could not be performed, and articles were therefore analyzed qualitatively. DW arbitrated disputes on the inclusion or exclusion of articles. Articles were assessed for quality using the Downs and Black questionnaire for randomized and nonrandomized trials by FM and AH and were discussed to reach a consensus [9].

Results

A total of 425 articles were retrieved with the initial search and exclusion criteria. After abstract review, 77 articles were identified. Fifteen of these were kept for more detailed review; the others were either not relevant ($n = 47$) or were review articles ($n = 14$) (Fig. 1).

The 15 articles represented 1 meta-analysis, 11 case series (9 single center and 2 multicenter), and 3 articles publishing registry data. The majority ($n = 12$) were from Asia, with 2 from the United States and 1 international collaboration (Europe/United States). There were no randomized control trials. Out of the 3 registry publications, 2 used the same source of data with overlapping time periods. For the purpose of analysis, the publication by Modlin et al. [7] was chosen in preference to Maggard et al. [11] because it covered a longer time period and had larger

Table 1 Studies identified for detailed analysis

Study no.	Year	Study	Type	Centric	Countries	*n*	Quality[a]
1	2013	Kim [12]	Case series	Mono	S. Korea	122	11
2	2012	Zhong [13]	Meta-analysis compares EMR vs. ESD from 4 articles [14–17]	Mono	China	246	15
3	2013	Son [18]	Case series	Mono	S. Korea	166	13
4	2012	Kim [19]	Retrospective comparing EMR vs. ESMR-L for tumors less than 10 mm	Mono	S. Korea	100	16
5	2012	Kim [20]	Retrospective comparing EMR vs. ESMR-L vs. ESD for tumors less than 10 mm	Mono	S. Korea	115	16
6	2012	Kasuga [21]	Case series	Mono	Japan	229	13
7	2010	KSC [22]	Case series	Mono	S. Korea	500	10
8	2010	Shields [23]	Multicenter international collaboration case series	Multi	IRCSG	202	16
9	2010	Yoon [24]	Case series	Mono	S. Korea	203	15
10	2009	Wang [25]	Case series	Mono	China	106	17
11	2008	Kim [26]	Case series	Mono	Korean	115	12
12	2007	Fen Yau-Li [27]	Multicenter retrospective case series	Mono	Taiwan	141	13
13	2004	Soga [28]	Nigata registry	Mono	Japan	849	14
14	2003	Modlin [7]	NCI and SEER registry, 1950–1999	Mono	United States	1,481	9
					Total	4,575	

KSC Korean Society of Coloproctology, *IRCSG* International Rectal Carcinoid Study Group (Ireland, United States, France, Germany, United Kingdom, Norway, Spain), *NCI* National Cancer Institute, *SEER* Surveillance, Epidemiology, and End Results (United States)

[a] From Downs and Black [9]; maximum value is 27

numbers. Therefore, there were 14 articles evaluated in this review. All 14 articles scored low to moderate on quality assessment, with a range of 9–17 out of a possible 27 [9] (Table 1; Appendix).

Demographics and tumor size

We excluded case series with fewer than 100 patients; the smallest series included had 100 patients and the largest was from registry data with 1,481 patients (Table 1) [7, 19]. The total number of patients from all studies was 4,575. The median age was 51.2 (range, 47.7–57.6) years for all studies, and there were more men (57 %) compared with women (43 %). The majority of tumors (79 %) were less than 10 mm in size compared with 16 % of those 10–20 mm in size and 5 % in those greater than 20 mm in size. Different studies quoted either mean or median; the mean tumor size in 8 studies was 6 mm (Table 2).

Staging

The data for staging were incomplete or not recorded in several of the studies [7, 13, 27, 28]. In fact, only 1,633 of 4,575 (36 %) had accurate staging recorded. Three studies analyzed a selected group of tumors up to the submucosa and are recorded in Table 3 but not analyzed [18–20]. A total of 1,260 of 1,418 (89 %) tumors were confined to the submucosa, 5 % invaded the muscularis propria, and 6 % were beyond the muscularis propria. A total of 104 of 1,637 (6 %) tumors had lymphovascular invasion, and 113 of 1,396 (8 %) had lymph node metastases. There was distant spread in 60 of 1,618 (4 %), but only 36 % of all the cases in this review were accurately staged.

Treatment

A total of 1,976 patients had their treatment accurately reported. A total of 1,540 (78 %) patients had endoscopic treatment; of these, 913 (46 %) had an unspecified endoscopic excision, 345 (17 %) endoscopic mucosal resection (EMR), 197 (10 %) endoscopic submucosal resection (ESD), and 85 (4 %) endoscopic submucosal resection with a ligation device (ESMR-L). A total of 187 (9 %) patients had a local surgical excision, and 249 (13 %) underwent radical excision (Table 4). The type of radical excision was poorly reported in most articles.

Table 2 Demographics and tumor size

Study	*n*	Sex, M/F	Age, years	Tumor size, mm				
				<10	10–20	>20	Mean	Median
Kim [12]	122	68/54	51	86	18	16	–	–
Zhong [13]	246	–	–	–	–	–	6.7	–
Son [18]	166	99/67	52	–	–	–	5.5	5
Kim [19]	100	66/34	50	91	9	–	6.1	–
Kim [20]	115	69/46	47.7	–	–	–	4.3	–
Kasuga [21]	229	131/98	56.3	214	22	3	7.1	–
KSC [22]	500	281/207	50	352	46	4	5.7	–
Shields [23]	202	112/90	55	84	59	32	–	10
Yoon [24]	203	121/82	51	177	20	6	–	6
Wang [25]	106	56/50	49	–	–	–	–	–
Kim [26]	115	62/50	53.8	96	10	9	7.2	–
Li [27]	141	100/41	57.6	102	25	9	–	–
Soga [28]	849	516/333	51.4	595	152	30	–	–
Modlin [7]	1,481	766/715	–					
Total (%) [range]	4,575	2,447/1,867 (57/43)	Mean 51.2 (47.7–57.6)	1,797 (79)	361 (16)	109 (5)	6	

Table 3 Depth of invasion, and local and distant spread

Study	*n*	Unselected series	Up to SM	Invades MP	Beyond MP	LVI	LN metastasis	Distant metastasis
Kim [12]	122	Y	103	4	13	12 (10)	17	3
Zhong [13][a]	246	N	–	–	–	–	–	–
Son [18]	166	Y	166	0	0	3 (1.8)	–	–
Kim [19][a]	100	N	100	0	0	0	–	–
Kim [20][a]	115	N	115	0	0	0	–	–
Kasuga [21]	229	Y	219	8	0	25 (11)	24	4
KSC [22]	500	Y	388	4	22	20 (4)	20	2
Shields [23]	202	Y	93	45	35	37 (18)	34	12
Yoon [24]	203	Y	190	7	6	7 (3)	9	9
Wang [25]	106	Y	0	0	0	–	–	11
Kim [26]	115	Y	101	3	11	–	–	11
Li [27]	141	Y	–	–	–	–	9	8
Soga [28]	849	Y	–	–	–	–	–	–
Modlin [7]	1,481	Y	–	–	–	–	–	–
Total (%)	4,575		1,260 (89/5/6)	71	87	104/1,637 (6.3)	113/1,396 (8.1)	60/1,618 (3.7)

SM submucosa, *MP* muscularis propria, *LVI* lymphovascular invasion, *LN* lymph node

[a] Excluded from analysis

Discussion

Rectal carcinoid tumors represent a challenging disease process. Although their incidence is increasing, most colorectal surgeons will see few cases in their career [29]. There is a misconception that rectal carcinoids behave in a benign fashion. Most will follow an indolent course, but there is a clear risk of local and distant metastases, with associated mortality. Although outcome for those with localized disease is excellent, there is a dramatic decline in outcomes for those with nodal disease and again for those with distant metastases. The 5-year survival was consistent with previously published literature at 86 % (range, 83–94 %) (Table 5).

The prevailing issue is how to manage a condition where the majority of patients will have a good prognosis but a certain proportion will need radical surgery to prevent distant spread. How do we stratify this subpopulation? The

Table 4 Ttreatments for rectal carcinoid [a]

Study	*n*	Unselected	Endoscopic treatment				Surgical	
			Not specified	EMR	ESD	ESMR-L	Local	Radical
Kim [12]	122	Y		67			28	25
Zhong [13]	246	N		137	106			
Son [18]	166	Y		53	47			
Kim [19]	100	N		55		45		
Kim [20]	115	N		33	44	40		
Kasuga [21]	229	Y	167				8	60
KSC [22]	500	Y	408				54	38
Shields [23]	202	Y	86				16	100
Yoon [24]	203	Y	159				28	10
Wang [25]	106	Y	–				70	36
Kim [26]	115	Y	93				11	5
Li [27]	141	Y	–	–	–	–	–	–
Soga [28]	849	Y	–	–	–	–	–	–
Modlin [7]	1,481	Y	–	–	–	–	–	–
Total (%)	4,575		913	345	197	85	187	249

EMR endoscopic mucosal resection, *ESD* endoscopic submucosal dissection, *ESMR-L* endoscopic submucosal resection with ligation device

[a] Total endoscopic, 1,540 (78 %); total local, 187 (9.4 %); and total radical, 249 (12.6 %)

most commonly used tool is the size of the tumor. Traditionally, 10 mm, 10–20 mm, and >20 mm are used to classify carcinoid tumors to predict the risk of spread and to guide management and treatment.

The risk factors for metastases include tumors greater than 10 mm, atypical surface, patient age greater than 60 years, and muscular, perineural, or lymphovascular invasion [12, 18, 21, 23, 24, 26, 27]. This has been corroborated by meta-analyses in 3 articles that demonstrated that tumor size greater than 10 mm [21, 23], pT stage [12], and lymphovascular invasion were independently associated with an increased risk of metastatic disease [21, 23]. Factors associated with survival were tumor size [27], muscular invasion [25, 27], and the presence of metastases [27].

By the rationale of these articles, it would appear that smaller tumors could be safely treated by local means, i.e., endoscopic or local surgical excision. However, most series demonstrate local and distant metastases even in tumors of this size. In two series from the East, lymph node positivity was 2–5 % and the metastasis rate between 2 and 5 % [21, 22]. Metastases in distant organs were found in less than 5 % of patients with tumors less than 10 mm [24].

There are no definitive guidelines, but previous studies have suggested that local excision is safe if the tumor fulfills the following criteria: less than 10 mm, no invasion of muscularis propria and no ulceration [30], or less than 10 mm with adequate endoscopic surveillance [31].

An international collaboration on prospectively collected data found that tumors greater than 10 mm with lymphovascular invasion were significantly associated with nodal disease, necessitating mesorectal excision; smaller tumors can safely be removed with a local excision [23]. The 2013 article published by Kim et al. [12] concluded that T1a tumors (<1 cm and confined to lamina propria/submucosa) could be safely treated with local excision with the proviso that tumors are assessed for complete resection, depth of invasion, size, and lymphovascular invasion. This allows for radical salvage surgery, if appropriate.

The term carcinoid means "carcinoma-like," and this adds to the confusion in their management. The term was necessary to distinguish carcinoids that usually behave in a more benign fashion compared to gastrointestinal carcinomas. Since then, carcinoids have been studied in greater detail, and new classification systems and histopathological markers have been identified. The World Health Organization (WHO) updated their classification system on carcinoids/neuroendocrine tumors [32], expanding the previous classification based on embryological origin, i.e., foregut, midgut, and hind gut. The 3 categories are neuroendocrine, neuroendocrine carcinoma, and adenoneuroendocrine carcinoma. These are further graded into 3 groups on the basis of rates of proliferation, mitotic indices, or proportion that stain positive for the Ki-67 antigen. The smaller tumors with no adverse features, which are suitable for local excision, likely represent the relatively benign carcinoids—that is, those that would be graded 1 or 2 on the WHO classification. Those small tumors with adverse features or larger aggressive tumors that can present with pain represent a higher grade of neuroendocrine tumor and thus require more aggressive treatment. In line with the WHO guidelines, neuroendocrine tumors should be graded as per other gastrointestinal tumors; the American Joint Committee on Cancer published a tumor, node, metastasis

Table 5 Follow-up and survival data

Study	*n*	Median follow-up, months	5-year survival, %				10-year survival, %	Recurrence	Metastasis in tumors < 10 mm, %
			Overall	Local	Node positive	Distant metastasis			
Kim [12]	122	34.7	88.4	100	51.4–80	0	–	12	–
Zhong [13]	246	12	–	–	–	–	–	4 (EMR only)	–
Son [18]	166	31	–	–	–	–	–	0	1.24
Kim [19]	100	–	–	–	–	–	–	–	
Kim [20]	115	13.1	–	–	–	–	–	0	0
Kasuga [21]	229	46.8	–	95.5	81.1	–	–	0 in localized	4.9
KSC [22]	500	–	–	–	–	–	–	–	1.99
Shields [23]	202	60	–	100	70	38	T1:100 N1:60	–	–
Yoon [24]	203	–	94	–	–	–	–	3 All > 15 mm	1.7
Wang [25]	106	67	87	93.6	Median survival 16 months		–	–	–
Kim [26]	115	19.3	–	–	–	–	–	0 in metastasis-free group	–
Li [27]	141	–	86.9	94.4	74.1	0	76.4	–	1
Soga [28]	849	–	88.1	98.9	65.1	–	–	–	13.2 [a]
Modlin [7]	1,481	60	83	88	44	28	–	–	–
Total	4,575		85.82	93.23	56.75	25.25			2.07 % [b]

EMR endoscopic mucosal resection

[a] Submucosal tumors only

[b] Excludes the Soga [28] study because it included only known submucosal tumors

(TNM) classification staging system for carcinoids in 2010 with the aim of providing a uniform means of reporting stage [8]. This will aid in future research and guidelines/protocols on management and treatment.

In terms of treatment modalities, endoscopic treatment was by far the most commonly used, in 78 % of all cases. This is probably partly the result of the improved quality of and increased access to endoscopic instruments. With advances in endoscopic diagnosis of disease have come new treatment modalities, such as EMR, ESD, and ESMR-L. There are limited data on the superiority of these endoscopic treatments, but a small meta-analysis and some articles published do favor ESMR-L and ESD over EMR with higher clear resection margins for small tumors (<10 mm) [13, 20]. The recent meta-analysis by Zhong et al. [13] concluded that tumors up to 16 mm operated with ESD had low recurrence rates and comparable complication rates with EMR. It has been previously published that tumors greater than 20 mm should have radical surgery [33], and currently the literature regarding endoscopic treatment of rectal carcinoids does not detail any attempts in tumors larger than this size [13, 18–20].

In this series, local surgical excision accounted for the treatment of 10 % of cases and radical surgery 12.6 %. The data, with regard to the type of radical surgery, were poorly reported in the articles from this review. There was large variability in rates of radical surgery from 4–50 % [12, 21–26]. It will be interesting to see whether there is a trend toward more radical surgery or whether the popularity and advancements in endoscopy will lead to radical surgery being reserved as a salvage operation where there is poor prognostic histopathology.

This article aimed to review the recent literature with regards to rectal carcinoids, detailing the management and treatment of over 4,000 patients. As with any publication of this nature, analyzing data from multiple international sources over a 20-year span will introduce error. There was wide variation in the data recorded from the various sources, so it was not possible to analyze all 4,575 patients for each parameter, and it was inappropriate to perform a meta-analysis. This systematic review has, however, corroborated previously published data in small and large series. The introduction of the TNM classification for rectal carcinoids will help homogenize the classification of tumors across the globe so we can compare like with like.

In light of the findings of this systematic review, we suggest that small rectal carcinoids up to 10 mm without adverse features can be treated with local/endoscopic excision. The treatment of carcinoids between 10 and 20 mm is still contentious, but those up to 16 mm without

adverse features are suitable for local/endoscopic excision followed by careful histopathological assessment. Patients with tumors greater than 16 mm or any size with adverse features should have radical surgery in view of the high lymph node metastasis rate in this subtype of tumor. Rectal carcinoid tumors need to be respected, and as such, they should be treated in a center that can provide a multidisciplinary approach with appropriate expertise in neuroendocrine tumors.

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