Rectal Carcinoids – A systematic review

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Rectal carcinoids are commonly thought of as relatively benign tumours but they have a potential for local and distant spread. This paper systematically reviews the optimal management of this challenging disease.

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Contributors: FM and AH performed the literature review and quality assessment of included papers. FM, AH, DC, HM, DW interpreted data. FM and AH wrote the manuscript. All authors reviewed and edited the final manuscript.

Keywords: Carcinoid; Rectal; Outcomes; Prognostic factors;

Category: Systematic Review

Abstract

Background

Rectal carcinoids are increasing in incidence worldwide. Frequently thought of as a relatively benign condition, there is limited data regarding optimal treatment strategies for both localised 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 Cochrane Libraries 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 less than 100 patients were excluded. Study endpoints included demographic information, tumour features, intervention and outcomes. All included papers were quality assessed.

Results:

Using the search parameters and exclusions as outlined above, a total of 14 papers were identified for detailed analysis. The quality of papers was low/moderate for all included scoring 9-17/ 27. The papers included 4575 patients diagnosed with a rectal carcinoid. Approximately 80% of tumours were less than 10mm, 15% 11 – 20mm and 5% >20mm. 8% presented with regional lymph node metastases and 4% presented with distant metastases. Tumour size >10mm, muscular and lymphovascular invasion are independently associated with increased risk of metastases. The 5-year survival was 93% in patients presenting with localised disease and 86% overall.

Conclusion:

Small tumours up to 10mm, without any adverse features can be managed with endoscopic or local excision. The management of carcinoids between 10 and 20mm is still contentious but those up to 16mm without adverse feature are suitable for local/endoscopic excision followed by careful histopathological assessment. Those >20mm or with adverse features require radical surgery with mesorectal clearance in suitable patients.

Background

Carcinoids were first described in 1867[1], defined histopathologically in 1888[2] and the phrase was coined in 1907 and means ‘carcinoma-like’[3]. Rectal carcinoid tumours continue to be an elusive condition with unclear guidelines or best evidence for treatment modalities and there is on-going debate regarding the nomenclature of neuroendocrine tumours[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 AJCC classification[8]. In a large US series, the 5-year survival rate in patients for all carcinoids was 67% and rectal carcinoids 88%. Clearly this is not a benign condition and, therefore, must be appropriately managed to reduce the risk of local and distant metastasis.

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

The aim of this paper was to systematically review the literature in order to present the most up to date information on this challenging condition.

Methods

Following PRISMA guidelines, an electronic literature search performed of Pubmed, Medline, Embase and Cochrane Libraries using the terms “Rectum” or “Rectal” AND “Carcinoid” and over a 20-year study period from January 1993 to May 2013. Non-English language studies, animal studies, and studies of less than 100 patients were excluded. Study endpoints included demographic information, tumour 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. Due to the heterogeneity of data, a meta-analysis could not be performed and, therefore, papers were analyzed qualitatively. DW arbitrated disputes on inclusion/exclusion of papers. Papers were assessed for quality using the Downs & Black

questionnaire for randomized and non-randomized trials by FM and AH and discussed to reach a consensus [9].

Results

A total of 425 papers were retrieved with the initial search and exclusion criteria. Following abstract review, 77 papers were identified. 15 of these were kept for more detailed review, the others were either not relevant (n = 47) or were review articles (n = 14). See PRISMA diagram Figure 1.

Figure 1: PRISMA diagram for literature review[10]

The 15 papers represented 1 meta-analysis, 11 case series (9 mono- and 2 multicentre) and 3 papers publishing registry data. The majority (n = 12) were from Asia with 2 from USA and 1 international collaboration (Europe/USA). There were no randomized control trials (RCTs). 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] as it covered a longer time period and had greater numbers. Therefore, there were 14 papers evaluated in this review. All 14 papers scored low to moderate on quality assessment with a range of 9 – 17 out of a possible 27 [9] (see Table 1 & appendix).

No	Year	Authors	Type	Centric	Countries	n =	Quality [9] Max 27
1	2013	Kim et al[12]	Case series	mono	S. Korea	122	11
2	2012	Zhong et al[13]	Meta-analysis compares EMR vs ESD from 4 papers[14-17]	mono	China	246	15
3	2013	Son et al[18]	Case series	mono	S. Korea	166	13
4	2012	HH Kim et al[19]	Retrospective comparing EMR vs ESMR-L for tumours less than 10mm	mono	S. Korea	100	16
5	2012	KM kim et al[20]	Retrospective comparing EMR vs ESMR-L vs ESD for tumours less than 10mm	mono	S. Korea	115	16
6	2012	Kasuga et al[21]	Case series	mono	Japan	229	13
7	2010	KSC[22]	Case series	mono	S. Korea	500	10
8	2010	Shields et al[23]	Multicentre international collaboration case series	multi	IRCSG	202	16
9	2010	Yoon et al[24]	Case series	mono	S. Korea	203	15
10	2009	Wang et al[25]	Case series	mono	China	106	17
11	2008	BNKim et al[26]	Case series	mono	Korean	115	12
12	2007	Fen Yau-Li et al[27]	Multicentre retrospective case series	mono	Taiwan	141	13
13	2004	Soga et al[28]	Nigata registry	mono	Japan	849	14
14	2003	Modlin et al[7]	NCI & SEER registry 1950 - 1999	mono	USA	1481	9
					TOTAL	4575	

Table 1: 14 papers identified for detailed analysis. KSC: Korean Society of Coloproctology, IRCSG: International Rectal Carcinoid Study Group (Ireland, USA, France, Germany, United Kingdom, Norway, Spain), NCI: National Cancer Institute & SEER: Surveillance, epidemiology and end results (USA).

Demographics and tumour size

This paper excluded case series with less than 100 patients; the smallest series included had 100 patients and the largest was from registry data with 1481 patients (see table 1)[7,19]. The total number of patients from all studies was 4575. The median age was 51.2 (47.7 – 57.6) years for all studies and there were more males with 57% compared with 43% females. The majority of tumours (79%) were less than 10mm in size compared with 16% in those 10 – 20mm and 5% in those greater than 20mm. Different studies quoted either mean or median; the mean tumour size, in 8 studies, was 6mm. (See table 2)

				Tumour size (mm)				
Paper	N =	Sex (M/F)	Age	<10	10-20	>20	Mean	Median
Kim et al[12]	122	68/54	51	86	18	16	-	-
Zhong et al[13]	246	-	-	-	-	-	6.7	-
Son et al[18]	166	99/67	52	-	-	-	5.5	5
HH Kim et al[19]	100	66/34	50	91	9	-	6.1	-
KM kim et al[20]	115	69/46	47.7	-	-	-	4.3	-
Kasuga et al[21]	229	131/98	56.3	214	22	3	7.1	-
KSC[22]	500	281/207	50	352	46	4	5.7	-
Shields et al[23]	202	112/90	55	84	59	32	-	10
Yoon et al[24]	203	121/82	51	177	20	6	-	6
Wang et al[25]	106	56/50	49	-	-	-	-	-
BNKim et al[26]	115	62/50	53.8	96	10	9	7.2	-
Fen Yau-Li et al[27]	141	100/41	57.6	102	25	9	-	-
Soga et al[28]	849	516/333	51.4	595	152	30	-	-
Modlin et al[7]	1481	766/715	-					
TOTAL (%) [range]	4575	2447/1867 (57/43)	Mean: 51.2 [47.7-57.6]	1797 (79)	361 (16)	109 (5)	6	

Table 2: Demographics and tumour size.

Staging (See Table 3)

The data for staging was incomplete or not recorded in several of the studies [7,13,27,28]. In fact, only 1633/4575 (36%) had accurate staging recorded. 3 studies analysed a selected group of tumours up to the submucosa and are recorded in Table 3 but are not analysed [18-20]. 1260/1418 (89%) tumours were confined to the submucosa, 5% invaded the muscularis propria and 6% were beyond the muscularis propria. 104/1637 (6%) tumours had lymphovascular invasion and 113/1396 (8%) had lymph node metastases. There was distant spread in 60/1618 (4%) but only 36% of all the cases in this review were accurately staged.

Paper	N =	Unselected Series	Up to SM	Invades MP	Beyond MP	LVI	LN mets	Distant mets
Kim et al[12]	122	Y	103	4	13	12 (10)	17	3
Zhong et al[13]	<i>246</i>	<i>N</i>	-	-	-	-	-	-
Son et al[18]	166	Y	166	0	0	3 (1.8)	-	-
HH Kim et al[19]	<i>100</i>	<i>N</i>	<i>100</i>	<i>0</i>	<i>0</i>	<i>0</i>	-	-
KM kim et al[20]	<i>115</i>	<i>N</i>	<i>115</i>	<i>0</i>	<i>0</i>	<i>0</i>	-	-
Kasuga et al[21]	229	Y	219	8	0	25 (11)	24	4
KSC[22]	500	Y	388	4	22	20 (4)	20	2
Shields et al[23]	202	Y	93	45	35	37 (18)	34	12
Yoon et al[24]	203	Y	190	7	6	7 (3)	9	9
Wang et al[25]	106	Y	0	0	0	-	-	11
BNKim et al[26]	115	Y	101	3	11	-	-	11
Fen Yau-Li et al[27]	141	Y	-	-	-	-	9	8
Soga et al[28]	849	Y	-	-	-	-	-	-
Modlin et al[7]	1481	Y	-	-	-	-	-	-
TOTAL	4575		1260	71	87	104/1637	113/1396	60/1618
(%)			(89/5/6)			(6.3)	(8.1)	(3.7)

Table 3: Depth of invasion, local and distant spread (SM – submucosa, MP – muscularis propria, LVI – lymphovascular invasion, LN – lymph nodes). Selected series excluded from analysis (italics).

Treatment (See table 4)

A total of 1976 patients had their treatment accurately reported. 1540 (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). 187 (9%) patients had a local surgical excision and 249 (13%) underwent radical excision. The type of radical excision was poorly reported in most papers.

Paper	N =	Unselected	Endoscopic Management				Surgical	
			Not Spec.	EMR	ESD	ESMR-L	Local	Radical
Kim et al[12]	122	Y		67			28	25
Zhong et al[13]	246	N		137	106			
Son et al[18]	166	Y		53	47			
HH Kim et al[19]	100	N		55		45		
KM kim et al[20]	115	N		33	44	40		
Kasuga et al[21]	229	Y	167				8	60
KSC[22]	500	Y	408				54	38
Shields et al[23]	202	Y	86				16	100
Yoon et al[24]	203	Y	159				28	10
Wang et al[25]	106	Y	-				70	36
BNKim et al[26]	115	Y	93				11	5
Fen Yau-Li et al[27]	141	Y	-	-	-	-	-	-
Soga et al[28]	849	Y	-	-	-	-	-	-
Modlin et al[7]	1481	Y	-	-	-	-	-	-
TOTAL (%)	4575		913	345	197	85	187	249
TOTAL endoscopic/local/radical: 1540/ 187/249 (78/9.4/12.6)								

Table 4: treatments for rectal carcinoid (EMR – endoscopic mucosal resection, ESD – endoscopic submucosal dissection, ESMR-L – endoscopic submucosal resection with ligation device).

Paper	n =	Med F/U (mths)	5 Yr Survival (%)				10 Yr Survival (%)	Recurrence	% Mets in tumours <10mm
			Overall	Local	Node+	Distant Mets			
Kim et al[12]	122	34.7	88.4	100	51.4-80	0	-	12	-
Zhong et al[13]	246	12	-	-	-	-	-	4 (EMR only)	-
Son et al[18]	166	31	-	-	-	-	-	0	1.24
HH Kim et al[19]	100	-	-	-	-	-	-	-	
KM kim et al[20]	115	13.1	-	-	-	-	-	0	0
Kasuga et al[21]	229	46.8	-	95.5	81.1	-	-	0 in localized	4.9
KSC[22]	500	-	-	-	-	-	-	-	1.99
Shields et al[23]	202	60	-	100	70	38	<i>TI:100 NI:60</i>	-	-
Yoon et al[24]	203	-	94	-	-	-	-	3 All>15mm	1.7
Wang et al[25]	106	67	87	93.6	Med survival 16 mths		-	-	-
BNKim et al[26]	115	19.3	-	-	-	-	-	0 in met free group	-
Fen Yau-Li et al[27]	141	-	86.9	94.4	74.1	0	76.4	-	1
Soga et al[28]	849	-	88.1	98.9	65.1	-	-	-	13.2*
Modlin et al[7]	1481	60	83	88	44	28	-	-	-
TOTAL	4575		85.82	93.23	56.75	25.25			2.07%**

Table 5: Follow up and survival data

(*Submucosal tumours only, **Excludes Soga et al paper as this study includes only known submucosal tumours)

Discussion

Rectal carcinoid tumours 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 metastasis, with an associated mortality. Although outcome for those with localised 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% (83 – 94%). (Table 5)

The prevailing issue is how to manage a condition where the majority will have a good prognosis but a certain proportion will need radical surgery to prevent distant spread. How do we stratify this sub-population? The most commonly used tool is the size of the tumour. Traditionally, 10mm, 10-20mm and greater than 20mm are used to classify carcinoid tumours with an attempt and to predict the risk of spread and guide management.

The risk factors for metastases include tumours greater than 10mm, atypical surface age greater than 60 and muscular, perineural or lymphovascular invasion [12,18,21,23,24,26,27]. This has been corroborated by meta-analyses in 3 papers that demonstrated tumour size greater than 10mm [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 tumour size [27], muscular invasion [25,27] and the presence of metastases [27].

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

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

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

The term carcinoid means 'carcinoid 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 Organisation (WHO) updated their classification system on carcinoids/ neuroendocrine tumours [32] expanding the previous classification based on embryological origin i.e. foregut, midgut and hindgut. The 3 categories are neuroendocrine (NET), neuroendocrine carcinoma (NEC) and adenoneuroendocrine carcinoma (MANEC). These are further graded into 3 groups based on rates of proliferation, mitotic indices or proportion that stain positive for the Ki-67 antigen. The smaller tumours with no adverse features, that are suitable for local excision, likely represent the relatively 'benign' carcinoids, i.e. those that would be graded 1-2 on the WHO classification. Those small tumours with adverse features or larger aggressive tumours that can present with pain represent a higher grade of neuroendocrine tumour and thus require more aggressive treatment. In line with the WHO guidelines neuroendocrine tumours should be graded as per other gastrointestinal tumours and The American Joint Committee on Cancer published a TNM classification 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.

In terms of treatment modalities, endoscopic treatment was by far the most commonly employed in 78% of all cases. This is probably partly due to 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 is limited data on the superiority of these endoscopic treatments but a small meta-analysis and some papers published do favour ESMR-L and ESD over EMR with higher clear resection margins for small tumours (<10mm) [13,20]. The recent meta-analysis by Zhong et al concluded that tumours up to 16mm operated with ESD had low recurrence rates and comparable complication rates with EMR [13]. It has been previously published that tumours greater than 20mm should have radical surgery [33] and currently the literature regarding endoscopic management of rectal carcinoids does not detail any attempts in tumours greater 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 regards to the type of radical surgery, was poorly reported in the papers from this review. There was large variability in rates of radical surgery from 4 – 50% [12,21-26]. It will be interesting to see if there is a trend

towards 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 paper aimed to review the recent literature with regards to rectal carcinoids, detailing the management of over 4000 patients. As with any publication of this nature, analysing 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 analyse all 4575 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 to homogenise the classification of tumours across the globe so that we can compare like with like.

In light of the findings of this systematic review, we suggest that small rectal carcinoids up to 10mm without adverse features can be managed with local/endoscopic excision. The management of carcinoids between 10 and 20mm is still contentious but those up to 16mm without adverse feature are suitable for local/endoscopic excision followed by careful histopathological assessment. Those greater than 16mm or any size with adverse features should have radical surgery in view of the high lymph node metastasis rate in this sub-type of tumour. Rectal carcinoid tumours need to be respected and, as such, should be managed in a centre that can provide a multi-disciplinary approach with appropriate expertise in neuroendocrine tumours.

Disclosures: Mr McDermott, Miss Heeney, Dr Courtney, Miss Mohan and Professor Winter have no conflicts of interest and no financial ties to disclose.

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