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Review Article

Appendiceal carcinoid tumours: indications for right hemicolectomy and appendectomy

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ABSTRACT

This is a review of the current best evidence pertaining to the surgical management of appendiceal carcinoid tumours and outlines a set of recommendations for right hemi colectomy and appendectomy in patients with histologically confirmed appendiceal carcinoid tumour. The management of appendiceal carcinoids is complex and several factors have been shown to influence prognosis. Surgical management is the mainstay of treatment with appendectomy and right hemi-colectomy being the surgical approaches of choice. There is still much debate as to the indications for appendectomy or right hemicolectomy. From our search of the literature eight studies were included for review and one set of guidelines. All studies included were retrospective cohort studies. There were no Cochrane reviews or systematic reviews pertaining to the management of appendiceal carcinoid tumours. There is conflicting evidence as to the management of tumours greater than 2cm. Involvement of the base of the appendix and mesoppendix involvement while not supported by the literature are supported by consensus expert opinion in two sets of guidelines as an indication for right hemicolectomy.

Keywords: Appendiceal carcinoid tumour, Neuroendocrine

INTRODUCTION

Neuroendocrine tumours are a heterogonous group of tumours with a wide variety of clinical presentations. They arise from enterochromaffin cells located in neuroendocrine tissue throughout the body. Neuroendocrine tissue is derived from cells which migrated from the neural crest to the gastrointestinal endoderm. There are many types of NETs, phaeochromocytoma's, small cell carcinoma's of the lung and merkel cell carcinoma's are just some examples. The focus of this review however lies with gastoenteropancreatic neuroendocrine tumours (GEP-NETs), more specifically appendiceal carcinoid tumours (ACTs). GEP-NETs can be described as either functioning (hormone secreting) or non-functioning.[1]

They may also be described in terms of the embryonic origin of their anatomical location, namely foregut, midgut and hindgut.The classification and terminology of GEP-NETs is not straightforward and has evolved over time. Currently neuroendocrine tumours of the gastroenteropancreatic system can be defined by their grade and stage.

The 2010 World Health Organisation classification of neoplasms of the digestive tract described neuroendocrine tumours based on their grade which was determined by the tumour's mitotic index and Ki-67 index.[2] Ki-67 is a marker of cellular proliferation. Classification describes two broad classes of digestive NETs:

- Well differentiated: Low- intermediate grade, having a low mitotic count and/or low Ki-67.
- Poorly differentiated: High grade, having a high mitotic count and/or high Ki-67.

Carcinoid tumours are what this classification describes as 'well differentiated' gastroenteropancreatic neuroendocrine tumours. Well differentiated tumours typically run an indolent course and poorly differentiated tumours run a more aggressive course being more likely to metastasize. A 2015 study however showed that there is a subset of tumours which appear histologically well differentiated with a low mitotic count however have a high Ki-67 index and are therefore classified as poorly differentiated and have a worse median survival than other well differentiated tumours.[3] Evidently it is not a clear cut dichotomy between well and poorly differentiated GEP-NETs. The WHO staging of gastroenteropancreatic NETs is based on a tumour, node, and metastases model devised by the European Neuroendocrine Tumour Society.[2,3] This staging system has been show to predict clinical outcome.[4-6] Tumours of the appendix are an uncommon finding, being present in just 0.9% of appendectomy specimens. ACTs are a common cause of appendiceal malignancy accounting for between 45% and 56% of appendiceal tumours.[7,8] They have a reported annual incidence of 0.15/100,000.[7,24] Most ACTs originate in the distal third of the appendix. A significant majority (55-95%) present as appendicitis due to obstruction at the proximal end of the appendix.[9,10] Presentation with carcinoid syndrome is rare.[9] They most commonly occur in the 5th decade of life but can occur at any age and are more common in women.[11] The relative frequency of appendiceal carcinoid tumours compared to all appendiceal malignancies has fallen over time.[11] Appendiceal carcinoids are no longer the most common site of ACTs. At the time of diagnosis only 4.5- 12% of carcinoids of the appendix will have metastasized.[11] There does not appear to be a difference in prevalence between Caucasians and African Americans however they do appear to be less common in Japanese people.[24]

The management of appendiceal carcinoids is complex and several factors have been shown to influence prognosis such as tumour size, grade, depth of invasion, vascular involvement, the presence of metastases and lymph node involvement. Surgical management is the mainstay of treatment with appendectomy and right hemi-colectomy being the surgical approaches of choice. There is still much debate as to the indications for appendectomy or right hemicolectomy. This article intends to review the most relevant evidence to date and make a set of recommendations pertaining to the surgical management of ACTs.

Objectives

- To review the current evidence regarding the management of ACTs.
- To recommend a set of indications for right hemi colectomy and appendectomy in patients with histologically confirmed appendiceal carcinoid tumour.

METHODS

Criteria for considering studies for this review

Types of Studies: We included published studies and studies in progress if preliminary results were available. We also included non-English studies in the review. There was no restriction on publication status or year of publication. We excluded studies which 1) examined carcinoid tumours of origin other than the appendix, 2) patients had carcinoid syndrome 3) had a cohort of less than 30 patients 4) were limited to patients with Goblet Cell Carcinoid Tumours 5) were limited to children.

Types of Participants: Adults with histologically confirmed carcinoid tumours originating in the appendix.

Types of Interventions: Right hemi colectomy

Comparisons: Appendecotmy.

Outcomes measured: 5 year survival rates, progression to metastatic disease, treatment related morbidity, recurrence rates.

Search methods for identification of studies

Electronic Searches: Medline, Pubmed, Cochrane

Searching other resources: We searched the reference lists of relevant articles retrieved by electronic searches for additional citations.

Table 1: Search terms used.

Search	Database, N=number of relevant studies
Small bowel and Carcinoid* and management or treatment	Medline N= 147 (6) PUBMED N= 227 (8) Cochrane N=0
Small bowel and Neuroendocrine Tumour and management or treatment	Medline N= 5(1) PUBMED N = 9(0) Cochrane N=0
Append* and Carcinoid* and management or treatment	Medline N= 313 (31) PUBMED N = 590 (33) Cochrane N=0
Append* and Neuroendocrine Tumour and management or treatment	Medline N= 5 (1) PUBMED N =11 (2) Cochrane N=0

Table 2: Description of included studies.

First author and year of publication	Study period	Country/ language	Ethnicity	Sample number lost to follow up	Mean age (range)	Gender M/F	Mean tumour size (cm)	Type of study	Objective	Outcome
Sandor et al [13]	1950-1991	USA/English	American	1570	42.2	Ratio 0.47/1	Not given.	Retrospective cohort study using the SEER database	To analyse the epidemiology of ACTs and compare it to other appendiceal tumours	Incidence 5 year survival Stage distribution
Nussbaum et al [14]	1998-2011	USA/English	American	916	49(39-60)	433/483	1.5 (1.1-1.8)	Retrospective cohort study of ACT 1-2cm using National Cancer Database	To compare long-term outcomes for patients treated by appendectomy vs. RHC	1 and 5 year survival Positive margin rates
Landry et al [15]	1977-2004	USA/ English	American	900	47.1(9-89)	348/552	2.4 (0.1-11.5)	Retrospective cohort study using SEER national database	To clinic pathologic features in patients with ACTs that affect prognosis and validate a newly created TNM staging system incorporating these parameters	TNM based survival rates incorporating tumour size, lymph node involvement, distant metastases.
Moertel et al [16]	1930-1981	USA/English	American	150 122 of which were followed for median of 26 years.	40 (6-76)	Predominantly female (cohort 1930-1966 39/97)	104 <1cm 23 1-2cm 14 2-3cm 9 >3cm	Retrospective Cohort Study	To determine if appendectomy was adequate treatment for tumours <2.0 cm in diameter, regardless of location or extent of invasion	Recurrence
Mullen et al [17]	1988-2003	USA/English	American	89	-	-	-	Retrospective cohort analysis using SEER database	To determine clinic pathological features determining lymph node involvement and survival	Lymph node involvement survival
Bamboat et al[18]	1980-2005	USA/ English	American	48 Mean 18 years follow up. 15 patients	41 (11-86)	14/34	58% <1cm 31%: 1.1-2cm 5% >2cm	Single centre retrospective cohort study	To assess the relationship between survival, tumour size, and the role of RHC vs appendectomy alone	Survival Recurrence Post-operative complications
Shapiro R et al[19]	1992-2007	Israel/ English	Israeli	44 Median 7 years follow up. 6 patients	29 (10-75)	13/31	0.7(0.2-1.6)	Single centre retrospective cohort Study	To report the clinical and pathologic characteristics of carcinoids found with long-term follow-up evaluation	Recurrence Post-Operative Complications
Butte et al[20]	1980-2007	Chile/Spanish	Chilean	40 Mean follow up 81.2 months.	37 (19-55)	15/25	28 ACT <1cm 6 ACT 1-2cm 3 ACT >2cm	Retrospective cohort study	To analyse the clinical and pathological features, the surgical treatment and long-term survival patients with ACT	5 year survival
Murray et al [21]	1994-2010	USA/English	American	31	36 (13-76)	4/27	0.5(0.1-1)	Retrospective cohort study of ACTs less than 1cm	To review the postresection surveillance regimens of ACT≤1 cm used to determine the appropriate follow-up for this patient population.	Recurrence 5 year Survival

Table 3: Critical appraisal of selected studies.

First Author and year of publication	Did the study address a clearly focused issue?	Was the cohort recruited in an acceptable way?	Was the outcome accurately measured to minimise bias?	Have the authors identified all important confounding factors?	Have they taken account of the confounding factors in the design and/or analysis?	Was the follow up of subjects long enough	Was the follow up of subjects complete enough	Can the results be applied to the local population?	Do the results of this study fit with other available evidence?	CASP score
Sandor et al [13]	✓	✓	✓	✓	✓	X	X	X	✓	6/9
Nussbaum et al[14]	✓	✓	✓	✓	✓	X	X	X	✓	6/9
Landry et al [15]	✓	✓	X	✓	X	X	X	X	✓	4/9
Moertel et al [16]	✓	✓	✓	✓	✓	✓	✓	✓	✓	9/9
Mullen et al [17]	✓	✓	✓	✓	✓	X	X	X	X	5/9
Bamboat et al[18]	✓	✓	X	X	X	X	X	✓	✓	4/9
Shapiro R et al[19]	✓	✓	✓	✓	✓	X	✓	X	✓	8/9
Butte et al [20]	✓	✓	✓	X	X	X	✓	✓	✓	6/9
Murray et al [21]	✓	✓	✓	✓	✓	X	X	✓	✓	7/9

Performed by first named author. Critical appraisal tools used: critical appraisal skills tool.[12]

DISCUSSION

Eight studies were included for review and one set of guidelines. All studies included were retrospective cohort studies. There were no Cochrane reviews or systematic reviews pertaining to the management of appendiceal carcinoid tumours. There were no prospective studies which met the inclusion criteria for this review. Three large studies were conducted in the United States with the use of the surveillance epidemiology and end Results database and the national cancer database.[13-15] All other studies were small single centre studies. Six out of the eight studies were based in the United States and seven out of eight studies were in English. The average age across studies was similar with the exception of a study by Shapiro et al which had a notably younger mean sample age.[18] A female predominance was observed in all studies. Tumours less than 1cm occurred more than tumours 1-2cm in all studies. The number of patients with tumours greater than 2cm was small. Interventions in all studies were either right hemicolectomy or appendectomy. Outcomes measured in all studies included tumour site, size, age at diagnosis and presence of metastatic disease. Most also measured 5 year survival and recurrence rates. Follow up of patients varied in duration and methodology. Duration of follow up ranged from 5 to 26 years. Methods of follow up were contact with GP, telephone contact with patient or family member, clinical notes, and imaging and procedure reports. A common limitation of most studies was recognition of loss of patients to follow up (range 6-15) and too short a follow up time. Two sets of guidelines are included in the review. The North American neuroendocrine tumour society (NANETS) published a set of guidelines for the management of small bowel NETs in 2010.[23] These guidelines covered the management of appendiceal carcinoid tumours as well as other NETS of the small bowel.

The guidelines were formulated by a panel of 38 specialists across a broad range of different specialities. There was no information given as to the guideline development process, potential conflicts of interest, potential sources of bias, sources of funding or as to the strength of evidence behind their recommendations. Nevertheless they are important to consider give the relative paucity of evidence in this area. The guidelines focused largely on data from the surveillance epidemiology and end results (SEER) database. The European neuroendocrine tumour society provides similar recommendations. They acknowledge the lack of large prospective studies in this area to base recommendations on.

Appendiceal carcinoid tumours have a good prognosis overall. The 5 year survival rate of 1570 patients from the SEER database was 85.7%. Prognosis was best for patients with localised disease and worse for regional spread and distant metastases with 5 year survival rates of 94%, 84.6% and 33.7% respectively.[13]

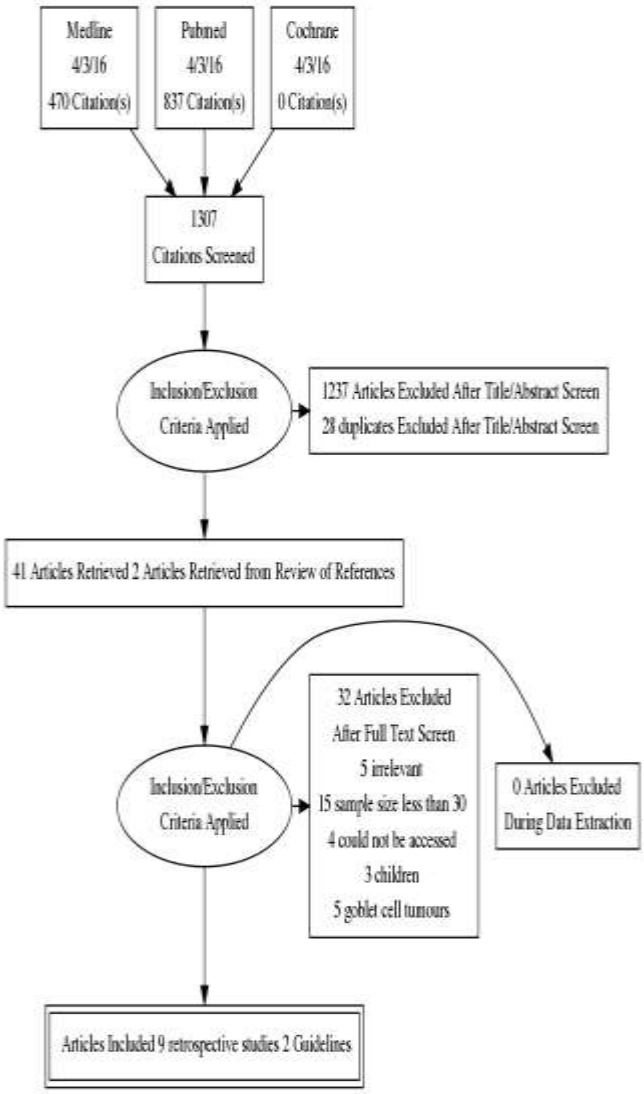

Figure 1: Description of study selection process using prisma flow diagram.

Tumour size

A retrospective review of 900 appendiceal carcinoid tumours from the SEER database showed a statistically significant improvement in overall survival for tumours less than 2 cm compared to tumours 2-3 cm, 3-4 cm and 5 cm or larger. Overall survival for tumours greater than 2 cm but less than 3cm showed no statistically significant difference compared to tumours 3-4 cm or 4-5 cm but there was a statistically significant difference improvement in survival compared to tumours greater than 5 cm. ACT size is evidently an important prognostic factor. Patients who underwent surgery had statistically significant improved outcomes compared to those than those who did not. The study however could not conclude when surgery should be performed or which surgical intervention should be performed due to a lack of information recorded in the SEER database.[14]

A 2015 study by Nussbaum et al involved 916 appendiceal carcinoid tumours of which 385 were managed by segmental bowel resection and 531 were managed by right hemicolectomy. Right hemicolectomy appeared to confer no prognostic benefit to patients with tumours 1-2 cm compared to segmental bowel resection. (5 year survival 88.7% vs. 87.4%) and resulted in an increased length of hospital admission. A potential bias of this study recognised by the authors was that patients undergoing what the National cancer database termed "segmental resection" may have also undergone lymph node resection which would not be considered a typical feature of an appendectomy. 43% of patients undergoing segmental resection had lymph node resections however there was no increased rate of positive lymph node status compared to the right hemicolectomy group and the authors concluded a treatment bias did not exist.[15]

A study of 44 patients with ACTs less than 2 cm carried out at single tertiary referral centre in Israel demonstrated the efficacy of appendectomy for tumours less than 2 cm.[15] Of the 44 patients, the authors were able to follow up 29. In a mean follow up period of 7 years (2.5-17.3) there was no evidence of recurrence for the 27 patients who underwent appendectomy. 2 patients underwent right hemi-colectomy for lymphovascular involvement and lymph node involvement respectively. There was no evidence of recurrence in their follow up period of 40 and 33 months respectively.

An initial 1967 study by Moertel et al supported the view that right hemi colectomy should be performed only for carcinoids greater than 2 cm.[23] However the authors acknowledged they had limited follow up of their patients with only 47 patients out of 108 being followed up for 15 years or longer. In light of this Moertel et al repeated their study in 1987. It is important to note that none of the patients with tumours less than 1cm or 1-2cm had metastatic disease at presentation, while 7 out of 23 patients with ACTs greater or equal to 2cm at presentation had metastatic disease. They had a cohort of 122 patients who underwent appendectomy for tumours less than 2cm. After 25 years of follow up all were disease free. Their study also showed that younger patients were more likely to have larger tumours and metastatic disease and elderly patients were more likely to have smaller clinically benign tumours. Recurrence of small bowel carcinoids occurs late and the authors felt appendiceal carcinoids were unlikely to recur in the lifetime of elderly patients with clinically benign small tumours. Based on their findings they advised right hemicolectomy only for younger patients with tumours greater than 2 cm. A 2011 study by Murray et al of 31 1-2 cm appendiceal carcinoid tumours the majority of which were managed by appendectomy showed no recurrence at 5 years. None of these ACTs had nodal involvement or distal metastases at presentation.[21]

A 2006 study by Bamboat et al concluded that right hemi colectomy was not necessary in appendiceal tumours greater than 2 cm.[18] This study had several limitations most notably a small cohort size with only 4 patient undergoing right hemi colectomy.

The ENETs and NANETs guidelines advocate that right hemicolectomy should be performed for all tumours greater than 2cm.[23,24]

Lymph node involvement

The presence of lymph node involvement has been shown to be a statistically significant predictor of survival.[13] There is also evidence to suggest that nodal metastases may occur in tumours 1-2 cm in size from an analyses of a subset of 34 patients from the Surveillance Epidemiology and End Results database with 1-2 cm carcinoids of which 16 had nodal involvement.[17] This would suggest it may be an indication for RHC, however further larger studies would be needed to validate this. ENETs and NANETs guidelines advise that right hemicolectomy should be performed in the presence of lymovascular invasion.[23,24] Mullen et al showed tumour size was a significant predictor of lymph node involvement.[17]

Their study examined whether lymph node involvement had a prognostic impact. They showed that for tumours less than 1 cm, 1-2 cm and greater than or equal to 2 cm that the presence of lymph node involvement did have a negative effective on prognosis but it was not statistically significant.

Mesoappendix involvement

Moertel et al in their initial 1967 study found that invasion of the mesoappendix meant likely nodal metastases.[22] However Sandor et al found that depth of tumour invasion was not a prognostic factor in their retrospective analyses of 1570 ACTs.[13]

The ENETs and NANETs guidelines included mesoappendix involvement as an indication for right hemicolectomy.

Tumour localisation within the appendix

None of the included studies supported the view that localisation of the tumour within the appendix affected prognosis. The ENETs guidelines advised right hemicolectomy for tumours involving the base of the appendix due to a hypothetical risk of incomplete resection subsequent opportunity for progression to metastatic disease.[24] The NANETs guidelines were also of this view.[23]

Summary

Tumour size is a significant prognostic factor. Based on the above studies it would appear tumours less than 2cm may be managed by appendectomy, tumours greater than 2cm in elderly patients may also be managed by appendectomy, tumours greater than 2cm in young patients with minimal comorbidities may be managed with right hemicolectomy. Lymph node involvement also appears to a valid indication for right hemicolectomy. Involvement of the base of the appendix and mesoppendix involvement while not supported by the literature are supported by consensus expert opinion in two sets of guidelines.

CONCLUSION

The evidence base for the management of appendiceal neuroendocrine tumours is complex and evolving. Large prospective studies are needed. There is good evidence showing appendiceal tumours greater than 2 cm are more aggressive than those less than 2 cm. There is conflicting evidence as to the management of tumours greater than 2 cm. Tumours less than 1 cm have been shown to be best managed by simple appendectomy. Tumours between 1-2 cm are best managed by appendectomy with certain exceptions e.g. nodal metastases, mesoappendix involvement. Younger patients with large tumours (greater than 2cm) should undergo right hemi-colectomy providing there is minimal comorbidity.

Recommendations

Right hemi colectomy is indicated if

- Lymph node metastases are present
- Mesoappendix is involved
- Base of the appendix is involved
- Younger patients with tumours greater than 2cm.

Right hemi colectomy is not indicated in

- Elderly patients with tumours greater than 2cm who have significant co-morbidities.

Appendectomy is indicated in

- Tumours less than 1cm with no evidence of mesoappendix, lymphovascular involvement not located at the base of the appendix.
- Tumours 1-2cm in size with no evidence of mesoappendix or lymphovascular involvement and not located at the base of the appendix.

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