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CLINICAL STUDY

# Natural behaviour and surgical treatment of appendiceal carcinoids: an analysis of 2,376 consecutive emergency appendectomies

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**Abstract:** *Objective:* Carcinoid tumor of appendix is a rare condition. Its rarity may give rise to variances in its management. We aimed to demonstrate the occurrence and form of presentation of carcinoid tumor of appendix, as well as variations in its treatment.
*Methods:* All appendicectomies that took place between 2000 and 2008 were considered for study.
*Results:* A total of 2,376 appendicectomies were performed during this period while carcinoid tumours were diagnosed in 27 patients (1.13 %). The mean age of patients with carcinoid tumor (26.7 years) was almost the same as that of patients with non-carcinoid pathology (28.1 years). The incidence of male patients was higher than that of females amongst the carcinoid tumor group (female/male ratio: 1/4). None of the carcinoid tumors were identified at operation. One patient (3.7 %) required right hemicolectomy. This patient was followed-up in an inconsistent manner.
*Conclusions:* Carcinoid tumour of the appendix remains an incidental diagnosis. Patients with carcinoid were significantly younger than those with non-carcinoid conditions in the study. Re-operation rate was low. The interval to definitive surgery was very short and only one patient was followed up. No consideration as to whether the surgery was complete or not was done in the study *(Tab. 1, Fig. 1, Ref. 29)*. Full Text in free PDF *www.bmj.sk.*
Key words: carcinoid tumour, appendiceal neoplasm, disease management.

Appendectomy is a most common emergency operation in the general surgical field. The most frequent underlying pathology is acute appendicitis however other pathologies are involved at times. Carcinoid as a neuroendocrine tumor is one example of such pathologies that need further evaluation and treatment. The recent years have seen the incidence of carcinoid tumor of appendix grow notably (1, 2, 3, 4). The awareness of detailed behavior of appendiceal neuroendocrine tumors and their biologic nature could lead to treatment options of adequate validity. There is a rare prospective randomized study to endorse the treatment data (level 1 evidence) available. It is thought that such study is not likely to take place in the future for methodological reasons (1, 2, 3, 5, 6).

Neuroendocrine tumors have a lot of complex clinical problems notably adding morbidity and hospital costs. There has been lack of research about the issue due to the rare incidence of these tumors. The rarity of occurrence and lack of research as well as the guidelines on the available treatment give space to variations in the management of carcinoid tumor of appendix. Little is known about the variations of appediceal carcinoid tumors (3–14). We aimed to assess the form of presentation and natural behavior of carcinoid tumors of appendix as well as variations in their management.

## Patients and method

The study period lasted from 2000 to 2008 in the biggest training hospital of the Army. The appendectomies carried out during this period were included in the study. Irrespective of their site, all carcinoid tumors from the above period were also analyzed retrospectively. The data were obtained from the databases of surgical and pathological clinics. The relevant cases were searched for gathering information on age, sex, preoperative diagnosis and foreseen diagnosis, reoperation and follow up. Statistical analysis was performed by using SPSS 15.0 version (SPSS®Inc, Chicago, US) Differences between groups were analyzed by using chi-square and student t-test. The value of $p<0.05$ was considered statistically significant.

## Results

A total of 2,376 appendectomies performed by open surgical procedure took place little over a period of 8 years. Twenty-seven cases (1.13%) were diagnosed histopathologically as carcinoid tumor of appendix. Mean age of incidence of carcinoid tumor of appendix was 26.7 years, which was statistically not different

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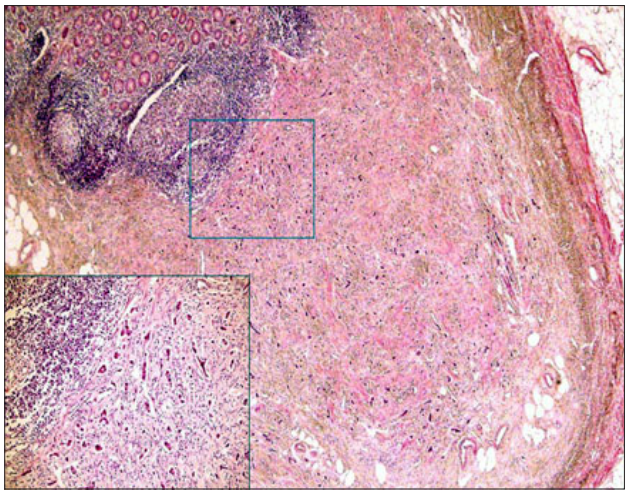

**Fig. 1. Carcinoid tumour in the body of appendix. The big part of figure: H&E x 40. The small part of figure: H&E x 100.**

form non-carcinoid condition of appendix (28.1). The incidence of male patients was higher than that of females in both, appendiceal carcinoid and non-carcinoid groups. In carcinoid group, 5 patients (18.5 %) were female and the others (n=22, 81.5 %) were males. In the group of acute appendicitis, 461 patients (19.6 %) were females and 1,888 (70.4 %) were males. All cases had acute inflammation of the appendix proved by histopathologic examination. Most of the appendiceal carcinoids (n=21, 77.7%) were located at the tip of the appendix. The remaining was raised from the body (Fig. 1). The size of the mass displayed a variation while 24 out of 27 carcinoids were less than 1 cm in size. Out of remaining cases, two were between 1 to 2 cm and the last one was more than 2 cm in size. Appendiceal carcinoids over 2 cm in size were defined as goblet type in the pathology report. The lesion invaded the fat tissue around the appendix within the perineal region. As to the depth of invasion, one appendiceal carcinoid invaded submucosa, 9 invaded muscularis propria, 5 cases reached subserosa, 11 invaded serosa and 1 reached soft-fat tissue around the appendix (Tab. 1).

**Tab. 1. The characteristics of 27 patients with carcinoid tumor.**

| |
|---|
| Preoperative Diagnosis Appendicitis (27 Cases) |
| Postoperative Diagnosis Appendicitis (27 Cases) |
| Incidence 1.13 % |
| |
| Female / Male 5/22 |
| Mean Age 26.66 (17–60) |
| |
| Localization 21 at the tip of the appendix |
| 6 at the body of the appendix |
| Diameter of the tumor ≤1 cm 24 cases |
| 1–2 cm 2 cases ≥2 cm 1 cases |
| |
| Type of tumour 26 Carcinoid / 1 Goblet type carcinoid |
| Invasion Submucosa 1 |
| Muscularis Propria 9 |
| Subserosa 5 |
| Serosa 11 |
| Periappendiceal fatty tissue 1 |
| Initial / Additional Surgery 7 appendectomies / 1 right hemicolectomy |
| Follow up (months) 51 (11–96) |

None of the carcinoid tumors were defined at the time of surgery. Whether inflammation was or was not present was assessed in a routine manner perioperatively. Nevertheless, the operational note did not suggest an atypical display of appendix. All specimens were sent for histopathologic examination. At the end of all pathologic examinations, no second malignant lesion was located.

One patient (3.7 %) required right hemicolectomy. According to the operational note, the patient presented an appendiceal mass over 2 cm in size including catarrhal inflammation of appendix. Carcinoid tumor of Goblet cell type was reported on histology. Right hemicolectomy was made soon after appendectomy. The characteristics of patients with carcinoid tumor are presented in Table 1.

Patients with carcinoid tumors are evaluated for distant metastases with an abdominal CT and 5 HIAA levels checked. There were neither distant metastases nor elevated 5 HIAA levels in patients. We did not make any further evaluation or treat the patients with carcinoid tumors smaller than 1 cm in diameter. If the tumor was greater than 1 cm, abdominal CT and 5 HIAA levels were repeated annually. Any local recurrences, distant metastases, elevated 5HIAA levels or mortality were detected during the follow up.

According to pathological examination, surgical margins were tumor-free in all cases. This is why only one patient with a 3-cm carcinoid tumor underwent right hemicolectomy.

## Discussion

The carcinoid tumor originating from neuroendocrine cells can be of enteric or non-enteric origin. “Karzinoid” is a word what was first used by Oberndorfer in 1907 to explain a tumor behaving in a fashion that is more benign than malign (15). However the complex nature of these tumors and experimental techniques deficiently defining the biologic nature of these lesions have impeded the clarification of the tumor biology of lesions.

The numbers of reports about carcinoid tumors are undependable or limited in series. In 1975 Godwin reported on a wide range of tumor sites including the lung, ovary, biliary system, and the whole gastrointestinal tract, particularly the appendix (35.5 % to 43.9 %), rectum (12–15 %) and ileum (11–14 %) which were the most common sites afflicted by the tumor (16). In the study by Modlin, the appendix was found to be the most common site of carcinoids (44.5 %), followed by the liver and intestines (4).

In the past two decades the incidence of carcinoids has increased. This reflects the improved diagnostic approaches, increased awareness of these types of lesions and enhanced surgical techniques. The peak age for carcinoids of appendix is 15–19 years for females and 20–29 years for males. However, an average diagnostic age for malignant appendiceal tumor is suggested to range from 38 to 49 years (2, 3, 5, 7). In the series, the average age for appendiceal carcinoid was 26.7 years, which matches that declared in literature. A consideration was made about the incidence of the appendiceal carcinoid, namely that it occurred

in 0.3–0.9 % of patients subdued to emergent appendectomy (2–5). In the series, the ratio for carcinoid tumor of appendix was 1.13 % which was higher than that available in English literature.

Epidemiologic studies have displayed a tendency of higher incidence of appendiceal carcinoids among female patients. The male/female ratio has been found to vary from 0.3 to 1 (3, 17). The increase in the incidence has been ascribed by some authors to enlarged appendicectomies performed by open surgeries and laparoscopies, particularly in young females. However other authors declared that the great incidence could not be explained by the appendicectomy rate thus suggesting a truly enlarged incidence (18). In our study, the male/female ratio was 4/1 which directly contradicts the statistics in literature. This contradiction is strongly influenced by the hospital status and thus by the composition of patients admitted in emergent circumstances, who were mostly young males. Almost the same ratio appeared in two groups of patients with appendiceal and non-appendiceal carcinoid tumors. Almost no patients except for one required a further diagnostic procedure relating to carcinoid tumor following appendicectomy. Lesions less than 1 cm in diameter need no staging unless recognized as malignant. The tumors of 1-2 cm in diameter may require further research. Goede et al (18) has declared an outline of right hemicolectomy which was issued within the Guidelines for the Management of Gastroenteropancreatic Neuroendocrine (including carcinoid) Tumours (19). The otherwise appendiceal carcinoid tumors are subdivided in four categories according to WHO classification, namely well-differentiated tumors associated with likely benign behavior, well-differentiated tumors with unclear behavior, well-differentiated endocrine carcinoma, and poorly differentiated carcinoma. Computerized tomography is an available diagnostic test for mesenteric and abdominal diseases, while octreotide scintigraphy is the first sensitive diagnostic test required for appendiceal carcinoma (14, 20, 21). Plasma chromogranin levels over 5,000 microgr/l with poor prognosis were found in 90% of patients with neuroendocrine tumors (21). A carcinoid tumor larger than 2 cm, metastatic disease, inadequate surgery or goblet cell carcinoid warrant further investigation mentioned above. In addition, a 24-h urinary 5-hydroxy indoleacetic acid level was examined (5, 13, 14). In our study, all patients underwent emergent surgery for acute appendicitis. None of the surgeons suspected carcinoid tumor of appendix during surgery except in one patient with hampered appendix. The pathologic reports for each appendiceal carcinoid revealed acute appendicitis with a tumor. There was no need of further investigation for the patients except for one with a tumor bigger than 3 cm in diameter with goblet cell appendiceal carcinoid. After the carcinoid tumor of appendix had been documented, the surgery proceeded to right hemicolectomy in two days. No remaining tumor and metastatic lymph node was displayed in the specimen.

Appendiceal carcinoid has a propensity for metastasis to regional lymph nodes rather than to the liver. In theory, the tumors less than 1 cm in diameter do not invade regional lymph nodes. However regional lymph metastasis can be seen in 20–85 % of patients when the diameter increases up to 2 cm (13, 14). Patients with local disease are stated to have a five-year survival rate of 92 %, while those with regional metastasis 81% and the smaller number of patients with distant metastasis 31 % (22). In this series, there was no case of death and known distant metastasis. In the patient who had undergone subsequent right hemicolectomy, the regional lymph nodes were not afflicted and no distant metastases were confirmed. Besides synchronous and metachronous occurrence of mostly colorectal cancer was no confirmed that can be reported a 33 % of which. As to the depth of lesion, in 26 cases, the tumor invaded the appendix wall with different intensity while in the remaining case it invaded the periappendicular fat tissue. We did not find any regional or distant metastases. The carcinoid syndrome occurred in less than 2 % of patients with particular distant metastases. Such findings as flushing, bronchoconstruction, diarrhea, right-side heart failure due to cardiac fibrosis were found in no patient in our series (9).

According to the guidelines, appendicectomy for appendiceal carcinoids with less than 1 cm in diameter is very likely curative with no indication of an extended follow up (5). When the size of the tumor varies between 1to 2 cm, the patient should be followed up for 5 years while right hemicolectomy is not necessary (5). In our series, out of 3 patients, two patients with a tumour of 1–2 cm and one patient with a tumour over 3 cm in size were followed with focus on biochemical measurements, abdominothoracic CT and octreotide scintigraphy.

Gode et al (5) recommend a right hemicolectomy for some carcinoid tumors ranging from 1 to 2 cm in size. The presence of mesoappendiceal invasion, tumor location at the radix and positive surgical margins, high grade tumor with higher mitotic index and Ki-67 expression are proposed as risk factors. There were two patients with a 1–2 cm carcinoid tumor in our series but they lacked the above risk factors. They were treated with appendectomy alone while both of them are still free from the disease. There was no carcinoid tumor located on radix with a positive surgical margin. No reoperation has been done. In 21 patients, the tumor was located in the distal part of appendix while in 6 patients it was in its middle part.

The treatment of choice for metastatic carcinoid tumor with carcinoid syndrome is based on cytoreductive chemotherapy and control of bioactive pharmacological substances (20). The therapy based on combination of streptozotocyn with 5-fluorouracil or doxorubicin has severe side effects, and is successful in only 40 % of patients.

Octreotid which is an analog of somatostatin is the most effective agent and may suppress symptoms of carcinoid syndrome in 60 % of patients (23, 24).

Interferon-á can reduce the hormonal index by more than 50 % in 40–60 % of cases with metastatic neuroendocrine tumor and control some symptoms as flushing and diarrhea. It has also an anti-proliferative effect on neuroendocrine tumors. Interferon-á may stop tumor growth in about 20–40 % and may provide downsizing in 12–15 % of patients. Unfortunately we cannot use it on a large scale because of its significant side effects (25, 26).

Tumor-targeted radiotherapy and local radiotherapies are current treatment options for metastatic carcinoid tumors. Hepatic

arterial chemoembolisation (HACE) is proposed for carcinoid tumor with unresectable diffuse liver metastases (27). A tumorocidal radiation dose may be given to tumor tissue with $^{111}$In or $^{90}$Y-labeled somatostatin analogs in somatostatin receptor-positive patients. The first reports about this therapy bring hope (28, 29).

The prognosis for patients with appendiceal carcinoids is significantly better than that for patients with midgut carcinoids (20). Five-year overall survival for appendiceal carcinoids is 92 % in localized disease, 81 % in patients with regional metastasis and 31 % in patients with distal metastases (1). In our patients, the mean follow-up time was about 51 months. All of them are still alive and free from disease.

Conclusion: Most appendiceal carcinoids are diagnosed during routine appendectomies performed for acute appendicitis. A careful evaluation of diagnosis is further needed for treatment indications. Extended surgery or further medical treatment must be planned for patients with previously defined risk factors. Even though the appendiceal carcinoid has a favorable prognosis, the incidence of synchronous or metachronous colorectal cancer is 13–33 % which is higher than in normal population (1). Surgeons have to be aware of the possibility of worst-case progression of disease.

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