Journal of Gastrointestinal Cancer (2021) 52:471–475
https://doi.org/10.1007/s12029-021-00628-8

REVIEW ARTICLE

Diagnosis and Treatment of Primary Tumors of the Appendix: a Critical Review

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Accepted: 14 March 2021 / Published online: 19 March 2021

Abstract

Introduction The aim of the current paper was to critically collect, select and summarize the evidence regarding diagnosis, treatment and follow up of primary tumors of the appendix.

Methods A literature review was performed by search and review of the scientific studies pertaining to the subject of our inquiry.

Results Recommendations regarding pimary tumors of the appendix were formulated on the basis of the collected evidence.

Conclusion Primary tumors of the appendix are rare and a high index of suspicion is required not to miss a potentially life threatening medical condition.

Keywords Cancer · Appendix · Adenocarcinoma · Neuroendocrine

Introduction

Primary tumors of the appendix are quite rare and their estimated incidence is less than one case per 100,000 people [1]. However, a malignancy is found in about 1% to 2% of specimens after appendectomy, and such an intervention is one of the most common procedures performed by general surgeons. The aim of the current paper was to critically collect, select, and summarize the evidence regarding diagnosis, treatment, and follow-up of primary tumors of the appendix. Given the rarity of these medical conditions, our recommendations are based on retrospective studies, but a large amount of data has been collected though time [2]. Despite the lack of high-quality evidence, no other sources are available since randomized controlled trials are scant or not feasible.

Methods

A literature review was performed by search and review of the scientific studies pertaining to the subject of our inquiry. The Pub Med database was queried with the strings "appendix", "appendicular", "appendiceal", "tumor", "cancer", "neoplasia", "carcinoma", "neuroendocrine tumor", "carcinoid", "adenocarcinoma", "mucin", and "mucinous" linked by Boolean operators. Time span was set to be comprised between the first of January 2001 and the current date. Only papers written in English were taken into consideration. Irrelevant papers, commentaries, case reports, and studies involving pediatric patients were excluded from the results. Then, we read the selected manuscripts and conducted an inspection of the references of each paper, to add relevant studies.

Classification

Primary malignancies of the appendix can be classified according to their histology in epithelial (adenocarcinoma, mucinous neoplasm, goblet cell adenocarcinoma, and neuroendocrine neoplasms) and non-epithelial neoplasms (lymphomas, GIST, etc.).

In the epithelial group, adenocarcinoma is further subdivided based on mucin production [3]. Mucin producing

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tumors tend to be more aggressive and show a worse prognosis [4]. There is no clear-cut difference between benign and malignant lesions, but certain histologic features may be associated with increased risk of malignant behavior. For example, high expression of Ki-67 and mitotic activity reflect an aggressive biology [5]. Adenocarcinomas of the appendix are considered a distinctive clinical entity according to the TNM 8th edition, but they resemble their counterparts of the colon with respect to histology. However, the long-term oncological outcomes are worse for appendiceal cancer than for colon cancer, attributed to higher perforation rate in appendiceal cancer [6].

Low-grade appendiceal mucinous neoplasms (LAMN) are composed by well-differentiated adenomas with minimal atypia. Terminology has been changing over time and has often been confusing. The terms mucocele and cystadenoma both referred to LAMN but are now considered deprecated for the sake of clarity. High-grade appendiceal mucinous neoplasms (HAMN) show higher atypia, cribriform growth pattern, and more numerous cells. The presence of round cells with intracytoplasmic mucin pushing the nucleus towards the cell membrane confers the aspect of signet ring cells, a hallmark of aggressive behavior [7]. Any adenocarcinoma can secrete mucin, but when extracellular mucin is present in more than 50% of the tumor, it is called mucinous adenocarcinoma. Mucin can dissect the wall of the appendix and perforate it, spreading through the peritoneal cavity.

Goblet cell adenocarcinomas, previously defined as goblet cell carcinoid, represent a distinct clinical entity, an amphicrine tumor composed by goblet-like mucinous cells and variable Paneth and neuroendocrine cells [8].

Neuroendocrine neoplasms are epithelial tumors similar to those found in the rest of the gastrointestinal tract. They are often asymptomatic and found on examination of the specimen after appendectomy. Neuroendocrine neoplasms are almost invariably well differentiated and thus defined neuroendocrine tumors (NET). Exceedingly rare are the poorly differentiated neuroendocrine carcinomas (NEC), either pure or associated with an adenocarcinoma component (MANEC) [37]. Even more rare tumors are stromal tumors and lymphomas.

General Recommendations

General recommendations are applicable to any kind of primary neoplasia of the appendix. Patients are often initially treated as being affected by acute appendicitis and the recognition of the underlying malignancy is sometimes acquired only after specimen examination. Guidelines should take this consideration into account to be applicable in real clinical scenarios. The incidence of primary tumors of the appendix has increased over time [9]. However, survival has ameliorated as well, reflecting a better overall awareness of the problem.

A careful history of the patient and physical examination is the first step. Symptoms at onset may vary including abdominal pain, fatigue, weight loss, and dyspepsia. Clinical presentation is often related to acute appendicitis (that ensues when the lumen is occluded by the tumor) or bowel obstruction in more advanced cases. In case of pelvic pain, an OB/GYN evaluation is warranted to exclude a gynecologic condition in women.

In several situations, for example, when symptoms are vaguer and pain is reported as a mild discomfort, one should consider the possibility of an occult malignancy. Risk factors for such an event are indeterminate imaging and the presence of periappendiceal abscess [10]. The importance to avoid missing a malignancy should represent an adjunctive motif to perform surgery in suspected acute appendicitis, at least in presence of the aforementioned risk factors. According to J. de Jonge MDMB, in his series, one out of three patients non-operatively treated for complicated appendicitis required an interval appendectomy. The incidence of appendicular neoplasms was high in these patients compared with those that had early surgery. Therefore, additional radiological imaging following non-operatively treated complicated appendicitis is recommended [11].

In addition, appendectomy should be performed if an appendix abnormally distended is found during an intervention performed for other reasons [12]. In such a case, care should be undertaken not to damage the wall of the appendix, because spillage of malignant cells may result in peritoneal seeding, thereby transforming a localized disease into an advanced one, compromising survival [13]. When the diagnosis of cancer is confirmed, a second look could be necessary to achieve oncologic radicality.

Patients affected by primary malignancy of the appendix are at an increased risk to harbor another mass in the intestine [14]. Therefore, a careful manual inspection of the gut and a colonoscopy should be performed.

Adenocarcinoma

Tumor markers are the same for adenocarcinomas of the colon and include CEA, CA 19.9, CA 125. They are usually sampled at tumor diagnosis as a prognostic predictor and during chemotherapy to assess tumor progression and response to therapy [15]. In mucin producing tumors, a normal baseline CA-125 correlates with the likelihood of achieving complete cytoreduction whereas CA 19-9 is useful to diagnose recurrence after cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) [16]. Taflampas et al. demonstrated a longer survival in

patients with normal preoperative markers. Current studies are focusing to detect genetic abnormalities to tailor treatment according to specific DNA patterns [17].

CT or MRI is the main imaging modalities to detect and stage primary adenocarcinomas of the appendix. Both the abdomen and the thorax should be included to precisely assess cancer spread. Imaging surveillance after surgical treatment should be tailored according to the features of the disease [18]. LAMN treated with radical resection can be surveilled with tumor markers sampling and MRI/CT every 6 months in the first 2 years, given that the majority of recurrences occur in this time span [19]. Patients with unfavorable histologic characteristics or locally advanced tumors should undergo CT or MRI every 4 to 6 months for the first 2 years and yearly thereafter for at least 5 years. For patients affected by low-grade tumors who underwent CRS and HIPEC, CT or MRI of the abdomen is recommended at 2 months postoperatively, followed by annual follow-up for at least 5 years [20].

LAMN are indolent malignancies and appendectomy alone is considered oncologically appropriate when performed in patients without perforation or peritoneal involvement [21]. In a study conducted by Sugarbaker et al. in patients with localized LAMN, right hemicolectomy did not increase disease specific or overall survival [22]. Right hemicolectomy is reserved for LAMN with positive margins after appendectomy [23]. The concept of "radical appendectomy" stands for resection of the soft tissues and lymph nodes adjacent to the appendix. In fact, a mucinous disease tends to produce a soft infiltration of the lymph nodes rather than a hard infiltrate as expected in a solid tumor. Radical appendectomy provides the maximal amount of information required for optimal decisions regarding patient management. There is a low incidence (6%) of positive lymph nodes in patients with LAMN.

For HAMN, on the other hand, lymph node invasion increases to 29% and right hemicolectomy is indicated [24]. Appendectomy alone does not produce an adequate lymph node sample; therefore, right hemicolectomy should be performed for all high-grade appendiceal adenocarcinomas [25]. Such an approach is useful for both staging and prognostic purposes. According to Xie et al., depth of invasion could be used as an indicator to determine the most appropriate surgical option [26]. In their study, if the tumor had invaded the mucosal layer, patients undergoing extended excision showed improved overall survival as compared with localized resections. In addition, the rate of lymph node metastases is substantial, even for small tumors: tumor size should play no role in the decision of whether to perform a hemicolectomy [27].

It is important to stress the fact that intraoperative rupture of a mucinous producing tumor may convert a localized disease into widely spread; therefore, careful tissue management is of utmost importance and conversion to an open procedure should be taken into consideration. Goblet cell carcinomas share the same recommendations, as they closely resemble adenocarcinoma with respect to aggressiveness [28].

In the setting of peritoneal metastasis, a multimodality treatment should be undertaken. Patients undergo appendectomy associated to CRS and HIPEC, because right hemicolectomy does not confer a survival advantage as compared with appendectomy [29]. It can be performed, however, for cytoreductive purposes. When a radical intervention with intention to cure is not feasible, cytoreduction is the surgical resection of macroscopically visible disease and is associated with chemotherapy such as HIPEC, which is directed to eradicate microscopic spread of cancer. Cytoreduction involves the resection of peritoneal surfaces, when these are involved. Peritoneal involvement may be quantified using Sugarbaker's Peritoneal Carcinomatosis Index or the Peritoneal Surface Disease Severity Score. Complete removal of all macroscopically visible disease is an independent predictor of survival.

The management of patients with limited peritoneal involvement of acellular mucin in the setting of LAMN remains controversial, particularly when isolated in the proximity of the appendix. Appendectomy with cytoreduction of the periappendiceal peritoneum in these cases has been associated with reasonably low peritoneal recurrence. Conversely, LAMN associated with cellular mucin deposits are associated with a higher risk of subsequent peritoneal involvement, therefore should undergo HIPEC [30].

Other forms of chemotherapy exist and provide the same benefits as HIPEC. For example, the early postoperative intraperitoneal chemotherapy or delayed postoperative approaches are available options and results in terms of survival look the same [31]. Systemic chemotherapy is also the subject of various studies and 5-fluorouracil is recommended by most authors for patients with high-grade peritoneal disease or nodal metastases [32].

Neuroendocrine Neoplasms

The history of a patient affected by well-differentiated neuroendocrine neoplasms, NET, is often not particularly useful to point to the diagnosis. It could include, but is extremely rare and sign of metastatic disease, the association with flushing, watery diarrhea, or other generic complains related to the substance secreted by the tumor within the carcinoid syndrome. When the diagnosis is suspected before the surgical intervention, patients can be studied with CT or MRI of the abdomen and chest, followed by colonoscopy to rule out further synchronous lesions [33]. Somatostatin receptor scintigraphy with Ga-PET/CT is usually able to identify the

site of NET. In case of advanced disease, such a study can help to tailor the use of somatostatin antagonists as systemic chemotherapy. Selected centers counsel the introduction of PET in the initial evaluation. However, there is ongoing debate regarding the cost effectiveness of such an approach.

Chromogranin A and 5-hydroxyindoleacetic acid can be measured in the urine. However, only large or advanced tumors actually produce visible symptoms and high levels of such metabolites are associated with a worse prognosis. As other markers, they have no diagnostic value per se and are used to confirm a suspected diagnosis.

Surgical treatment is based on tumor size and other parameters: invasion of the mesoappendix, grade and vascular or lymphatic spread. Tumors with major diameter less than 1 cm without unfavorable prognostic factors can be safely treated with appendectomy alone. On the other hand, tumors with size greater than 2 cm are best treated with formal right hemicolectomy, because increasing tumor size is associated with the risk of lymph node involvement. It has been demonstrated that such an event represents a major step in tumor progression [34]. Tumors comprised between 1 and 2 cm should be treated with right hemicolectomy when one or more of the aforementioned unfavorable prognostic factors are present [35]. Patient condition and comorbidities should be considered as well in the decision-making process.

Surveillance after treatment is not standardized given the rarity of the disease and its indolent course, unless tumor burden is not advanced at presentation. Intervals of examination vary, but it should extend until about 10 years after surgery. CT and MRI are used to assess tumor recurrence, with the association of urine sample collection to search for tumor markers chromogranin A and 5-HT [36].

The rare poorly differentiated NEC and MANEC fare an aggressive behavior and should be managed and staged as the adenocarcinoma [37].

Declarations

Conflict of Interest The authors declare that they have no conflict of interest.

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