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THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Diagnosing and Managing Carcinoid Heart Disease in Patients With Neuroendocrine Tumors

An Expert Statement

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ABSTRACT

Carcinoid heart disease is a frequent occurrence in patients with carcinoid syndrome and is responsible for substantial morbidity and mortality. The pathophysiology of carcinoid heart disease is poorly understood; however, chronic exposure to excessive circulating serotonin is considered one of the most important contributing factors. Despite recognition, international consensus guidelines specifically addressing the diagnosis and management of carcinoid heart disease are lacking. Furthermore, there is considerable variation in multiple aspects of screening and management of the disease. The aim of these guidelines was to provide succinct, practical advice on the diagnosis and management of carcinoid heart disease as well as its surveillance. Recommendations and proposed algorithms for the investigation, screening, and management have been developed based on an evidence-based review of the published data and on the expert opinion of a multidisciplinary consensus panel consisting of neuroendocrine tumor experts, including oncologists, gastroenterologists, and endocrinologists, in conjunction with cardiologists and cardiothoracic surgeons. (J Am Coll Cardiol 2017;69:1288–304)
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Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

Neuroendocrine tumors (NETs) are rare neoplasms, with an incidence ranging from 2.5 to 5 cases per 100,000 population (1). They can occur anywhere in the body but most often originate in the gastrointestinal tract. Gastrointestinal NETs were originally termed "carcinoids," and those originating from the distal small intestine and proximal colon are synonymously called midgut carcinoids (2). Other sites include the stomach, duodenum, and bronchus (foregut carcinoids), and, less frequently, the distal colorectal tract (hindgut carcinoids). Carcinoid tumors usually grow slowly, over years, commonly causing few or no symptoms until they are large or have metastasized to the liver and, less frequently, to other sites (e.g., the lungs or bone).

Approximately 30% to 40% of patients (mainly with midgut carcinoids) present with features of the carcinoid syndrome, manifested by episodes of vasomotor changes (flushing and hypotension; less frequently, hypertension), diarrhea, and bronchospasm, or they develop these symptoms during the course of the disease (3). Carcinoid syndrome occurs in the vast majority of patients when tumors metastasize to the liver, as the vasoactive substances produced by the primary tumor or metastases reach the systemic circulation via the hepatic vein. However, about 5% of patients, particularly those with primary ovarian or pulmonary sites, as well as those with midgut carcinoids with retroperitoneal metastases, may present with carcinoid syndrome without liver metastases (4).

Carcinoid heart disease, which represents the development of plaque-like, fibrous endocardial thickening involving heart valves (mainly in the right heart), is a frequent occurrence in patients with carcinoid syndrome and is accountable for substantial morbidity and mortality. The pathophysiology of carcinoid heart disease is poorly understood; however, chronic exposure to excessive circulating serotonin (5-hydroxytryptamine [5-HT]) is considered one of the most important contributing factors. Symptoms of right heart failure may develop and can also considerably impair quality of life (5). Because the presence of carcinoid heart disease represents an independent negative prognostic factor in patients with advanced 5-HT–secreting NETs, there is an unmet need to improve early diagnosis and interdisciplinary management of the carcinoid syndrome and carcinoid heart disease. International consensus guidelines specifically addressing the diagnosis and management of carcinoid heart disease are currently lacking. Guidelines in this area are important because there is considerable variation in multiple aspects of screening and management of the disease (6).

The purpose of the present guidance document was to provide succinct, practical advice on the diagnosis and management of carcinoid heart disease, as well as its surveillance. Recommendations and proposed algorithms for the investigation, screening, and management of carcinoid heart disease have been developed on the basis of the expert opinion of a multidisciplinary consensus panel, consisting of NET experts, including oncologists, gastroenterologists, and endocrinologists, in conjunction with cardiologists and cardiothoracic surgeons who convened at the first International Symposium for carcinoid heart disease (London, United Kingdom, September 2014, under the auspices of the European Neuroendocrine Tumor Society and British Heart Valve Society). Information for the recommendations and proposed algorithms were also gathered from an evidence-based review of all relevant published data. This guidance covers pathophysiology and epidemiology, clinical features, biochemical markers, imaging, medical and interventional therapies, heart valve surgery and post-surgical management, and surveillance for carcinoid heart disease.

ABBREVIATIONS AND ACRONYMS

2D = two-dimensional

3D = three-dimensional

5-HIAA = 5-hydroxyindoleacetic acid

5-HT = 5-hydroxytryptamine (serotonin)

CgA = chromogranin A

CMR = cardiac magnetic resonance

IV = intravenous

LAR = long-acting repeatable

NET = neuroendocrine tumor

NT-proBNP = N-terminal pro-B-type natriuretic peptide

TAE = transcatheter arterial embolization

TTE = transthoracic echocardiography

MATERIALS AND METHODS

Data relating to the diagnosis, surveillance, management, and follow-up care of carcinoid heart disease in patients with NETs were identified by searches of the MEDLINE database using the following general search terms: carcinoid heart disease; diagnosis; treatment; epidemiology; and prognosis. The search was limited to human studies. The search results were supplemented by manual searching of relevant journals, reference lists in key articles and other appropriate documents, and expert input.

All recommendations are offered on the basis of the best available evidence, supplemented by the authors' experiences in managing carcinoid heart disease. Each recommendation was graded according to the Oxford Centre for Evidence-Based Medicine Levels of Evidence (**Table 1**) (7,8).

PATHOPHYSIOLOGY OF CARCINOID HEART DISEASE

The pathogenesis of carcinoid heart disease is complex and not completely understood. A variety of vasoactive substances secreted by the tumor seem to be involved. These include 5-HT, prostaglandins, histamine, bradykinin, and other substances with

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