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REVIEW ARTICLE

Management of Patients with Hereditary Colorectal Cancer Syndromes

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Abstract Colorectal cancer (CRC) is one of the most important causes of death in the world. Hereditary CRC is found in 5–10% of CRC patients. In this review, we will focus on the major forms of hereditary CRC and their management according to the most recent literature available.

PALAVRAS-CHAVE
Neoplasias Colorretais;
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Avaliação de Doentes com Síndromas Hereditários Associados ao Cancro Coloretal

Resumo O cancro coloretal (CCR) é uma das mais importantes causas de morte ao nível mundial. O cancro coloretal hereditário está associado a cerca de 5 a 10% de todos os casos de CCR. Neste artigo faz-se uma revisão da abordagem dos principais síndromas hereditários associados a CCR de acordo com a literatura mais recente.

1. Introduction

Colorectal cancer (CRC) is one of the most important causes of death in the world. In Portugal, CRC has the second highest incidence after breast cancer in female and prostate cancer in men[1] and the second cause of cancer-related death.

The cause of CRC is multifactorial, with inheritance and environment assuming the most relevant roles. Approximately 70–80% of CRC cases seem to be sporadic, while the remaining 20–30% is associated with an inherited pattern. Patients with a familial risk make up approximately 20% of all patients with colorectal cancer, whereas approximately 5–10% of the total annual burden of colorectal cancer is hereditary and Mendelian in nature.

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Screening for hereditary cancer syndromes in patients with CRC should include review of personal and family histories and genetic evaluation according to more or less established criteria.

A diagnosis of Lynch syndrome, familial adenomatous polyposis, or another genetic syndrome can influence clinical management of patients with CRC and their family members. A timely identification of individuals at risk for hereditary CRC syndromes offers an opportunity to a sooner intervention or prevention.

In this review we will focus on the major forms of hereditary colorectal cancer, Lynch syndrome, familial adenomatous polyposis, MUTYH polyposis, juvenile polyposis, Peutz–Jeghers syndrome and serrated/hyperplastic polyposis syndrome.

2. Lynch syndrome

Lynch syndrome (LS) is an autosomal dominant condition caused by a defective mismatch repair (MMR) gene.

Although this syndrome has also been known as HNPCC (hereditary non-polyposis colorectal cancer), this terminology is now reserved to patients and/or families who fulfill the Amsterdam criteria. The LS denomination must be only applied to patients and families in which the genetic basis can be linked to a germline mutation in one of the DNA MMR genes or the *EPCAM* gene.

Lynch-like syndrome patients display alterations in MMR molecular immunohistochemical or microsatellite instability (MSI) without an identifiable germline mutation. Familiar colorectal cancer type X refers to patients that meet Amsterdam I criteria without LS MSI characteristics.

LS is responsible for approximately 3% of all of the newly diagnosed colorectal cancer and is probably the most common hereditary CRC.[2] In fact, the major clinical consequence of LS is CRC with a life-time risk varying between 15% and 70% depending on sex and MMR mutated gene. Mean age of CRC diagnosis is 10–15 years earlier than sporadic cases.[3]

These CRC are predominantly right colon located and have a very rapid adenoma–carcinoma progression, with frequent reports of CRCs arising within three years of a clearing colonoscopy. However, CRC prognosis in LS patients is better when compared to sporadic matched stage CRC.[4]

The presence of CRC, endometrial, ovary, urinary tract, stomach, small bowel or brain cancer, especially at young ages and with cancer family history, should lead to investigate a probable hereditary cancer. In this clinical setting the genetic counseling has a major role and can include personal and family cancer history, risk assessment, education, informed consent and genetic testing.

Multiple clinical criteria have been developed to identify at risk patients. Obviously, all members of an already known Lynch family should be tested. In individuals without previously Lynch diagnosis, the two most used are Amsterdam criteria (sensitivity 22% and specificity 98%) and Revised Bethesda Guidelines (sensitivity 82% and specificity 77%) but other clinical criteria, like endometrial cancer below 50 years, and computational prediction systems have been applied as well[5] (Tables 1 and 2).

Patients meeting Amsterdam criteria should undergo direct germline testing. On the other hand, for those who meet Revised Bethesda criteria, evaluation by immunohistochemical testing for the MLH1/MSH2/MSH6/PMS2 proteins and/or testing for microsatellite instability is suggested.

Table 1 Amsterdam I and II criteria for diagnosis of hereditary non-polyposis colorectal cancer.

Amsterdam I criteria
1. Three or more relatives with histologically verified colorectal cancer, 1 of which is a first-degree relative of the other two. Familial adenomatous polyposis should be excluded.
2. Two or more generations with colorectal cancer.
3. One or more colorectal cancer cases diagnosed before the age of 50 years.
Amsterdam II criteria
1. Three or more relatives with histologically verified HNPCC-associated cancer (colorectal cancer, cancer of the endometrium, small bowel, ureter, or renal pelvis), 1 of which is a first-degree relative of the other 2. Familial adenomatous polyposis should be excluded.
2. Cancer involving at least 2 generations.
3. One or more cancer cases diagnosed before the age of 50 years.

Universal testing for all newly diagnosed CRC (or CRC patients under 70 years old) is currently a hot topic under discussion (Fig. 1). In this setting, tumor immunohistochemistry testing seems to be more sensitive and cost-effective for identifying LS patients and achieves the aim of reduced morbidity and mortality. However, implementation of this screening system is complicated and requires effective multidisciplinary approach.[6–9]

As long as the clinical criteria to search LS are fulfilled, different options can be adopted for detecting MMR defect.

Tumor testing can be done on archived formalin-fixed tissue for surgical resection or biopsies specimens. Microsatellite instability testing (sensibility 85%, specificity 90%) or preferably immunohistochemistry testing of tumor tissue for searching the lack of expression of MMR gene

Table 2 Revised Bethesda guidelines.

1. CRC diagnosed at younger age than 50.
2. Presence of synchronous or metachronous CRC or other LS-associated tumors.
3. CRC with MSI-high pathologic-associated features (Crohn-like lymphocytic reaction, mucinous/signet cell differentiation, or medullary growth pattern) diagnosed in an individual younger than 60 years old.
4. Patient with CRC and CRC or LS-associated tumor diagnosed in at least 1 first-degree relative younger than 50 years old.
5. Patient with CRC and CRC or LS-associated tumor (colorectum, endometrium, stomach, ovary, pancreas, ureter, renal pelvis, biliary tract, brain, small bowel, sebaceous glands, and kerotoacanthomas) at any age in 2 first-degree or second-degree relatives.