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Review Article

Narrative review comparing the epidemiology, characteristics, and survival in sporadic colorectal carcinoma/Lynch syndrome

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ABSTRACT

Introduction: Colorectal carcinoma is the third most prevalent neoplasm in the world, and the second cause of death by cancer. The most part of these neoplasms are sporadic by somatic mutations, but around 15% are hereditary, such as Lynch syndrome or hereditary nonpolyposis colorectal cancer (HNPCC). Despite being the same tumor, it has differences between these two contexts as well as different prognosis. In Lynch syndrome cases, the survival of these individuals was greater than that observed in sporadic cases.
Methods: This review focuses on the different characteristics and development of colorectal carcinoma in sporadic and Lynch syndrome cases, in order to conclude what may motivate the greater survival in the tumors associated with this syndrome.
Results: Although the histopathological features drive into a worse prognosis, the colorectal carcinoma in the Lynch Syndrome presents a greater survival comparing to sporadic colorectal carcinoma.
Discussion: The greater survival in the colorectal carcinoma in the HNPCC compared to the sporadic carcinomas has been linked to factors such as high microsatellite instability, diploid predominance, earlier screening for colo-rectal carcinoma, deficient DNA repair mechanism, low p53 mutation rate, and presence of lymphoid aggregates involving the neoplasm.
Conclusion: Further studies should be conducted to provide new insights about survival of colorectal carcinoma in Lynch syndrome, as well as the therapeutic alternatives for this neoplasia.

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Revisão narrativa na comparação da epidemiologia, características e sobrevivência no Carcinoma Colorretal esporádico/Síndrome de Lynch

Palavras-chave:
Carcinoma colorretal
Síndrome de lynch
Sobrevida

RESUMO

Introdução: O carcinoma colorretal é a terceira neoplasia mais prevalente no mundo, bem como a segunda causa de morte por câncer. A maioria destas neoplasias são esporádicas, devidas a mutações somáticas, mas cerca de 15% são hereditárias como a síndrome de Lynch ou *Hereditary Nonpolyposis Colorectal Cancer* (HNPCC). Apesar de ser a mesma neoplasia, esta apresenta características clinico-patológicas e moleculares distintas, bem como diferentes prognósticos. Nos casos de síndrome de Lynch, a sobrevida parece ser maior quando comparada com os carcinomas esporádicos.
Métodos: Realizamos uma revisão bibliográfica sobre as diferentes características e desenvolvimentos do carcinoma colorretal esporádico e no contexto da síndrome de Lynch, para concluir o que causa a maior sobrevida no caso das neoplasias associadas a esta síndrome.
Resultados: Apesar das características histopatológicas apontarem para um pior prognóstico, o HNPCC apresenta uma maior sobrevida em relação ao carcinoma colorretal esporádico.
Discussão: A maior sobrevivência nos carcinomas colorretais associados ao HNPCC em comparação com os carcinomas colorretais esporádicos tem sido atribuída a fatores como a elevada instabilidade microssatélite, a predominância diploide, a realização de rastreio para o carcinoma colorretal mais precoce, deficiente mecanismo de reparação de DNA, menor taxa de mutação da p53 e existência de agregados linfoides a envolver a neoplasia.
Conclusão: Consideramos que deve ser encorajado o estudo mais aprofundado dos fatores que levam à maior sobrevida do carcinoma colorretal na síndrome de Lynch, bem como de alternativas terapêuticas para esta neoplasia.

Introduction

This study had as main objectives:

- Identify the epidemiology and risk factors for the onset of sporadic colorectal carcinoma;
- Identify the epidemiology of Lynch syndrome (LS), particularly regarding the onset of colorectal carcinoma, understanding what distinguishes it from sporadic colorectal carcinoma, as well as the diagnostic criteria of these cases;
- Given the survival and mortality rates of the two presentations of colorectal carcinoma, to identify which presented the longest survival and understand the reasons for this difference.

Brief methods

The authors carried out a literature review, taking into account the articles indexed online on the PubMed website (http://ncbi.nlm.nih.gov/pubmed) between September and November 2018, published between 1996 and 2018. The following MeSH terms were used: "Colorectal Cancer"; "Lynch Syndrome"; "Hereditary Nonpolyposis Cancer"; "Colorectal Neoplasms AND Survival".

After selecting English and Portuguese articles, and reviewing their title and abstract, 37 articles were selected.

Colorectal carcinoma

Epidemiology

Colorectal carcinoma (CRC) is the third most prevalent neoplasm in the world;[1] around one million new cases are diagnosed annually.[2,3] It is the third most frequently diagnosed cancer in males (after lung and prostate cancer), and the second in females (after breast cancer).[4–7] It accounts for approximately 10% of cancer deaths, being the second most common cause of death in Europe[7] and the fourth worldwide.[1]

Due to improvements in early detection of carcinoma precursor lesions and preventive methods (such as endoscopic polypectomy), its incidence has been decreasing in more developed countries.[1]

Characteristically, the incidence of CRC is low at ages below 45–50 years, progressively increasing with age. When compared with females, males are at a higher risk of developing this cancer compared to females.[7]

In most cases (approximately 90%), CRC is sporadic, as a consequence of accumulation of mutations or epigenetic modifications in some genes.[3] The remaining 10% are cases of familial CRC, namely LS and familial adenomatous polyposis (FAP).[8]

Risk factors

The risk factors for the onset of sporadic CRC may be modifiable or non-modifiable. Modifiable factors are primarily related to the individual's habits: excessive alcohol consumption, high consumption of red and processed meat, low fiber diet (vegetables and fruits), overweight and obesity, physical inactivity, and smoking. Altering these habits may reduce the risk of developing this neoplasm.[1,4,5,7] Some studies indicate protective factors of CRC onset, such as regular aspirin use, postmenopausal estrogen therapy, and intake of vitamin D, calcium, and dairy products.[1,4]

In turn, non-modifiable factors are primarily associated with a greater genetic predisposition of some individuals to the onset of CRC.[8]

Patients with ulcerative colitis and Crohn's disease present an increased risk of CRC.[4] Individuals with a history of inflammatory bowel disease, history of first-degree relatives with CRC, and/or previous history of adenomatous polyps of the colon and rectum also have an increased risk of developing CRC.[4]

Hereditary CRC results from germline mutations; the two main syndromes are FAP and LS, which account for 10–15% of CRCs.[7]

Lynch syndrome

Epidemiology and etiology

LS is an autosomal dominant disease[8,9] and is the syndrome that presents the most predisposition for CRC onset.[10,11] It has a high penetrance (80–85%)[8,12] and is the most common form of hereditary CRC in the world.[10,13] CRC is also the most frequent cause of cancer death in families with this syndrome.[14]

Individuals with history of LS have an 80% risk of developing CRC; in a family with a genetic mutation for LS, a member has a 50% risk of being affected by it.[8,15]

Some authors divide LS into Lÿnch Iänd Lÿnch II.Ẅhat distinguishes them is the location of the neoplasm: in Lynch I, the neoplasm is confined to the colon, while in Lynch II there is the presence of extracolonic neoplasms.[8] These extracolonic neoplasms include endometrial, ureter, and renal pelvis carcinoma, hematological neoplasms, and carcinomas of the skin, larynx, stomach, small intestine, ovaries, pancreas, and biliary tract.[9,12] Despite the higher propensity for developing CRC, some cases first have extracolonic carcinomas.[13]

Typical germline mutations in DNA repair genes (mismatch repair [MMR] genes) are involved in the etiology of LS.[13] Mutations occur primarily in one of the following four genes: *MutL Homolog* 1 (MLH1), *MutS Homolog* 2 (MSH2), *MutS Homolog* 6 (MSH6), or *Post Meiotic Segregation Increased* 2 (PMS2). In addition to these mutations, LS may occur by deletions of the epithelial cell adhesion molecule (EPCAM) gene.[16,17]

MMR genes are responsible for maintaining the DNA intact during replication, by repairing base pair errors, chemotherapy-induced nucleotide changes, or errors in base pair repeating units (known as microsatellites). Insertion or deletion mutations are very common in these microsatellite sequences. If there is a defect in the MMR genes, the altered microsatellites will not be corrected, leading to the accumulation of a variety of lengths of these sequences, which is referred to as microsatellite instability (MSI), the hallmark of this syndrome.[18,19]

Table 1 – Amsterdam Criteria I.

Presence of histologically confirmed colorectal carcinoma in at least three relatives, when:
One of the family members is a first degree relative of the other two;
At least two successive generations are affected by the neoplasm;
At least one diagnosis of colorectal carcinoma was made when the patient was under 50 years of age;
Familial adenomatous polyposis or other familial syndromes are excluded.

In addition to the germline mutation, the phenotypic expression of LS requires a somatic mutation and, as a consequence, the inactivation of both alleles and loss of expression of the affected gene.[13]

Considering the mutated genes involved in the pathogenesis of LS, 90% of the cases are related to mutations in the MLH1 and MSH2 genes (which may be deletions or rearrangements), 10% with mutations in the MSH6 gene, and 6% with mutations in the PMS2 gene. EPCAM deletion may lead to MSH2 silencing and may be responsible for LS onset in 6.3% of cases.[15,19,20]

Colorectal carcinoma in Lynch syndrome

As previously mentioned, LS patients are at a high risk of developing CRC; in this context, this carcinoma has some specific characteristics. The onset of these cases of CRC occurs at an earlier age (mainly between 44 and 61 years) than sporadic CRC (around 69 years).[19] Furthermore, there is a predominance of localization in the proximal colon (approximately 70% of cases).[10,19,21] Histologically, these tumors tend to be mucinous and poorly differentiated (features associated with poor prognosis), with lymphocyte infiltrates and high microsatellite instability (MSI), as well as presence of signet ring cells.[12,19,21]

LS patients have an accelerated adenoma-carcinoma progression: in this syndrome, the estimated time of progression to malignancy of a polyp is around 35 months, *versus* 10–15 years in sporadic CRC.[10,15,19]

In addition to the aforementioned features, individuals with LS also have a high risk and consequent development of multiple metachronous and synchronous neoplasms.[12,15]

Regarding the diagnosis of LS, it is important to mention that it can only be suspected through family history and clinical criteria.[22] In 1990, the Amsterdam I criteria (Table 1) were established for the diagnosis of hereditary nonpolyposis colorectal cancer (HNPCC), and all criteria had to be met to establish the diagnosis. In 1999, the Amsterdam II criteria were established (Table 2), adding to the diagnosis the presence of extracolonic tumors. The sensitivity of the second criteria is 22%, with a specificity of 98% for the diagnosis of LS.[16,19]

In addition to the Amsterdam criteria, the revised Bethesda guidelines (Table 3) were released in 2004 to identify patients at high risk for LS, who should be assessed by MSI evaluation and/or immunohistochemistry testing. These guidelines have a sensitivity and specificity of 81% and 98%, respectively.[16,19]

MSI is assessed by studying the different sizes of microsatellites in tumor tissue when there is a defect in

Table 2 – Amsterdam Criteria II.

Presence of colorectal carcinoma or extracolic carcinoma (endometrium, ovary, small intestine, gastric, pancreas, hepatobiliary, upper urothelial tract, cerebral, sebaceous adenomas, keratoacanthomas), histologically proven in at least three family members.
One of the family members is a first degree relative of the other two;
At least two successive generations are affected by the neoplasm;
At least one diagnosis of colorectal carcinoma was made when the patient was under 50 years of age;
Familial adenomatous polyposis or other familial syndromes are excluded.

Table 3 – Revised Bethesda Criteria.

Patient assessment for microsatellite instability analysis in colorectal carcinoma:
Diagnosis of colorectal carcinoma before the age of 50 years;
Presence of colorectal carcinoma or other synchronous or metachronous extracolic carcinomas, regardless of age;
Colorectal carcinoma with high microsatellite instability histology (MSI-H) – tumor lymphocyte infiltration, lymphocytic Crohn-like reaction, mucinous differentiation, presence of signet ring cells, and medullary growth pattern before 60 years of age;
Diagnosis of colorectal carcinoma in a patient with one or more first-degree relatives with extracolic tumors, one of the carcinomas having been diagnosed before the age of 50 years;
Colorectal carcinoma diagnosed in a patient with two or more first or second degree relatives with extracolic tumors, regardless of age.

MMR gene function. If there are no variations in size, there is microsatellite stability. If only one mutation is found, MSI is considered to be low; if more than two mutations are observed, MSI is considered high. Immunohistochemistry is important to understand whether there is loss of function of MMR genes and/or loss of DNA expression that encodes proteins of these genes in neoplastic tissue. Both assessments have a sensitivity of 83%.[19]

Genetic screening for mutations in MMR genes is the gold standard for diagnosis and characterization of LS; these mutations are identified in 80% of families with this syndrome.[15]

Several studies have shown a decrease in CRC mortality in patients with LS who are regularly screened for this neoplasia through colonoscopy, diagnosing tumors earlier. Given its early onset, colonoscopic screening should start at around 20–25 years and should be performed every 1 to 2 years, or 10 years before the age of onset of the youngest CRC case in the family.[10,11,13] Patients with MSH6 mutation tend to develop CRC later, so screening is performed from 30 years of age onwards.[10]

Results

As for CRC, studies indicate a general decrease in mortality from this cancer in more developed countries, due to better screening programs and better treatment options.[6] Screening with colonoscopy decreased the incidence of CRC by 33% and mortality by 43%.[7] The earlier the carcinoma is detected, the better its prognosis: when detected early, the five-year survival rate is approximately 90%, while in stage IV this rate drops to 10%.[3] The five-year survival rates for CRC depend on the stage of the cancer: 93.2% for stage I, 82.5% for stage II, 59.5% for stage III, and 8.1% for stage IV.[6] The five-year survival rate of a CRC patient ranges from 55% in developed countries to 40% in developing countries.[8]

In the case of families with LS, the screening programs implemented reduced the incidence of CRC by 62% and mortality by 65–70%.[14]

Comparing with sporadic CRC, studies demonstrate that, at the same stage, CRC in the context of LS has a higher survival rate. Regarding the cumulative five-year survival rates in patients under 65 years, sporadic CRC has a 44% rate *versus* the 65% rate observed in this carcinoma in the context of LS.[19,23]

In addition to the TNM classification, some individual characteristics influence the prognosis of a neoplasia, namely the location, age, sex, and histological and molecular characteristics.[24]

In the case of LS, colon neoplasms are preferably proximally located. One of the features that may justify a better prognosis in tumors located in this region is the progressive increase in the incidence of proximal to distal aneuploidy. Tumors of this proximal location are often diploid (about 80%), encompassing neoplasms in the context of LS. Tumors with aneuploid predominance have a high expression of growth factors that promote greater tumor growth, consequently leading to a worse prognosis.[25]

Another feature that has been shown to lead to a better prognosis is the presence of high MSI, *i.e.*, a large variety of mutated microsatellite sizes that have not been corrected by the MMR genes. Although the mechanisms that lead to this advantage are still unknown, it is a very frequent feature in CRC in LS.[26,27] Different studies have shown that this high instability is mainly associated with cases of poorly differentiated, mucinous carcinomas located in the proximal colon with lymphocytic peri-tumoral infiltration, characteristic of CRC in the context of LS.[26,28] This high MSI is also associated with a lower tumor stage[27] and younger-onset neoplasms.[29]

As previously mentioned, neoplasms that present this high MSI have been associated with the appearance of lymphocytic infiltrates, which in turn are also associated with a better prognosis.[27,28] These infiltrates have a pattern that includes nodular peri-tumoral lymphocytic reaction (termed "Chron's-like reaction," which corresponds to germ-centered lymphoid aggregates surrounded by fibrosis)[30] with mostly B lymphocytes, as well as the presence of intraepithelial lymphocytes (cytotoxic T lymphocytes).[31] This amount of tumor-associated lymphocytes will recognize abnormal antigens on tumor cells, causing their preferential lysis.[27] The greater this lymphocytic infiltration, the greater the association with a lower stage of the neoplasia, DNA repair deficiencies, high T-cell density, and mature peri and intra-tumoral dendritic cells, all of which suggest an immune response against tumor adaptation.[30] Moreover, the immune reaction to the tumor may cause enlargement of the lymph nodes, which may contribute to an increase in the number of recovered nodes and, consequently, improved CRC staging.[32]

Several studies have shown that the use of 5-fluoracil (5-FU) chemotherapy for CRC with microsatellite stability or reduced MSI improved the survival of these patients. However, this improvement has not been demonstrated in patients with high-MSI CRC, among which LS patients are included.[26] After

treatment with 5-FU, studies have shown that colon cancer patients with microsatellite stability or reduced MSI benefited from treatment with this drug, while those with high MSI presented no alterations in survival or even presented a worsened prognosis.[33] It has been shown *in vitro* that treatment of high MSI strain cancer cells with 5-FU did not present a good response: part of this drug was incorporated into the DNA, showing the possibility of recognition by the mismatch repair system. However, cells capable of performing this process were killed by 5-FU compared to cells with high MSI that were preserved.[33]

Approximately half of the CRCs present mutation of the TP53 gene, encoding the p53 protein, with a higher frequency of mutation in the rectal and distal colon neoplasms, and less frequently in proximal colon neoplasms and in neoplasms with MSI.[34] Mutations in aneuploid and non-mucinous neoplasms were also more frequently observed.[34] In most CRCs there is an allelic loss in the region of chromosome 17p that contains the p53 gene; along with mutation of the second allele, there is a bi-allelic inactivation of this gene. This leads to the loss of p53 function in CRC, which is in some studies proposed as the last step in the transition from adenoma to carcinoma, contradicting the tumor suppressive action to which the TP53 gene is associated.[34,35] Some studies have also shown that loss of the TP53 gene is associated with the degree of cellular atypia. This loss is more often found in moderately differentiated carcinomas, unlike LS neoplasms, which are poorly differentiated.[35] In LS, as the CRC has a more proximal location and is diploid neoplasms, loss of p53 function is not frequent.[35]

Discussion

In contrast to sporadic CRC, histologically, CRC in the context of LS has poor prognostic characteristics: they are poorly differentiated mucinous tumors, present a high proportion of signet ring cells, and have rapid adenoma-carcinoma progression. Despite these characteristics, survival is higher in these carcinomas than in sporadic CRC.[16,19,23,26]

One of the main features that confer longer survival for patients with CRC in LS is the fact that these tumors have high MSI (a feature not so commonly present in sporadic CRCs), although this characteristic explains the poor response of these tumors to chemotherapy with 5-FU.[26]

Through flow cytometric analysis in colorectal tumors of patients with LS, studies have shown a diploid predominance that is indicative of a better prognosis compared with sporadic carcinomas, which are often aneuploid.[36]

Another factor influencing higher survival rates in LS and CRC patients is that screening for individuals with this family history is initiated earlier. Lesions are detected and also treated earlier.[36]

It is believed that the malignant potential of carcinomas in the context of LS does not develop as fully as in cases of sporadic CRC. In LS, the DNA repair mechanism is impaired at the cellular level, causing an increased frequency of mutations. Thus, this same genetic defect responsible for initiating and assisting the tumor in its progression may also reduce the viability of tumor cells and hinder tumor proliferation.[36]

Colon cancer is often associated with mutations of different genes, whether oncogenes or tumor suppressor genes, such as the TP53 gene encoding the p53 protein. However, comparing the neoplasms that appear in the context of LS with those that appear sporadically, the latter have a much higher mutation rate of this protein: p53 is mutated in only 13% of cases of CRC in LS, thus favoring apoptosis, *versus* 48% in cases of sporadic CRC. Therefore, the ability to suppress the development of a neoplasia will be more affected in sporadic CRCs, presenting a worse prognosis.[37]

Another characteristic is the fact that CRC in LS have lymphoid aggregates surrounding the neoplasm, which indicates a host immune defense response, with survival advantage.[23]

Conclusion

Individuals with CRC in the context of LS have a longer survival when compared with those who develop sporadic CRC.

Although this longer survival may be justified by a number of factors such as tumor diploidy, its high MSI, and the presence of peri- and intra-tumoral lymphoid aggregates, it would be interesting for studies to investigate more correlations among genotype, phenotype, staging, and survival of individuals with these neoplasms in the context of this syndrome.

Moreover, given the poor response of CRC in the context of LS to 5-FU chemotherapy, further studies of other therapeutic alternatives for this neoplasia are also warranted.

Conflicts of interest

The authors declare no conflicts of interest.

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