CIRUGÍA ESPAÑOLA

www.elsevier.es/cirugia

Review article

Lynch syndrome: genetics and surgery

Manuel Ferrer Márquez, Ángel Reina Duarte, Vanesa Maturana Ibáñez, Ricardo Belda Lozano, Francisco Rubio Gil, Isabel Blesa Sierra, María del Mar Rico Morales*

Servicio de Cirugía General y del Aparato Digestivo, Hospital Torrecárdenas, Almería, Spain

ARTICLE INFORMATION

Article history:
Received January 23, 2010
Accepted June 8, 2010

Keywords:
Lynch
Colorectal cancer
Genetics
Surgery

A B S T R A C T

Hereditary nonpolyposis colorectal cancer or Lynch Syndrome, caused by germinal mutations in mismatch deoxyribonucleic acid (DNA) repair genes, is the most common form of hereditary colorectal cancer. The identification of these individuals is not easy and is based on clinical and molecular criteria. A review is presented on the genetics and diagnosis in Lynch Syndrome, as well as on its surgical management and prevention

Síndrome de Lynch: genética y cirugía

Palabras clave:
Lynch
Cáncer colorrectal
Genética
Cirugía

R E S U M E N

El cáncer colorrectal hereditario no polipósico o síndrome de Lynch, causado por mutaciones germinales en genes reparadores de bases desapareadas de ácido desoxirribonucleico (ADN), es la forma más frecuente de cáncer colorrectal hereditario. La identificación de estos individuos no es fácil y se basa en criterios clínicos y moleculares. Se expone a continuación una revisión sobre genética y diagnóstico en el síndrome de Lynch, así como sobre su manejo quirúrgico y prevención.

Introduction

Eighty per cent of colorectal cancers are sporadic, 10% are familial and the remaining 5%-10% are hereditary.[1] The most common hereditary colorectal cancers are familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC)[2] (Figure 1). The name Lynch Syndrome is preferred for families that have mutation in one of the DNA mismatch repair (MMR) genes. The main characteristics of Lynch Syndrome are that colorectal cancer

*Corresponding author.
E-mail address: manuferrer78@hotmail.com (M. Ferrer Márquez).

0009-739X/$ - see front matter

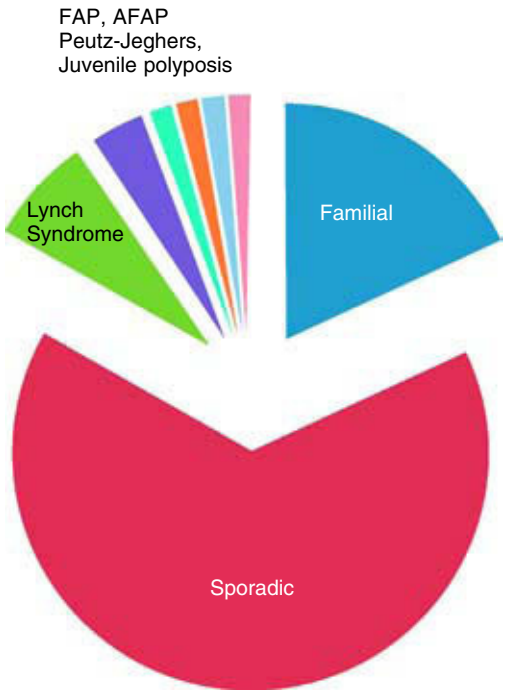

Figure 1 –Syndromes in which colorectal cancer can appear.

develops at an early age (around 45 years old), is likely to be right-sided for more than 70% of cases, increases the incidence of synchronous and metachronous tumours, presents high carcinogen levels, and an increased risk of extracolonic neoplasia (endometrium, ovary, gastric system, urinary tract, small intestine, brain, hepatobiliary system).[3]

It is an autosomal dominant disorder, caused by MMR genes, mainly *MSH2* and *MLH1* (90% of all genes) and less often by *MSH6* and *PMS2*.[2]

One of the main challenges in clinical practice is to identify MMR carriers so that colorectal cancer can be prevented through genetic counselling.[4]

Methods

This article has been prepared based on a literature review of relevant Lynch Syndrome-related articles. All articles were found using a bibliographic search on the MEDLINE database, using the following key words: 'Lynch Syndrome', 'Nonpolyposis Colorectal Cancer', 'Mismatch Repair Gene', 'Diagnosis', 'Management' and 'Screening'. Articles from September 1992 until March 2010 were included.

Genetics and diagnosis

Conceptually, three possible strategies can be used to identify Lynch Syndrome patients: 1) using clinical criteria; 2) using molecular techniques: microsatellite instability (MSI) and immunohistochemistry (IHC) testing; or 3) a combination of both.

Different criteria have been developed to identify Lynch Syndrome families. The Amsterdam I criteria,[5] (Table 1) published in 1991, were pivotal in establishing a definition of Lynch Syndrome, allowing its genetic base to be identified. These criteria only considered the risk of colorectal cancer. However, the Amsterdam II criteria,[6] published in 1999, included related extracolonic tumours. Given the low sensitivity of the Amsterdam criteria, and having found Lynch Syndrome's genetic base, the recently revised Bethesda criteria were designed[7] with the aim of identifying colorectal cancer patients. A molecular study of the tumour is performed on these patients to identify DNA-repair deficiencies (MSI testing) or loss of protein expression in the relevant mutation gene (IHC testing) suggesting that a germinal mutation is present. The criteria include family history, age at diagnosis, and the pathologic characteristics that are suggestive of tumour microsatellite instability (Table 1).

As well as the criteria mentioned above, several predictive models have recently been developed to determine the MMR gene mutation carrier status (Barneston,[8] PREMM,[9] and MMRpro[10] models).

Table 1 – Revised Amsterdam and Bethesda Criteria

Amsterdam I Criteria
There are at least three relatives with colorectal cancer, and should meet the following criteria:
One affected person is a first-degree relative of the other two.
At least two successive generations are affected.
At least one person was diagnosed with colorectal cancer before the age of 50 years.
Familial adenomatous polyposis has been excluded.
Revised Bethesda guidelines for MSI testing
Tumours from any of the following should be tested for MSI:
Individuals with colorectal cancer diagnosed at age <50 years.
Individuals with synchronous, metachronous colorectal cancer or other HNCPP-associated tumours, regardless of age.
Individuals with colorectal cancer with MSI-H, histologically diagnosed at age <50 years of age.
Colorectal cancer diagnosed in one or various first-degree relatives with HNCPP or related tumours at age <50 years.
Colorectal cancer in one or more first- or second-degree relatives, regardless of age.

DNA damages continuously and spontaneously occur in all of the body's cells, during replication in cell division, and as a reaction to agents in the environment. The main alteration in Lynch Syndrome development is the presence of mutations that affect the germline of a given group of genes that is very important for maintaining genome stability (*MSH2*, *MLH1*, *MSH6* and *PMS2* are among the most important). These genes codify proteins involved in recognising mutations in base pairing and mismatch repair to prevent mutations developing. Mutations in this system generate microsatellite instability, representing an authentic genomic instability marker that is found in 90% of HNPCC cases and 15% of sporadic cases.[3] Microsatellites are very short DNA segments (usually between 1 and 5 nucleotides long) which repeat in a row along the genome. Loss of genomic stability seems to be a key process which occurs in the first stages of carcinogenesis. DNA is extracted from the patient's colorectal tumour and healthy tissue to study microsatellite instability. MSI refers to the microsatellite repeat patterns observed when comparing the tumours' amplified DNA with the normal adjacent tissue. Establishing the MSI condition can sometimes be very imprecise. This is mainly because there is not a single criterion with regards the number of loci that must be analysed to diagnose MSI and the proportion of unstable markers that must be considered for MSI classification. In 1997, 5 MSI markers were proposed for this purpose (BAT-25, BAT-26, D2S123, D5S346, D17S250).[11] In compliance with the international criteria, MSI is considered to be high frequency (MSI-H) if 2 or more recommended markers in a row present mutations. MSI is considered low frequency (MSI-L) when a single marker is unstable, and MSI stable (MSI-S) when none of the markers exhibit changes in the sequence length. Some authors[11] believe that there are no pathologic or clinical differences between colorectal tumours with MSI-L and MSI-S. MSI-H tumours represent 15% of colorectal cancers and are predominantly located in the proximal colon, have unique histopathological characteristics and are associated with a less aggressive clinical development.[12,13]

MSI analysis methods vary greatly. Single-strand conformation polymorphism (SSCP) is one of the most used as it is simple and versatile. It is based on the relationship between the electrophoretic mobility of a single-stranded DNA segment and its folded conformation, which in turn depends closely on the nucleotide sequence or the segment size.

Some institutions have introduced MSI testing as a form of initial colorectal cancer screening for diagnosed patients under 50 years, or patients with histological characteristics suggestive of MMR gene mutations. Patients with MSI-H are referred for a molecular genetic study.[14]

Occasionally families fulfil the Amsterdam I criteria, but do not show any evidence of MSI or repair gene mutation, i.e. tumours are microsatellite-stable. Lindor et al name these families "familial colorectal cancer type X".[15]

IHC is another technique employed to diagnose HNCPP. It can either accompany MSI testing or replace it.[16] Loss of MMR proteins can be observed in Lynch Syndrome tumours (*MLH1* 50%, *MSH2* 39%, *MSH6* 7%, and *PMS2* <4%). Loss of *MLH1* expression can generally be associated with the secondary loss of *PMS2* expression. Similarly, loss of *MSH2* can often be associated with the loss of *MSH6*. However, isolated loss of *MSH6* or *PMS2* expression, which indicate these gene mutations, are rare and isolated.[13,17] Internal positive controls (stroma, lymphocytes) are used in IHC testing to determine that the absence of expression in a tumour is not due to a technical problem. Loss of expression is considered when IHC staining is not observed in any of the neoplastic cells. Results should determine the presence or absence of expression of each of the proteins. They must be considered unassessable if no suitable internal controls are obtained. Most patients with germinal mutations display the results shown in Table 2 for IHC testing, although false positives and false negatives may also appear. As an initial method, IHC has the advantage of being a simple and cost-effective technique. It is also able to identify the unexpressed protein, and as such the mutated gene. Several studies have shown that when using this technique for *MLH1*, *MSH2*, *PMS2* and *MSH6,* Lynch Syndrome diagnosis sensitivity is similar to that of MSI, with values over 90%.[16,18]

Table 2 – Results from immunohistochemistry test, based of germinal mutation

	Protein (– absent +present)			
Germinal mutation in:	MLH1	MSH2	MSH6	PMS2
MLH1	–	+	+	–
MSH2	+	–	–	+
MSH6	+	+	–	+
PMS2	–	–	–	–

Microsatellite instability and loss of *MLH1* expression also occurs in 10%-15% of sporadic colorectal cancers as a result of promoter hypermethylation of this gene. In order to exclude this possibility before carrying out germline *MLH1* mutational analysis, it is useful to analyse whether the BRAF V600E mutation is present in the tumour, given that this mutation is associated with *MLH1* promoter hypermethylation. The BRAF mutation test can therefore be added to the genetic testing algorithm for Lynch Syndrome before conducting the genetic study.[19]

Once identified by means of clinical criteria, and using different molecular studies (MSI, IHC, BRAF), the genetic analysis can continue to confirm Lynch Syndrome diagnosis. Peripheral blood lymphocytes DNA is examined for the germline analysis (Figure 2).[3,20]

The European Expert Group recommends the following to improve hereditary colorectal cancer diagnosis: public information campaigns; complete family study recommended for previously diagnosed patients, with the number of family members affected, type of neoplasia and age at diagnosis; reference guides with specialised genetics centres, and guides with information about familial colorectal cancer and follow-up recommendations; consider MSI or IHC testing in colorectal cancer patients regardless of age at diagnosis with appropriate counselling.[21]

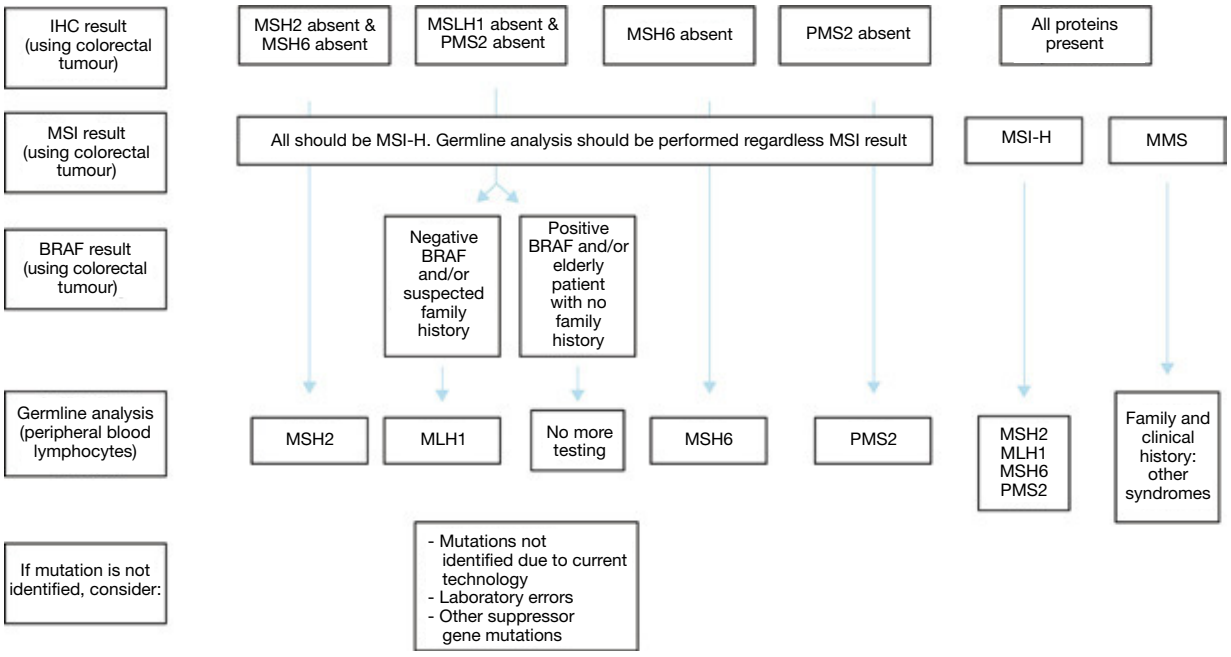

Figure 2 – Lynch Syndrome genetic algorithm.

Screening

Once Lynch Syndrome has been diagnosed, it should be treated and screened considering the natural history of the syndrome. Colon cancer screening plays an important role, and several studies show how colonoscopy surveillance can benefit these patients.

In a study on HNCPP families, Järvinen et al show that the incidence of invasive colorectal cancer decreased by 63% for asymptomatic patients who underwent colonoscopy surveillance compared with those families that were not screened.[22] Furthermore, mortality decreased for patients who underwent screening and colonoscopy, compared to those who did not.[23] Based on evidence, Lindor et al recommend closely monitoring Lynch Syndrome patients with colonoscopy every 1-2 years, starting at 20-25 years old (or at 30 years for *MSH6* families).[24]

Many families fulfil the Amsterdam criteria but have negative MSI and IHC test results. Less regular screening is recommended for these patients, a colonoscopy every 3-5 years, starting at 45 years, or every 5-10 years before the age of the youngest family member diagnosed with colorectal cancer.[25]

The second most frequent cancer after colorectal cancer observed in Lynch Syndrome patients is endometrial carcinoma (40%-60% for women with mutation), then ovarian cancer (12%-15% of women with mutation). Lindor et al recommend transvaginal ultrasound and an annual smear test, starting at 30-35 years.[24]

Studies on screening for extracolonic cancers are limited. European and North-American expert groups recommend: urinalysis with cytology every 1-2 years, starting at 30-35 years for patients with family history of urinary tract neoplasm; gastroscopy every 1-2 years from 30-35 years for those patients with family history of gastric cancer and people that live in towns where there is a high incidence of gastric neoplasm.[3,24]

Surgical treatment, surveillance

Patients who have been diagnosed with Lynch Syndrome and have developed colorectal cancer should firstly undergo a complete colonoscopy, as they present a high risk of developing a synchronous tumour. Risk of metachronous cancer should be considered when choosing which surgical technique should be adopted, which is 16% at 10 years in some studies.[26] Extension of the resection has also been much debated during recent years.[3,27] Although no controlled studies have been conducted, most experts champion subtotal colectomy with ileo-rectal anastomosis.[3] De Von tot Nederveen Cappel et al compare segmental colectomy resection with subtotal colectomy in colorectal cancer patients diagnosed with Lynch Syndrome. The study identified an increase in life expectancy of 2.3 years in young patients (<47 years) who underwent subtotal colectomy. There are limitations in this study because the data are not adjusted to quality of life, but the authors suggest that subtotal resection could improve patients' quality of life by reducing the need for periodic colonoscopies, and by reducing concerns of a second neoplasm developing.[28] A recent study that compares extended colectomy with limited resections performed on Lynch Syndrome patients does not show any

survival differences between the two groups. It does however recommend subtotal colectomy, as the group that underwent limited resection had a higher risk of developing a second colorectal cancer, and which therefore increased the amount of subsequent abdominal surgery.[27] Patient age is also a factor that must be considered when choosing a surgical technique. Older patients have a lower risk of developing a second neoplasm, but when using a more aggressive technique (subtotal colectomy) they have higher morbidity and mortality.[29] The patient should therefore be informed of the different technical possibilities, and the risks associated with each intervention. A decision should therefore be taken based on the patient factors and his or her preferences, with special focus on his or her age and ability to be monitored closely.[30,31]

Patients that undergo limited resections should be closely monitored using colonoscopies. Extensive resections (subtotal colectomy), should undergo periodic proctoscopic examinations, which are less invasive.[27]

Prophylaxis

Secondly, the doctor must decide what therapeutic option should be used for Lynch Syndrome patients who have not developed colorectal cancer. Prophylactic surgery avoids close endoscopic surveillance. The types of prophylactic surgery available would be subtotal colectomy with ileo-rectal anastomosis and proctocolectomy. Post-surgical surveillance is required for subtotal colectomy by means of rectoscopy as the patient might develop metachronous rectal cancer. While most colorectal cancers for Lynch Syndrome patients develop on the right side of the colon, risk of rectal cancer is estimated to be from 11%.[32] No studies have recommended practice of prophylactic surgery. However, authors who argue for this type of surgery are supported by the fact that there is an 80% risk of HNCPP patients developing colorectal cancer sometime during their lifetime. However, according to recent studies, penetrance of Lynch Syndrome seems to be less than 80%[33] and possibly reduces in older patients.[34] Prophylactic surgery would mean that surgery is performed on a group of patients that is not going to develop colorectal cancer during their lifetime, with the operative morbidity and mortality risk that is entailed. More prospective studies would be necessary to estimate the penetrance of colorectal cancer depending on the age of Lynch Syndrome patients and to assess the benefits of prophylactic surgery.

Prophylactic surgery is also used for gynaecological neoplasia. The best evidence of this is from a retrospective study of 315 women with mutations in DNA mismatch repair genes, 61 of which underwent prophylactic surgery. During 10-year surveillance, none of the patients who had undergone prophylactic surgery developed ovarian or endometrial cancer, while in the other group 33% developed endometrial cancer and 5.5% ovarian cancer. These data suggest that prophylactic hysterectomy and oophorectomy can be a reasonable option for Lynch Syndrome patients who have already had children, discussing the risks, benefits and limitations related to the procedure.[24]

Different studies have shown how non-steroidal anti-inflammatories and aspirin effectively reduce the incidence of sporadic adenomatous colorectal polyps and cancer. However, their efficiency for Lynch Syndrome patients is still unknown.[24] Oral contraceptives have shown to reduce the risk of ovarian and endometrial cancer in the general public, but there is no data to suggest the benefit in extracolonic cancers in Lynch Syndrome patients. The effect that chemotherapy has on MSI-H and HNCPP patients has been reported in very few studies, yet many show that these patients do not benefit from 5-FU treatment. To date, there is not enough evidence regarding chemotherapy use, meaning that controlled and prospective studies should be conducted for future recommendations.[3,24]

Genetic counselling

Genetic counselling is a process that provides the patient and his or her family members with information about the risk of developing or transmitting a given genetic susceptibility to developing a neoplasm. The patient or family is also informed about molecular diagnosis testing to prevent it or diagnose it early.[35]

We should consider the patient's and the family's emotional state, as they generally require psychological support. A detailed and focused session needs at least 60-90 minutes. Using experienced genetic counsellors during the Lynch Syndrome family counselling session, allows the specialist to use his or her time more efficiently, being able to focus on the clinical treatment.[13] That is why, patient(s) and/or families with clinically suspected Lynch Syndrome should be referred to a hereditary cancer unit or genetic counselling to assess their situation.[36]

The genetic counselling process assesses the personal and family risk to hereditary susceptibility to cancer by completing an extensive medical history regarding personal and family events. Risk assessment quality will depend on this family history.

Conflict of interest

The authors affirm that they have no conflict of interest.

REFERENCES

1. Lynch HT, Watson P, Smyrk TC, Lanspa SJ, Boman BM, Boland CR, et al. Colon cancer genetics. Cancer. 1992;70 (Suppl 5):1300-12.
2. Lynch HT, De la Chapelle A. Hereditary colorectal cancer. N Engl J Med. 2003;348:919-32.
3. Al-Sukhni W, Aronson M, Gallinger S. Hereditary colorectal cancer syndromes: Familiar adenomatous polyposis and Lynch syndrome. Surg Clin N Am. 2008;88:819-44.
4. Quispe I, Balmaña J. Desarrollo y aplicación de modelos predictivos en el síndrome de Lynch. Med Clin. 2010;134: 412-7.
5. Vasen HF, Mecklin JP, Khan PM, Lynch HT. The International Collaborative Group on Hereditary Non-Polyposis Colorectal Cancer (ICG-HNPCC). Dis Colon Rectum. 1991; 34:424-5.
6. Vasen HF, Watson P, Mecklin JP, Lynch HT. New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative group on HNPCC. Gastroenterology. 1999;116: 1453-6.
7. Umar A, Boland CR, Terdiman JP, Syngal S, De la Chapelle A, Rüschoff J, et al. Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. J Natl Cancer Inst. 2004;96: 261-8.
8. Barnetson RA, Tenesa A, Farrington SM, Nicholl ID, Cetnarskyj R, Porteous ME, et al. Identification and survival of carriers of mutations in DNA mismatch-repair genes in colon cancer. N Engl J Med. 2006;354:2751-63.
9. Balmaña J, Stockwell DH, Steyerberg EW, Stoffel EM, Deffenbaugh AM, Reid JE, et al. Prediction of MLH1 and MSH2 mutations in Lynch syndrome. JAMA. 2006;296: 1469-78.
10. Chen S, Wang W, Lee S, Nafa K, Lee J, Romans K, et al. Prediction of germline mutations and cancer risk in the Lynch syndrome. JAMA. 2006;296:1479-87.
11. Boland CR, Thibodeau SN, Hamilton SR, Sidransky D, Eshleman JR, Burt RW, et al. A National Cancer Institute workshop on microsatellite instability for cancer detection and familial predisposition: development of international criteria for the determination of microsatellite instability in colorectal cancer. Cancer Res. 1998;58:5248-57.
12. Rudzki Z, Zazula M, Okon K, Stachura J. Low-level microsatellite instability colorectal carcinomas: do they really belong to a "gray zone" between high-level microsatellite instability and microsatellite-stable cancers? Int J Colorectal Dis. 2003;18:216-21.
13. Lynch HT, Lynch PM, Lanspa SJ, Snyder CL, Lynch JF, Boland CR. Review of the lynch syndrome: history, molecular genetics, screening, differential diagnosis, and medicolegal ramifications. Clin Genet. 2009;76:1-18.
14. Gruber SB. New developments in Lynch Syndrome (hereditary nonpoliposis colorectal cancer) and mismatch repair gene testing. Gastrenterology. 2006;130:577-87.
15. Lindor NM, Rabe K, Petersen GM, Haile R, Casey G, Baron J, et al. Lower cancer incidence in Amsterdam-I criteria families without mismatch repair deficiency: familial colorectal cancer type X. JAMA. 2005;293:1979-85.
16. Lindor NM, Burgart LJ, Leontovich O, Goldberg RM, Cunningham JM, Sargent DJ, et al. Immunohistochemistry versus MSI testing in phenotyping colorectal tumors. J Clin Oncol. 2002;20:1043-8.
17. Boland CR, Koi M, Chang DK, Carethers JM. The biochemical basis of microsatellite instability and abnormal immunohistochemistry and clinical behavior in Lynch syndrome: from bench to bedside. Fam Cancer. 2008;7:41-52.
18. Piñol V, Castells A, Andreu M, et al, Gastrointestinal Oncology Group of the Spanish Gastroenterological Association. Accuracy of revised Bethesda guidelines, microsatellite instability, and immunohistochemistry for the identification of patients with hereditary nonpolyposis colorectal cancer. JAMA. 2005;293:1986-94.
19. Loughrey MB, Waring PM, Tan A, Trivett M, Kovalenko S, Beshay V, et al. Incorporation of somatic BRAF mutation testing into an algorithm for the investigation of hereditary non-polyposis colorectal cancer. Fam Cancer. 2007;6:301-10.
20. Trano G, Sjursen W, Wasmuth HH, Hofsli E, Vatten LJ. Performance of clinical guidelines compared with molecular tumour screening methods in identifying possible Lynch syndrome among colorectal cancer patients: a Norwegian population-based study. Br J Cancer. 2010;102:482-8.
21. Vasen HF, Möslein G, Alonso A, Aretz S, Bernstein I, Bertario L, et al. Recommendations to improve identification of hereditary and familiar colorectal cancer in Europe. Fam Cancer. 2010;92:109-15.
22. Järvinen HJ, Mecklin JP, Sistonen P. Screening reduces colorectal cancer rate in families with hereditary nonpolyposis colorectal cancer. Gastroenterology. 1995;108:1405-11.
23. Järvinen HJ, Aarnio M, Mustonen H, Aktan-Collan K, Aaltonen LA, Peltomäki P, et al. Controlled 15-year trial on screening for colorectal cancer in families with hereditary nonpolyposis colorectal cancer. Gastroenterology. 2000;118:829-34.
24. Lindor NM, Petersen GM, Hadley DW. Recommendations for the care of individuals with an inherited predisposition to Lynch syndrome: A systematic review. JAMA. 2006;296: 1507-17.
25. Vasen HF, Möslein G, Alonso A. Guidelines for the clinical management of Lynch syndrome (hereditary non-polyposis cancer). J Med Genet. 2007;44:353-62.
26. De Vos tot Nederveen Cappel WH, Nagengast FM, Griffioen G, Menko FH, Taal BG, Kleibeuker JH, et al. Surveillance for hereditary nonpolyposis colorectal cancer: a long-term study on 114 families. Dis Colon Rectum. 2002;45:1588-94.
27. Natarajan N, Watson P, Silva-López E, Lynch HT. Comparison of extended colectomy and limited resection in patients with Lynch syndrome. Dis Colon Rectum. 2010;53:77-82.
28. De Vos tot Nederveen Cappel WH, Buskens E, Van Duijvendijk P, Cats A, Menko FH, Griffioen G, et al. Decision analysis in the surgical treatment of colorectal cancer due to a mismatch repair gene defect. Gut. 2003;52:1752-5.
29. Álvaro E, Perea J, Lomas M, Urioste M, Hidalgo M. Influencia de la edad en el tratamiento quirúrgico del síndrome de Lynch. Cir Esp. 2010;88:338-40.
30. Perea J, Justo I, Álvaro E, Lomas M, Tasende JD, Marín JC, et al. Surgical management of hereditary colorectal cancer: surgery based on molecular analysis and family history. Rev Esp Enferm Dig. 2009;101:536-40.
31. Maeda T, Cannom RR, Beart RW, Etzioni DA. Decision model of segmental compared with total abdominal colectomy for colon cancer in hereditary nonpolyposis colorectal cancer. J Clin Oncol. 2010;28:1175-80.
32. Alarcón F, Lasset C, Carayol J, Bonadona V, Perdry H, Desseigne F, et al. Estimating cancer risk in HNPCC by the GRL method. Eur J Hum Genet. 2007;15:831-6.

33. Jenkins MA, Baglietto L, Dowty JG, Van Vliet CM, Smith L, Mead LJ, et al. Cancer risks for mismatch repair gene mutation carriers: a population-based early onset case-family study. Clin Gastroenterol Hepatol. 2006;4:489-98.
34. Schmeler KM, Lynch HT, Chen LM, Munsell MF, Soliman PT, Clark MB, et al. Prophylactic surgery to reduce the risk of gynecologic cancers in the Lynch syndrome. N Engl J Med. 2006;354:261-9.
35. Lynch HT, Lynch JF, Attard TA. Diagnosis and management of hereditary colorectal cancer syndromes: Lynch syndrome as a model. CMAJ. 2009;181:273-380.
36. Mc Cann S, MacAuley D, Barnett Y, Bunting B, Bradley A, Jeffers L, et al. Family communication, genetic testing and colonoscopy screening in hereditary non-polyposis colon cancer: a qualitative study. Psycho-oncology. 2009;18: 1208-15.