Extent of surgery in Lynch syndrome: limited resection or take out the whole thing?

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INTRODUCTION

- Nearly 5% of colorectal cancers are related to constitutional genetic abnormalities.
- In Lynch Syndrome (LS), the abnormality is a mutation of the deoxyribonucleic acid (DNA) repair system.

INTRODUCTION

- From a classification standpoint, the two terms LS and HNPCC were formerly used synonymously Currently identify two distinct entities.
- LS is defined molecularly by the finding of an authenticated genetic mutation.
- HNPCC syndrome is defined clinically as patients who present clinically with Amsterdam II or I criteria without a genetic mutation that has been identified to date.
- Finally, the term "LS-like" corresponds to the families of patients with a MMR system abnormality without mutation identified to date.

INTRODUCTION

- Different spectra of disease are associated with LS.
- The narrow spectrum includes cancers with a high relative risk: colorectal cancer (CRC), endometrial cancer, urinary tract cancers and small intestinal cancer.
- The broader spectrum includes ovarian tumors, glioblastoma, cutaneous tumors (keratoacanthomas and sebaceous tumors), biliary duct tumors, and gastric tumors.

INTRODUCTION

- The clinical diagnosis of LS was initially based on the Amsterdam I and II Criteria published
- in the 1990s and subsequently on the revised Bethesda Criteria, which expanded the criteria and identified patients who should be screened for LS.
- For patients with LS, learned societies recommend early and regular endoscopic screening because of the high incidence of CRC, i.e., every one to two years from the age of 25 and then annually from the age of 40 or starting 10 years before the age of appearance of the youngest case of CRC in the family.

INTRODUCTION

- Professional recommendations on prophylactic surgery to prevent cancers in patients with genetic predisposition were published in 2009.
- There is no formal indication for prophylactic colectomy in LS.
- Numerous advances have been made in the understanding of LS, allowing a better knowledge of the prevalence of CRCs and associated cancers, with better endoscopic monitoring and a decrease in the prevalence and mortality of CRC.

In whom should one suspect Lynch Syndrome?

- The clinical diagnosis of LS was initially based on clinical criteria (Amsterdam I and II criteria) published in the 1990s
- The Amsterdam criteria are the presence of CRC (Amsterdam 1) or narrow spectrum (Amsterdam 2) in three first-degree relatives over two generations, including at least one case occurring before 50 years of age. These criteria lacked sensitivity despite good specificity, leading to their revision as the Bethesda Criteria, which broadened the criteria and identified patients who should be screened for LS.
- However, these criteria are insufficient since nearly one in three patients with LS would remain undiagnosed
- Thus, among the patients carrying a mutation of the MMR system, only 40% present with these Amsterdam criteria.
- Conversely, only 50 to 60% of patients with Amsterdam criteria will carry a mutation.

How to diagnose Lynch Syndrome?

- The diagnosis of LS is based on the detection of the deficiency of the MMR system in CRC tumor tissue, expressed either by the MSI phenotype, by molecular biology, or by the loss of expression of one of the four proteins of the MMR system by immunohistochemical study.
- This MMR immuno-phenotyping makes it possible to orient the molecular diagnosis towards a specific gene.
- Recommendations are to use a single method when suspicion is low but to do both immunohistochemistry and molecular biology techniques when there is strong suspicion.
- If both techniques are normal, LS is virtually eliminated.

Characteristics

- *Microsatellite instability leads to the activation of oncogenes and the inactivation of tumor suppressor genes and results in accelerated carcinogenesis.*
- *Compared with sporadic CRC, LS-associated CRC is characterized by: early age (20 years younger on average); a localization in the right colon; a stage with less locally-advanced stage at diagnosis (25% stage I and 40% stage II); less distant metastasis (5%); more favorable histological features (poorly-differentiated, mucinous component, strong T-cell infiltration, "Crohn-like" type); better survival after surgical resection; but poorer sensitivity to 5-FU.*
- *The decreased sensitivity to 5-FU seems to be canceled by the addition of oxaliplatin, particularly in stages III.*

Role of Endoscopy

- *In consideration of the high incidence of CRC in LS patients*
- *learned societies recommend early and regular endoscopic screening, i.e., every one to two years from the age of 25 onward and then annually from age 40, or starting 10 years before the age of appearance of CRC in the youngest patient in the family.*
- *Compared with no surveillance, a program of endoscopic screening increases the detection of adenoma (Odds Ratio (OR) = 3.81) while decreasing the prevalence of CRC (OR = 0.23), of metastatic CRC synchronous (OR = 0.28) and of CRC-related mortality (OR = 0.06).*

Role of Endoscopy

- *Upper endoscopic surveillance of the esophagus, stomach and duodenum is also proposed because of the risk of gastric cancer (wide spectrum).*
- *Recent ASCO/ESMO recommendations support testing for and eradication of Helicobacter pylori.*
- *In populations with high incidence of gastric cancer, endoscopic monitoring is recommended every one to three years.*
- *Upper endoscopy should include careful examination of the distal duodenum and the ampulla of Vater.*

Place of prophylactic surgical treatment in Lynch Syndrome

- ***In 2009, a professional recommendations on the prophylactic cancer preventing surgery in patients with a genetic predisposition was published, which are still current.***
- ***In theory, there are three types of prophylactic surgery for LS.***

1. Primary prophylactic surgery

- There are no formal indications for prophylactic colorectal surgery in LS.
- this corresponds to the excision of an organ that is cancer-free organ
- Prophylactic colorectal surgery is not recommended when the patient is free from colonic lesions because endoscopic management reduces the risk of death by 70%.
- the benefit of a total carcinological colectomy at the age of 25 would increase survival by 1.8 years compared with endoscopic surveillance.

1. Primary prophylactic surgery

- This primary prophylactic surgery could be considered in some families with LS, with high penetrance and an early age of CRC.
- Primary prophylactic colon surgery can be proposed for LS patients with endometrial cancer (EC) requiring a hysterectomy
- There is however very little data on this specific point and on the extent of the colonic resection.

2. Secondary prophylactic surgery

- The majority of surgical indications for LS are therefore based on the treatment of either a CRC or of an endoscopically-unresectable dysplasia or adenoma.
- Either segmental or total colectomy can be proposed depending on the location of the lesion.
- For rectal lesions, a proctectomy with or without sphincter preservation or a total coloproctectomy can be discussed.

2. Secondary prophylactic surgery

- In addition to location, the choice of the technique must take into account patient factors (age, co-morbidities, personal choice), the morbidity of the gesture, the functional sequelae engendered, the impact on the quality of life, and, finally, the risk of developing a metachronous lesion.
- These considerations are necessary in order to provide patients with the most complete enlightened information.
- This decision can be difficult to make because the certainty of the diagnosis of LS is not always known at the time of surgery.

3. Tertiary prophylactic surgery

- This concerns patients who have undergone segmental colonic or rectal resection with the diagnosis of LS made post-operatively.
- The prophylactic strategy is based either on endoscopic surveillance or on the extension of surgical resection

What type of surgical resection?

1. ***Lynch Syndrome with Rectal Cancer (RC)***

   a. About 20-30% of patients with LS will develop RC, including 15% as an initial presentation

   b. The American Society of Colon and Rectal Surgeons (ASCRS) recommends treatment of the rectal lesion alone, in the absence of other synchronous colon cancer localizations (level of recommendation: grade 2C)

   c,. This strategy is all the more justified if a neo-adjuvant treatment is indicated

2. Lynch syndrome with colon cancer (CC)

1. *The recent recommendations of the ASCRS call for a total colectomy (TC)*

(evidence grade 1B) because of the higher risk of metachronous CC .

2. *However, the ASCRS also recognizes a role for the segmental colectomy (SC) disease in view of the sequelae of TC (evidence grade 2C).*

Key points

1. Lynch syndrome (LS) is linked to a constitutional mutation of one of the genes involved in the repair of replication errors of DNA repair (MMR: mismatch repair): MLH1, MSH2, MSH6, PMS2 or a deletion of the 3'end of the EPCAM gene leading to the inactivation of MSH2

2. Clinical Diagnosis of Lynch Syndrome is based on Amsterdam II and Bethesda Criteria

3. Colorectal tumors that develop in patients with LS are not very sensitive to 5FU. This lack of sensitivity seems to be canceled by the addition of oxaliplatin, in stage III.

Key points

4. Early and regular endoscopic screening is recommended, i.e., every one to two years starting at the age of 25, then annually starting at age 40 or starting 10 years before the age of appearance of the youngest case of cancer colorectal in the family

5. There is no formal indication for primary colorectal prophylaxis surgery in LS

Conclusion

- unless the LS shows significant penetration in the family as evidenced by many CRCs, by a young age of first CRC, or unless the patient is unlikely to comply with a programmed endoscopic surveillance, and if there is no other indication for extended colectomy, the decision to perform a SC vs. TC should be made on a case-by-case basis, having fully informed the patient of the operative and functional risks as well as the risk of developing a metachronous lesion.
- Whatever the resection performed, an annual post-operative colorectal endoscopic monitoring is imperative, as well as gynecological surveillance according to the recommendations.
- prophylactic surgery eliminates any risk of EC and ovarian cancer.
- This surgery can be offered to any LS patient with proven mutations or high risk, once desired childbearing years are past, at 40 -45 years. This decision must be validated in a multi-specialty consultation; the patient must be informed that this will result in menopause and possible hormone replacement therapy.

Thank you