Hereditary nonpolyposis colorectal cancer

Ravn Leonard Pater

Clarification of terms.

- The terms HNPCC and Lynch syndrome are often used interchangeably in clinical practice, but the following distinction is preferred in the literature:

- HNPCC syndrome: fulfilment of the anamnestic criteria without the necessary proof of a germline mutation.
- Lynch syndrome: HNPCC in which a germline mutation of the described genes could be clearly detected.
- Source: Pox et al.: S3-Leitlinie Kolorektales Karzinom. Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (DGVS). Stand: 14. Juni 2013.
- **For the sake of simplicity, only the term HNPCC is used in the following.**

HNPCC, is only the colon affected?

- In general, people who have been diagnosed with HNPCC have an increased lifetime risk of various cancers, including those of the colon, stomach, genitourinary tract, small intestine, bile ducts, CNS and skin.
- Female individuals also have a significantly increased lifetime risk of endometrial and ovarian cancer. However, the exact lifetime risk depends on the underlying genetic defect.

- One HNPCC variant is Muir-Torre syndrome (MRTES), in which sebaceous gland adenomas and keratoacanthomas also occur.

Who has an increased risk?

- Individuals from families that fulfil the Amsterdam criteria or one of the Bethesda criteria with evidence of microsatellite instability (MSI) and their relatives who can be considered mutation carriers on the basis of inheritance are at risk for HNPCC.
- Source: S3-Leitlinie Kolorektales Karzinom Langversion 2.1. – Januar 2019 AWMF-Registernummer: 021/007OL

Amsterdam criteria

- The Amsterdam I criteria are distinguished from the Amsterdam II criteria. The latter are a further development and also take into account carcinomas associated with HNPCC, but otherwise do not differ from the Amsterdam I criteria.
- If all points of the Amsterdam criteria apply, there is a high suspicion of the presence of an HNPCC syndrome! If, despite a suspicion, not all Amsterdam criteria apply, the Bethesda criteria are used.

Amsterdam II criteria

- 1. at least three family members with colorectal carcinoma or HNPCC-associated carcinoma.
- 2. at least two consecutive generations of people with the disease.
- 3. one of the sufferers is a first-degree relative of the other two
- 4. at least one of the patients must be younger than 50 years of age
- 5. exclusion of familial adenomatous polyposis (FAP).

Revised Bethesda criteria:
Less specific than the Amsterdam criteria, but more sensitive.

- Patients who fulfil at least one criterion should be examined molecularly.
- 1. diagnosis of colorectal carcinoma before the age of 50 years
- 2. diagnosis of syn- or metachronous colorectal or other HNPCC-associated tumours (regardless of age at diagnosis)
- 3. diagnosis of colorectal cancer before the age of 60 with typical histology of an MSI-H tumour
- 4. diagnosis of colorectal cancer (regardless of age) and at least one first-degree relative with an HNPCC-associated tumour before 50 years of age
- 5. diagnosis of colorectal carcinoma (regardless of age) and at least two first or second degree relatives with an HNPCC-associated tumour (regardless of age).

Molecular genetic diagnostics

In case of positive Amsterdam or Bethesda criteria, the following molecular genetic investigations are indicated:

- Examination of tumor tissue (biopsy or resectate).
    - Immunohistochemical staining of DNA repair proteins
        - In case of mutation in one of the DNA-repair genes (MSH2, MLH1, MSH6, PMS2), the corresponding proteins are missing and therefore cannot be stained.
        - In case of loss of MLH1: additional examination for mutation in BRAF-V600 protooncogene, which mutates in non-hereditary colorectal carcinomas and may be associated with loss of MLH1 → presence of BRAF-V600 mutation argues against hereditary colon carcinoma.

    If necessary, search for microsatellite instability (MSI) by PCR (indirect indication of defective DNA repair genes).

    If a mutation is detected in the tumor tissue, testing for a germline mutation is required

        - Mutation analysis of the DNA-repair genes (MLH1, MSH2, MSH6, PMS2) by sequencing from patient's blood sample
        - Detected germline mutations can then be specifically searched for in relatives

MMR DNA mismatch repair proteins

- DNA mismatch repair proteins are proteins in almost all living organisms that can recognize and excise a mismatch in DNA double strands. The repair process is completed by normal enzymes also used in replication.
- The MMR proteins are divided into two groups MutS and MutL, each responsible for recognition and incision of the incorrect base. The following excision is accomplished by a special exonuclease. The processes are generally a part of DNA repair.
- In humans, five MutS homologs and three MutL homologs are known. Mutations in the coding genes are among others the **cause of hereditary colorectal cancer susceptibility**.
- Source: K. Fukui: *DNA mismatch repair in eukaryotes and bacteria.* In: *Journal of nucleic acids* Band 2010, 2010, S.

Microsatellite instability

- The term "microsatellite instability" (MSI, MSI-H or MSI-high) is used to describe deviations in the number of short, repetitive segments of genetic material - the microsatellites.
- Such deviations are caused by a defect in the DNA repair mechanism: In affected individuals, the mismatch repair system (MMRD), which is responsible in particular for correcting small errors in the base sequence, is disturbed.
- Such errors can occur during replication when DNA duplicates in preparation for cell division. If mismatch repair is disturbed, small mutations accumulate in the cells in the course of cell divisions. Inherited disorders in the mismatch repair system underlie hereditary nonpolyposis colorectal cancer.
- Source: Mikrosatelliteninstabilität im Tumorgewebe: Direkter Nachweis mittels Bildverarbeitung Dtsch Arztebl 2019; 116(35-36): [26]; DOI: 10.3238/PersOnko.2019.06.10.05 Zylka-Menhorn, Vera

HNPCC... and now?

- If carcinoma is already present.

  Treatment of HNPCC is no different from that of sporadic colorectal carcinoma.

  As reminder, the Stage-appropriate therapy of colon carcinoma (next Page)

CRC-UICC stage	TNM	Guideline-based therapy recommendation

0–I	Tis to T1	Endoscopic resection
		Further procedure depending on histopathology
		• **Low-Risk-Situation** *(Well (G1) or moderately differentiated (G2) and no lymphatic vessel invasion (L0).)* : No re-resection
		  • **Incomplete resection**: complete endoscopic/local surgical re-resection.
		  • If R0 resection is not achievable by this means: radical surgical resection.
		• **High-risk situation**: Radical surgical resection
		• **No adjuvant Chemotherapy**

	T2, N0, M0	• **Radical surgical resection** • **No adjuvant chemotherapy**
II	To T4, N0, M0	• Radical surgical resection • Adjuvant chemotherapy consider individually
III	every T, N1, M0	• Radical surgical resection • Adjuvant chemotherapy
IV	every T, every N, M1	Individual procedure depending on findings… Tumor conference

Sources: Körber et al.: ***Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): S3-Leitlinie Kolorektales Karzinom***
Leitlinienprogramm Onkologie der AWMF, Deutschen Krebsgesellschaft e.V. und Deutschen Krebshilfe. Stand: 1. Januar 2019. Abgerufen am: 3. Juli 2019.

HNPCC... and now?

- Genetic counseling: Persons at risk who are of age, genetic counseling is recommended

- Predictive genetic diagnostics in clinically healthy at-risk individuals should only be performed if a mutation has already been detected within the family
    - If the mutation can be excluded in an at-risk individual, no increased risk compared to the normal population is expected and thus no HNPCC-specific screening is necessary

- Source: Pox et al.: *S3-Leitlinie Kolorektales Karzinom*. Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (DGVS). Stand: 14. Juni 2013. Abgerufen am: 17. Oktober 2017.

HNPCC... and now?

- Screening: Screening for HNPCC patients and those at risk.
- From the age of 25
  - Annual colonoscopy (five years prior to recent familial carcinoma, if applicable), to be continued even after oncologic resection
  - Annual gynecological examination with transvaginal sonography
  - Annual abdominal sonography
- *From the age of 35*
  - Annual esophagogastroduodenoscopy if there is a family history of gastric cancer
  - Annual endometrial biopsy

Source: Pox et al.: S3-Leitlinie Kolorektales Karzinom. Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (DGVS). Stand: 14. Juni 2013. Abgerufen am: 17. Oktober 2017.

Exceptions

- First-degree relatives of patients from families that meet the Amsterdam criteria and have concomitant microsatellite instability (MSI) in the carcinoma:
  - Additional screening diagnosis for endometrial carcinoma and gastric carcinoma
    - every 3-5 years, provided that only one carcinoma from the family was examined and a MSS was detected
    - After age 25, perform colonoscopy every 3-5 years, provided at least two unrelated carcinomas in the family have been found to have MSS
    - First-degree relatives of patients from families meeting Bethesda criteria but not Amsterdam criteria: Perform colonoscopy at least every 3 years.

Source: Pox et al.: S3-Leitlinie Kolorektales Karzinom. Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (DGVS). Stand: 14. Juni 2013. Abgerufen am: 17. Oktober 2017.