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# Lynch syndrome (HNPCC)

# Zespół Lyncha (HNPCC)

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Summary

Lynch syndrome, also referred to as hereditary non-polyposis colorectal cancer (HNPCC), accounts for somewhere between 2 and 5% of all CRC. It has been shown that Lynch syndrome (LS) is a result of germline mutations in genes involved in DNA mismatch repair (MMR) MSH2, MLH1, MSH6, and PMS2, whereas as HNPCC refers to families that adhere to the Amsterdam criteria or iterations of it. More recently, it has been reported that loss of EPCAM is associated with Lynch syndrome, by virtue of it changing the epigenetic status of the promoter region of MSH2. Mutation carriers are at high risk of developing colorectal cancer (CRC), and endometrial cancer (EC) at unusually young ages. Other, extra-colonic tumor types such as ovarian, small bowel, urinary, biliary tract, gastric, and brain tumors, have also been associated with HNPCC. Over half the cancer deaths in HNPCC families are due to extra-colonic malignancies. The benefit of surveillance for gynecological cancers is not yet proven and there is no consensus on the optimal surveillance recommendations for women with MMR mutations.

We performed a systematic review of the literature and evaluated cancer risk in Polish HNPCC families classified into either Lynch syndrome (LS, MMR mutations detected) or HNPCC (fulfillment of the Amsterdam or modified Amsterdam criteria).

CRC detection screening strategy based upon colonoscopy has been documented to decrease CRC mortality. Published data clearly indicates no benefit for ovarian cancer screening in contrast to risk reducing surgery.

Due to the high cumulative risk of CRC full colonoscopy is recommended in HNPCC families beginning from age of 20-25 yrs every one-two years. Due to the high risk of EC it is reasonable to offer, after the age of 35 years, annual clinical gynecologic examinations with transvaginal ultrasound supported by routine aspiration sampling of the endometrium for women from either LS or HNPCC families. An alternative option, which could be taken into consideration for women preferring surgical prevention, is risk reducing total hysterectomy (with bilateral salpingo-oophorectomy) for carriers after childbearing is complete. Due to the increased risk of OC and absence of any benefit from gynecological screening reported in the literature it is recommended that prophylactic oophorectomy for female carriers of MMR mutations after 35 year of age should be considered as a risk reducing option. Annual transvaginal ultrasound supported by CA125 or HE4 marker testing should be performed after prophylactic surgery in these women.

Streszczenie

Zespół Lyncha, nazywany także dziedzicznym rakiem jelita grubego niezwiązanym z polipowatością (ang. *hereditary non-polyposis colorectal cancer* – HNPCC), stanowi 2-5% wszystkich raków jelita grubego. Wykazano, że zespół Lyncha jest wynikiem mutacji germinalnych genów biorących udział w naprawie DNA (ang. *mismatch repair* – MMR): MSH2, MLH1, MSH6 i PMS2, podczas gdy określenie „HNPCC" odnosi się do rodzin, które spełniają kryteria Amsterdamskie. Ostatnie doniesienia sugerują, że utrata genu EPCAM jest związana z zespołem Lyncha poprzez epigenetyczną zmianę statusu regionu promotorowego MSH2. Nosiciele mutacji są narażeni na zwiększone ryzyko rozwoju raka jelita grubego i raka trzonu macicy w młodym wieku. Inne, pozajelitowe nowotwory, jak rak jajnika, jelita cienkiego, dróg moczowych, dróg żółciowych, rak żołądka i nowotwory mózgu również są związane z HNPCC. Ponad połowa zgonów z powodu nowotworów

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w rodzinach z HNPCC spowodowana jest właśnie nowotworami pozajelitowymi. Korzyści z nadzoru nowotworów ginekologicznych nie są jeszcze udowodnione i nie ma również zgodności co do zaleceń nadzoru dla kobiet z mutacjami w MMR.

Przeprowadzono systematyczny przegląd piśmiennictwa i ocenę ryzyka raka w polskich rodzinach HNPCC, zakwalifikowanych do zespołu Lyncha (wykryte mutacje MMR) lub HNPCC (spełniające kryteria Amsterdamskie lub zmodyfikowane kryteria Amsterdamskie).

Udowodniono skuteczność programu profilaktyczno-diagnostycznego opartego na kolonoskopii w rodzinach z zespołem Lyncha poprzez zmniejszenie śmiertelności z powodu raka jelita grubego. Opublikowane dane wyraźnie wskazują na brak korzyści z badań przesiewowych w kierunku raka jajnika.

Ze względu na wysoce skumulowane ryzyko raka jelita grubego, pełna kolonoskopia jest zalecana w rodzinach HNPCC, począwszy od wieku 20-25 lat, co rok lub co dwa lata. Ze względu na wysokie ryzyko raka trzonu macicy uzasadnione jest proponowanie, po ukończeniu 35. roku życia, badań ginekologicznych z wykorzystaniem USG przezpochwowym z rutynowym pobieraniem próbek endometrium u kobiet z zespołem Lyncha lub rodzin HNPCC. Alternatywną opcją, która mogłaby być wzięta pod uwagę dla kobiet preferujących prewencję chirurgiczną, jest, zmniejszająca ryzyko, całkowita histerektomia (z obustronną resekcją przydatków) u nosicielek po ukończeniu okresu rozrodczego. Ze względu na zwiększone ryzyko raka jajnika i brak korzyści z ginekologicznych badań przesiewowych, według piśmiennictwa zaleca się profilaktyczną adneksektomię u kobiet nosicielek mutacji w MMR po ukończeniu 35. roku życia. Opcja ta powinna być traktowana jako redukująca ryzyko. Coroczne przezpochwowe badanie USG wspierane przez badanie markera CA125 lub HE4 powinny być wykonywane po zabiegu profilaktycznym u tych kobiet.

Publication of this review is based on the authors' own experience and data from the literature concerning the diagnosis, prevention and treatment of disease in families with Lynch syndrome (HNPCC).

The disease encapsulated by the term is HNPCC is one defined by a definition, known as the Amsterdam criteria. The Amsterdam criteria identify a clinical entity but do not provide information about the genetic predisposition to epithelial malignancies, Lynch syndrome. A unique perspective is provided by special, as distinct from standard, criteria of diagnosing "suspected HNPCC", according to studies undertaken by the author so that a diagnosis can be established when:

1. The proband or at least one first or second degree relative is affected by colorectal cancer (CRC).
2. A patient with CRC and the matching criteria of 1) or one of his I° relatives is affected by at least one cancer from the HNPCC spectrum of malignancy – that include CRC, endometrial cancer, a small bowel malignancy or a urinary tract tumour.
3. At least one of cancers matching described in criteria 1) or 2) has been diagnosed in a patient who is under 50 years of age.
4. Familial adenomatous polyposis (FAP) is excluded.

It is estimated that a highly penetrant genetic predisposition is associated with the cause of somewhere between 10 and 20% of all colon cancers (1-5).

Among the well recognized inherited syndromes associated with a cancer predisposition that manifestprimarily as familial CRC, they include syndromes demonstrating a Mendelian pattern of inheritance that include hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome), familial adenomatous polyposis (FAP); Gardener, Zankas, Turcot, Peutz-Jaghers syndromes and juvenile polyposis.

## LYNCH SYNDROME (HNPCC)

HNPCC was first described by Warthin about 100 years ago and further defined by Lynch (6) in the 1960's accounts for somewhere between 2 and 5% of all CRC. It has been shown that HNPCC is a result of germline mutations in genes involved in DNA mismatch repair MSH2, MLH1, MSH6, and PMS2. Mutation within MSH2 and MLH1 are the most frequently mutated in Lynch syndrome (7-10). More recently, it has been reported that loss of EPCAM is associate with Lynch syndrome, by virtue of there being a change in epigenetic status of the promoter region of MSH2 (11).

**The characteristic clinical feature of Lynch syndrome include:**

- early age of CRC diagnosis (about 45 yrs),
- more frequent right sided colonic tumour localization,
- two or more CRC cases among I° relatives,
- synchronous and metachronous CRC tumours,
- occurrence of disease in consecutive generations (vertical transmissions),
- increased frequency of cancers of the endometrium, small bowel and urinary tract in relatives.

According to the international group of experts (International Collaborative Group on HNPCC – ICG-HNPCC) Lynch syndrome can be definitively diagnosed, if constitutional mutations within one of the four genes connected with HNPCC, such as MSH2 or MLH1 is identified or if the following clinical and pedigree criteria are matched (tab. 1) (12, 13).

Due to incomplete disease penetrance (normally typical for dominant Mendelian disorders), deaths caused by various diseases, or due to difficulties in achieving complete clinical information about all

relatives, the large proportion – perhaps majority – of families actually with HNPCC, can not be diagnosed using the clinical definition of HNPCC as defined by the Amsterdam criteria (tab. 1). Therefore several centres are using less stringent criteria, the fulfillment of which can not provide a definitive diagnosis of HNPCC, but it is useful for the identification of families who are most likely to be associated with this entity (13-16). According to our experience the criteria summarized in table 2 are of particular value for the identification of cases suspected of HNPCC.

**Table 1.** Diagnostic criteria of HNPCC according to ICG-HNPCC (13).

| | |
|---|---|
| 1. | At least 3 relatives are affected by histologically verified CRC or cancer of the endometrium, small bowel or urinary tract; at least one of them is I° relative to the other two; FAP is excluded* |
| 2. | At least 2 of above persons are I° relatives from two different generations |
| 3. | At least 1 of above persons with cancer diagnosed at age under 50 yrs |

All other parameters (right site localization, syn- or metachronous tumours) should be treated like non-diagnostic features.
*colorectal polyposis, congenital hypertrophy of the retinal pigment epithelium, cysts and osteomas of the mandible/maxilla and desmoids are excluded

**Table 2.** Diagnostic criteria of "suspected HNPCC" (20).

| | |
|---|---|
| 1. | Among I° relatives of CRC patients (or in himself) at least one cancer of the CRC, endometrium, small bowel or urinary tract |
| 2. | At least one of above cancers diagnosed under age of 50 yrs |
| 3. | FAP is excluded* |

*see table 1

## TUMOR SPECTRUM

Recent analysis of the cancer spectrum in 368 MMR genes mutation carriers (mainly non-Hispanic white US citizens) from 176 families confirmed that the two most common LS cancers were: CRC (58% of all cancers) in both sexes and EC (14%) followed by ovarian cancer (OC) as the third most common malignancy (3.5%). Cancers of the urogenital tract (kidney/uterus/bladder) constituted 3.1%, stomach/small intestine 2.7%, breast 1.9% and prostate 1.1% of all malignancies in these families (17). Another study from Europe performed on 2118 German and Dutch MMR gene mutation carriers revealed a similar tumor spectrum and a high incidence of gynecological cancers: CRC 50%, EC 16%, OC 4.4%, breast 4.4%, urological 3.6%, stomach 1.6% (18). LS-associated OC has been reported to exhibit a variety of histopathological subtypes, mostly invasive, with 22% presenting with synchronous primary EC (19).

Consistent with reports in the literature, a comparison of the cancer spectrum between 278 LS families and 353 HNPCC families (with no MMR mutations) diagnosed at the International Hereditary Cancer Center (IHCC, Szczecin, Poland) confirmed the high incidence of gynecological cancers in Polish families. There were 21 OCs among 573 tumors (3.6%) in LS families and 18 OCs among 588 tumors (3.1%) in the HNPCC families. EC was more prevalent among LS families (138/573 tumors, 24% of all cancers) compared to HNPCC families (81/588 tumors, 14% of all cancers).

## MOLECULAR DIAGNOSTICS FOR CONSTITUTIONAL MUTATIONS IN GENES ASSOCIATED WITH HNPCC

DNA testing is recommended for families fulfilling at least the "suspected HNPCC" criteria. After exclusion of FAP (characteristic symptoms that include polyposis, congenital hypertrophy of the retinal pigment epithelium, lipomas and osteomas of bones of the maxilla and mandible and desmoid tumors) immunohistochemical analyses (IHC) of *MLH1*, *MSH2*, *MSH6* and *PMS2* expression in malignant tissues should be performed (where the absence of the immunohistochemical staining for the respective DNA mismatch repair proteins may indicate the mutated gene).

Results of several studies performed in our centre characterized the frequencies and spectrum of MSH2 and MLH1 mutations in Poland (20). Similar to other populations, the most frequent causes of Lynch syndrome in Poland are MLH1 and MSH2 mutations, constituting 90% of all mutations associated with this entity. Partial or whole gene deletions identified by the multiplex ligation probe amplification (MLPA) assay detects 10% of these mutations. In over 60 % of all Lynch syndrome families recurrent mutations can be found. Thus, after IHC, gene sequencing and MLPA analysis for MSH2 and MLH1 should be performed. Once found DNA tests searching for recurrent mutations should be applied so that family members can benefit from this knowledge (21).

Another promising method when there are common founder mutations is the designer iPLEX/TaqMan test plexes, which comprise seven mutations of the *APC* gene and 29 mutations from three of the mismatch repair genes. This approach appears to be an outstanding tool for the identification of recurrent mutations among hereditary colorectal cancer patients (22).

The detection of family specific mutations for Lynch syndrome patients is of clinical importance because: 1. allows exclusion of approximately 50% of relatives from the high risk group of gene mutation carriers; 2. It facilitates decision making in terms of time for surgery and who would benefit from such an invasive prophylactic procedure especially when in addition to colectomy hysterectomy and possibly ovariectomy would be considered for women coming from families where there is a high incidence of these diseases.

## MANAGEMENT OF FAMILIES WITH HNPCC

**Our knowledge about Lynch syndrome suggests that special prevention and treatment options should be discussed with patients at risk.** Different approaches are performed by particular centres (4, 23, 24). According to the guidelines for the clinical management of Lynch syndrome, established by a group of European experts in hereditary

gastrointestinal cancer (the Mallorca-group), relatives from families fulfilling Amsterdam criteria II or revised Bethesda criteria (1. CRC diagnosed in a patient aged 50 years; 2. Presence of synchronous, metachronous colorectal or other Lynch syndrome-related tumours, regardless of age; 3. CRC with MSI-H phenotype diagnosed in a patient aged 60 years; 4. patient with CRC and a first-degree relative with a Lynch syndrome-related tumour, with one of the cancers diagnosed at age 50 year; 5. patient with CRC with two or more first-degree or second degree relatives with a Lynch syndrome-related tumour, regardless of age) (25) or with Lynch syndrome should consider the following options for medical management:

**Diet optimization**

Persons with high risk of CRC should consider a low fat diet with limited red meat intake, but increased amounts of foods rich in fibre (26). Recently it has been reported that 600 mg aspirin per day for a mean of 25 months substantially reduced cancer incidence after 55 months in carriers of hereditary colorectal cancer (27).

**Pharmacological prevention**

There are reports that group of drugs lowering the risk of CRC include: aspirin, sulindac, prioxicam, calcium and vitamin C. It has recently been shown that aspirin is particularly beneficial in reducing colorectal cancer in Lynch syndrome (24, 26, 28, 29).

**Colonoscopy**

Full colonoscopy is recommended beginning from age of 20-25 yrs every one-two years. In families in which CRC has been diagnosed at earlier ages colonoscopy should begin 5 years earlier than the age of the youngest person with CRC. In cases were endoscopy of the colon could not be assessed properly, barium enema is indicated (24, 30).

**Extra colonic tumour diagnostics**

***EC RISK***

For female LS patients, the lifetime risk of developing EC is estimated to be between 30% and 70% with a standardized incidence ratio (SIRs) ranging from 10 to 62 (31-34). The mean age of diagnosis for EC has been reported to be 48, 49 and 54 years in MLH1, MSH2 and MSH6 mutation carriers respectively (35, 36). The cumulative risk for EC in Polish LS families was calculated to be 67% (Hered cancer Clin Pract, submitted).

***OC RISK***

For female LS patients, the lifetime risk of developing OC is estimated to be somewhere between 3% and 20% with a standardized incidence ratio (SIR) ranging from 7 to 14 (31, 32, 37-39). The mean age of OC has been reported to be between 40 and 47 years of age (18, 31, 32). In a recent Danish study the mean age of OC was reported to be significantly lower in LS families (41 years) compared to HNPCC families (66 years) or HNPCC-suspected families (64 years) (40).

Statistical analysis of the age of onset of gynecological cancers in Polish LS patients confirmed that the mean age of OC was significantly lower in these families (43 years, age range 31-52) when compared to the general Polish population (54 years, $p < 0.0001$) and to HNPCC families (53 years, age range 27-80, $p < 0.001$). Statistical showed a significantly increased risk of OC (OR = 4.6, 95% CI 2.75-7.78; $p < 0.001$) in comparison to the general population estimates. An especially high risk of OC was found for women under 50 years of age: OR = 32.6, 95% CI 12.96-81.87; $p < 0.0001$. The cumulative OC risk to 50 year of age was calculated to be 10% for Polish female LS patients (Hered cancer Clin Pract, submitted).

## MANAGEMENT OF OVARIAN CANCER

Current guidelines for gynecological screening in HNPCC recommend transvaginal ultrasound (TVUs) and CA125 testing, every 1-2 years starting at 30-35 years of age (41-43). Recently it has been suggested that HE4 marker might be useful for diagnosing OC due to its high specificity, especially in the premenopausal population and combining of HE4 and CA125 could be considered as an option in the OC management (44, 45).

Literature data of four published studies that included a total of 585 women screened for OC (the screening protocols included both TVUS and CA125 (applied in three studies) or TVUS only (one study) showed no benefit for OC surveillance or the diagnosis of early stage ovarian cancer (46-49).

Another retrospective study reported on impact of gynecological screening in 174 MSH2 carriers. The authors concluded that screening did not result in any earlier cancer detection and despite screening, 2 young women died from OC. The authors suggest that prophylactic surgery be considered in female mutation carriers who have completed childbearing (50) to reduce their risk of presenting with incurable disease.

Recently an impact of gynecological screening (biennial TVUS+CA125) was retrospectively evaluated in 236 women (2067 women years) from Danish LS families (40). Consistently with previous reports, the study showed OC screening in female LS patients to be futile.

In 2006 risk-reducing bilateral salpingo-oophorectomy has been shown to be an effective strategy for preventing OC (51). Modeling studies of prophylactic surgery versus gynecologic surveillance for LS women showed that risk-reducing surgery is associated with the lowest costs and would increase life-expectancy (52-54).

According to the revised guidelines for the clinical management of Lynch syndrome prophylactic oophorectomy can be an option to be discussed with mutation carriers who have completed their families especially after the age of 40 years (55).

Given the published evidence and our own data showing a high risk of OC for young women from LS families and the absence of any positive effect of screening we conclude that it is justified to recommend the option of prophylactic oophorectomy for female carriers of MMR mutations after 35 year of age. Since three cases of primary peritoneal cancers after prophylactic bilateral salpingo-oophorectomy in HNPCC patients have been reported (56, 57) and previous studies involving women with *BRCA* mutations have also reported an incidence of primary peritoneal cancer after prophylactic bilateral salpingo-oophorectomy of 0.8 to 1.0 percent (58, 59), annual TVUS and CA125 screening could be performed after such surgery.

## MANAGEMENT OF ENDOMETRIAL CANCER

Literature data focusing on EC screening consists of six reported studies that included a total of 1518 women screened for EC (40, 46-49, 60). In the studies that used TVUS as the only screening method, interval ECs were diagnosed (48, 60). In the studies in which protocols also included endometrial biopsies the detection of premalignant lesions and EC was significantly improved. A comparison of the results of routine endometrial biopsy (46, 49) and optional biopsy (performed in cases with abnormalities – bleeding, irregular endometrium, endometrium thickness > 4 mm (40, 47) or > 5 mm (46) in postmenopausal women) revealed better efficiency in disease detection in the protocols that included routine biopsies where the EC detection rate exceeded 70% in comparison to a 50% detection rate when optional sampling was performed.

Additionally, in another recent screening with TVU alone would have missed one endometrial carcinoma and one premalignant lesion in that study (61).

A large meta-analysis of sporadic endometrial cancers advocated Pipelle endometrial sampling as an equally effective, if not superior, method compared with transvaginal ultrasound for detecting endometrial cancer in both pre- and postmenopausal women (62). A recent prospective study showed that conducting endometrial sampling at the time of colonoscopy (for colorectal cancer risk assessment) is a patient-centered option that is feasible, acceptable, and may improve adherence to LS screening recommendations (60).

Comparison of the results of the screening performed in 236 LS patients revealed that EC surveillance should only be targeted to this group of women (40).

Until now no prospective study has evaluated the impact of the EC screening on the survival of LS or HNPCC patients and the efficiency of screening for EC that generally presents with symptoms at an early stage is not clear. However, given the high risk of EC in female LS patients, according to the revised guidelines for the clinical management of LS, transvaginal ultrasound and aspiration biopsy (starting from the age of 35-40 years) should be offered as an appropriate risk reducing strategy (55). Recently a retrospective study was published on the impact of gynecological screening in 174 MSH2 female carriers (50). The authors argued that risk-reducing hysterectomy and bilateral salpingo-oophorectomy after childbearing is complete is the most effective risk reduction strategy.

Modeling studies have shown that prophylactic hysterectomy and bilateral salpingo-oophorectomy can increase life expectancy and can also be a cost-effective strategy (50-52).

Total hysterectomy was shown to significantly reduce the risk of EC in women with Lynch syndrome (51). However, given better outcomes than those observed for OC, the screening efficiency in detecting EC and high survival rates for this cancer (63) it remains unclear whether surgical prevention of EC in MMR carriers would significantly impact on morbidity and mortality.

**In conclusion**, our present knowledge on Lynch syndrome indicates that special prevention and treatment options should be applied to patients with LS. Due to the increased risk of OC, conflicting data regarding the prognosis of this disease in HNPCC and lack of any benefit from gynecological screening, it is recommended that prophylactic oophorectomy for female carriers of MMR mutations after 35 year of age should be considered as a risk reducing option. Annual transvaginal ultrasound (TVUS) supported by CA125 or HE4 marker might be considered as an option of the follow-up after prophylactic surgery in these women.

Due to the high risk of EC it is reasonable to offer, after the age of 35 years, annual clinical gynecologic examinations with transvaginal ultrasound (TVUS) supported by routine aspiration sampling of the endometrium to women from either LS or HNPCC families. Another option that could be taken into consideration for women preferring surgical prevention as a risk reducing alternative is total hysterectomy (with bilateral salpingo-oophorectomy) for carriers after childbearing is complete.

## OTHER CANCERS

Additionally, in some cases it is indicated to perform examination aimed to detect other tumours more frequently observed in a given family (for example stomach, urinary tract, breast disease) (5, 24).

### Surgery

Endoscopic polypectomy is recommended when poylyps are benign and non recurrent. However in patients with adenomas (multiple and/or recurrent and/or with a significant degree of dysplasia and/or villous architecture), prophylactic colectomy should be considered (30). Most experts agree that prophylactic surgery is not recommended to patients without any pathologic changes in the colon even if such persons are carriers of a mutated DNA mismatch repair gene (21). A high proportion of synchronous tumours (found in more than 15% of patients at the time of diagnosis) or metchachronous tumours (about 45% during the first

10 years following surgery of the primary tumour) uggests that for preventive surgery as for surgery in patients from HNPCC families with histopathology diagnosed CRC the following types of surgical treatment should be recommended (24, 64):

- proctocolectomy with ileostomy,
- colectomy with ileo-rectal anastomosis,
- proctocolectomy with ileo-anal "pouch" – S, J, W or H.

The first of these proposed procedures is the most radical but the later risk of recurrence is very low, however such treatment is highly traumatic and frequently leads to urinary tract abnormalities and sexual dysfunction.

Colectomy with ileorectal anastomosis does not lead to as many complications, however, it should be followed by frequent examination due to the risk of cancer in the unresected fragment of bowel.

Proctocoloctomy with ileo-anal "pouch" S, J, W or H is a surgical method with a relative short history therefore at the current time it is difficult to conclude much about its efficacy.

In women with Lynch syndrome undergoing surgery for CRC who are at perimenopausal age or older, it is recommended that they undergo prophylactic surgery to remove their endometrium and ovaries to reduce the risk of malignancires in these organs (24, 65).

All of the above procedures are characterized by an increasing frequency of complication. Their efficiency in the prolongation of the life requires additional evaluation, up to now no prospective studies have been published. However, they are recommended due to high risk of second primary CRC (syn- or matachronous) for these patients (66-68).

It has been shown that the application of appropriate programs for the management HNPCC families is leading to an increased detection rate of early asymptomatic CRC. Additionally, prospective studies have confirmed that as a result of appropriate management the lifetime risk of CRC is reducing in Lynch syndrome, from 80% to 30% with a higher proportion patients having significantly improved. The appropriate management strategies applied in carriers of MSH2/MLH1 mutations is resulting in significantly improved survival such that it is unlikely that patients will die as a result of CRC (69).

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