Risk Management for Lynch Syndrome

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Information for families with Lynch Syndrome
Contacting family members about hereditary cancer

Lynch Syndrome is an autosomal dominant condition caused by germline mutations in the mismatch repair genes *MLH1*, *MSH2*, *MSH6* or *PMS2*.

Target group

- known mismatch repair (MMR) gene mutation carrier
- 50% risk of being a MMR gene mutation carrier

Exclusion criteria

Not suitable for:

- individuals from families fulfilling **Amsterdam I or II** clinical criteria with **active exclusion of MMR defect** by tumour testing or in whom no molecular tumour testing or germline testing is possible
- familial gastric cancer syndrome
- individuals and first degree relatives of individuals with a tumour showing loss of functional MMR pathway but in whom no germline MMR mutation has been identified

Lifetime risk of cancer

Cancer	Lynch syndrome to age 70 yrs*, **,[1]	General population to age 85 yrs
Colorectal (male)	38%	10%***
Colorectal (female)	31%	6.6%***
Endometrial	33%	2 - 3%
Gastric	7%	1%
Ovarian	9%	1 - 2%
Urothelial	≤3%	1%
Brain	≤3%	0.6%
Small Bowel	≤3%	0.01%
* Higher figures obtained in papers not corrected for ascertainment bias		
** Combined data for MLH1, MSH2, MSH6, **but risks shown do vary per gene**		
*** This data does not take into account the impact of surveillance. Data Source: NSW Central Cancer Registry 2008 final dataset and NSW Health Outcomes Information Statistical Toolkit (HOIST).		

Cancer risk management guidelines

All patients should be entered on a local hereditary cancer registry for information and surveillance reminders. (**Link to Hereditary Cancer Registry**)

Cancer type	Recommendations

Colorectal	Surgical	▪ consider subtotal colectomy in selected individuals
	Surveillance	▪ annual colonoscopy from age 25 yrs or 5 yrs younger than youngest affected if <30yrs ▪ review frequency of colonoscopy at age 60 yrs with a view to reduced frequency
	Risk-reducing medication	▪ there may be a reduction of risk in taking aspirin however the appropriate dose is not yet defined (preliminary data)
Endometrial	Surgical	▪ recommend hysterectomy after childbearing complete or from age 40yrs
	Surveillance	▪ there is no evidence for transvaginal ultrasound (TVU) and/or aspiration biopsy
Ovarian	Surgical	▪ recommend risk reducing salpingo-oophorectomy (RRSO) at time of hysterectomy
	Surveillance	▪ there is no evidence for serum CA125 and/or transvaginal ultrasound (TVU)
Gastric	Surveillance	▪ consider second yrly gastroscopy from age 30 yrs in families with gastric cancer or those at high ethnic risk - e.g. Chinese, Korean, Chilean and Japanese
Urothelial	Surveillance	▪ no evidence of benefit but patients encouraged to report symptoms e.g. haematuria

Management of associated health problems and side effects

Management of early menopause

As there is no conclusive data regarding an increased risk of breast cancer in Lynch Syndrome the use of Hormonal Replacement Therapy (HRT) after oophorectomy is not contraindicated.

Evidence for risk management guidelines

Colorectal cancer

Surgical

No controlled trials regarding partial versus total colectomy for the management of colorectal cancer (CRC) are available. One decision analysis has reported an increase in life expectancy with subtotal colectomy[2].

Surveillance

A study of 114 Lynch Syndrome families comparing outcomes of screening at intervals of ≤2yrs with >2yrs demonstrated CRCs diagnosed at higher stage with longer interval surveillance. Evidence supports screening 1-2yrly[3].

Since 57% of the neoplasms in Lynch Syndrome occur proximal to the splenic flexure[4], visualisation to the caecum is essential. Given the high metachronous CRC risk in Lynch Syndrome (16% 10 yrs after a partial colectomy)[3], total colectomy should be discussed if a CRC is detected on surveillance.

Endometrial cancer

Surgical

Hysterectomy and RRSO are the only proven interventions which significantly reduce the risk of both endometrial and ovarian cancer[5].

Surveillance

There is no evidence to support a survival benefit from TVU and aspiration biopsy[3]. Where possible, surveillance should be offered in the context of a clinical trial[5].

Ovarian cancer

Surgical

Risk reducing salpingo-oophorectomy (RRSO) reduces the risk of developing ovarian cancer in mutation carriers. One study demonstrated no cases of ovarian cancer amongst women who had undergone RRSO compared with 5% of controls being diagnosed with ovarian cancer with mean follow up of 7yrs[6].

Surveillance

Data extrapolated from other high risk groups demonstrates annual TVU and serum CA125 levels do not detect ovarian cancers at an earlier stage, nor do they affect outcomes[5] . This form of screening is also associated with a high false positive rate requiring surgical intervention[7].

Gastric cancer

Surveillance

There is no evidence supporting the role of gastroscopy in the surveillance for gastric cancer in Lynch syndrome patients[8], however, InSiGHT has recommended gastroscopy in families at high risk of gastric cancer[9].

Urothelial transitional cell carcinoma

Surveillance

There is no evidence for the role of urine cytology in the surveillance of urothelial carcinomas in MMR gene carriers. One study of individuals with confirmed or suspected Lynch Syndrome demonstrated urine cytology had a sensitivity for malignancy of only 29%[10].

Support and information

First degree relatives, (parents, brothers/sisters and children) are at 50% risk of having inherited the condition. First degree relatives should be referred to a local Family Cancer Clinic.

Link to an **information sheet on contacting relatives**

Website resources

Centre for Genetics Education NSW Health
Association of Genetic Support of Australasia INC (AGSA)
Link to Hereditary Cancer Registry

References

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