Jurnal Medical Aradean (Arad Medical Journal)
Vol. XIX, issue 4, 2016, pp. 39-47

SURGICAL AND MEDICAL MANAGEMENT OF HEREDITARY NON-POLYPOSIS COLO-RECTAL CANCER MANAGEMENT OF HNPCC

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ABSTRACT: Hereditary non-polyposis colo-rectal cancer is an autosomal dominant disease and is described by markedly higher risk for colon and endometrial cancers. This disorder is characterised by loss of mismatch repair protein expression and DNA microsatellite instability. Clinical criteria (Amsterdam II) have served in identifying hereditary non-polyposis colo-rectal cancer families. To facilitate determination of colo-rectal tumours requiring molecular analysis, certain clinical criteria have been developed (Bethesda Guidelines). The recommendations for screening are for yearly/biennial colonoscopy and annual trans-vaginal ultrasound and endometrial sampling as early as 20 to 35 years of age. The management of this disorder, given the increased risk of developing endometrial and ovarian cancer, bilateral salpingoophorectomy and prophylactic hysterectomy should be presented to and discussed with HNPCC patients and also options for such patients' management include completion colectomy and ileo-rectal anastomosis, monitoring or chemo-prevention, in case of colo-rectal cancer.
KEYWORDS: colo-rectal cancer, endometrial cancer, colectomy, hysterectomy

INTRODUCTION:

Hereditary non-polyposis colo-rectal cancer (HNPCC) consists of an autosomal dominant disorder determined by a germline mutation involving one of several DNA mismatch repair genes (MMR). HNPCC is accountable for 2 - 3% of global colon cancers as well as for ca. 2% of endometrial cancers. HNPCC is described by markedly higher risk for colon and endometrial cancers and associated with a more reduced risk for several other types of associated cancers. The risk of cancer depends on environmental and/or geographic factors. Typically, HNPCC-associated cancers are characterised by loss of MMR protein expression and DNA microsatellite instability (MSI). Loss of MMR protein expressions is detectable by immuno-histo-chemistry (IHC) (Umar et al., 2004), whereas to detect the instability of microsatellite DNA sequences described by manifestation of random expansions or contractions in the length of simple sequence repeats, polymerase chain reaction-based methods can be used (Liu et al., 2000; Moslein et al., 1996). Both techniques have been largely used for purposes of colo-rectal cancer patients screening for testing with regard to line mutations in the MMR genes, and, more recently, for cancers occurring at other sites (Leenen et al., 2012), resulting in identification of various MMR-deficient tumours in organs not customarily known as included in the HNPCC spectrum.

HNPCC Identification

A family history of cancer plays an important role in the recognition of HNPCC. Clinical criteria (Amsterdam I and II) have served in identifying HNPCC families for clinical or research purposes (Vasen et al., 1991; Vasen et al., 1999). Amsterdam I criteria include the following:

- at least three relatives with histologically verified colo-rectal cancer, one of whom a first-degree relative to the other two;
- at least two successive generations affected;
- colo-rectal cancer diagnosed in one of the relatives under 50 years of age;
- familial adenomatous polyposis is excluded.

In 1999, new selection criteria were proposed by the International Collaborative Group on HNPCC (currently known as the Amsterdam criteria II), which involved inclusion of HNPCC associated extra-colon cancers as well (Vasen et al., 1991).

To facilitate determination of colo-rectal tumours requiring molecular analysis, certain clinical

criteria have been developed (the so-called Bethesda Guidelines) (Rodriguez-Bigas et al., 1997; Lynch et al., 2003). Molecular genetic studies (by either immuno-histo-chemical analysis of MMR proteins or MSI analysis of the tumour) may be required for patients in whom presence of the Bethesda criteria is confirmed. Identification of mutations occurring at family level requires such measures as genetic testing and genetic counselling be provided to all relatives at risk, which allows more effective and resource-saving shift of clinical screening to mutation carriers and exclusion of non-carriers from recurring examinations.

Colo-rectal Cancer

Colonic tumours are the most frequently encountered HNPCC-associated tumours, accountable for ca. 60–70% of global incidence (Mecklin et al., 1986; Vasen et al., 1990). Therefore, it has been considered important to research on the lifetime risk for CRC (colo-rectal cancer) occurrence.

In that respect, as revealed by study reports in that respect, at age 70 there is a 70% overall risk for CRC incidence in mutation carriers (range 30–80%) (Aarnio et al., 1999; Vasen et al., 1996; Dunlop et al., 1997), which does not rule out however a variation in risk estimation depending on type of mutation and gender. As a study conducted in Finland shows (Aarnio et al., 1999), for unknown reasons, men displayed superior standardised CRC incidence ratio (83) as compared to women (standardised CRC incidence ratio: 48), revealing a 1.7 male-to-female ratio.

In an attempt to explain such gender-dependence, Dunlop et al. (Dunlop et al., 1997) suggested presence of some sort of protection in women manifest in result of a gender-associated modifier gene or action of certain environmental factors.

Regarding the same risk of CRC occurrence, MLH1 and MSH2 mutation carriers have not been observed to differ, in spite of Hendriks et al. (Hendriks et al., 2004) finding of a significantly lower CRC risk in the female MSH6 mutation carriers than in MSH2 and MLH1 mutation carriers.

On the other hand, from a clinical perspective, the syndrome associates with a number of typical colonic tumour clinical characteristics, such as most frequent occurrence at proximal colon level (30% in random CRC as compared to 60–70% in HNPCC). In what age of occurrence is concerned, it has been observed that HNPCC-related CRC develops at younger ages (mean: 40–45 years) as compared to sporadic CRC (mean: 60–65 years).

At the same time, HNPCC mutation carriers display a more significant risk for development of multiple synchronous and metachronous types of CRC (Mecklin et al., 1986; Vasen et al., 1990).

Just as with sporadic CRC, the adenoma-carcinoma sequence also seemingly is involved in development of HNPCC-related colo-rectal tumours (Mecklin et al., 2007), with the notable difference however of HNPCC associated adenomas occurring at younger ages; in addition, in comparison to sporadic CRC cases, there is a tendency to larger size and more severe dysplasia (Mecklin et al., 1986; Lynch et al., 1993; Jass et al., 1995; Lanspa et al., 1990). Moreover, it has become apparent from studies that adenomas occurring in patients with HNPCC are mainly situated at proximal colon level (Lanspa et al., 1990; Gaglia et al., 1995). Most frequently, in adenomas developed in mutation carriers the absence of immuno-histo-chemical staining in MMR proteins or MSI can be observed (de Jong et al., 2004).

As regards HNPCC-related cases of CRC, study reports have shown 85–90% frequency of MSI (Aaltonen et al., 1994). For HNPCC, suggestions have been formulated related to an accelerated adenoma-carcinoma succession (i.e. progression from adenoma to carcinoma in 2-3 years vs. typical 8-10 years) (Vasen et al., 1995). The general CRC vs. HNPCC-related study also reveals CRC special features of histopathology, as for instance CRC frequently mucinous and poorly differentiated aspect (Mecklin et al., 1986; Lynch et al., 1993). At the same time, HNPCC apparently commonly reveals singlet-ring cancers and diploid tumours (Mecklin et al., 1986; Kouri et al., 1990), which, even if non-specific, may be used as supplementary markers of this syndrome and therefore facilitating diagnostic.

In order to prevent cancer development, recommendations refer to colonoscopic surveillance of HNPCC mutation carriers. For proof, a controlled, long-term study may be cited, conducted by Järvinen et al. on members of families at HNPCC risk, where colonoscopic screening (at 3-year intervals) was compared with lack of screening (Järvinen et al., 2000), confirming a significant reduction due to such surveillance in both CRC occurrence (16% in no screening patients vs. 6% in screened patients) and overall mortality (22% in controls and respectively 8% in screened patients). This is the basis for the recommendation of a group of hereditary gastrointestinal cancer European experts concerning yearly/biennial colonoscopy screening for mutation carriers beginning as early as age 20 to 25 (Vasen et al., 2007).

Endometrial Cancer

As compared to sporadic cancer cases, in patients with HNPCC, endometrial cancer develops at earlier ages, confirmed in practice by the mean diagnosis age (i.e. 49 years old vs. 60 years of age, generally) (Aarnio et al., 1995). According to studies undertaken, the endometrial cancer risk of families undergoing mutations of MSH6 run is higher (64–71%) than the same risk for families with MSH2 or MLH1 mutations (40–50%) (Dunlop et al., 1997; Hendriks et al., 2004). Similar to random endometrial cancer, most HNPCC-related uterine cancers are of the endometrial type (Broaddus et al., 2006). No dissimilar outcomes have been revealed in studies with regard to HNPCC-associated endometrial cancer as compared sporadic cancer cases (Boks et al., 2002).

To prevent early development of cancer, women with confirmed HNPCC have been

recommended regular screening for endometrial cancer (Vasen et al., 2007). This is based on results of studies undertaken with regard to gynaecological surveillance efficacy in HNPCC.

Thus, Dove-Edwin et al. have conducted a study (Dove-Edwin et al., 2002) involving a group of 269 female participants from among HNPCC family members; the study consisted of trans-vaginal ultrasound performed annually or every two years. In spite of results recording no asymptomatic endometrial cancers, two interval cancers were however found relying on symptoms.

In their study, Rijcken et al. (Rijcken et al., 2003) conducted a program for gynaecological screening performed in 41 mutation carriers. Study results showed no instances of asymptomatic endometrial cancer, recording however 3 patients displaying pre-malignant lesions.

A further Finnish study was conducted on 175 mutation carriers, consisting of surveillance performed by means of aspiration biopsy and trans-vaginal ultrasound (Laura et al., 2006). Results noted 14 cases of endometrial cancer, 11 of which were detected due to screening; it should be mentioned that identification of 6 of the reported 11 diagnosed cancers was due to aspiration biopsy and not ultrasound.

An additional aspect revealed by respective results referred to more favourable stage distribution and related survival rate in screened vs. non-screened patients.

With regard to the manner of endometrial carcinoma development, a study by performed by Nieminen et al. (Nieminen et al., 2009) suggests gradual development by way of complex hyperplasia, whereas altered molecular genetics may be observed well in advance of cancer itself.

Relying on study findings and confirmations (Dove-Edwin et al., 2002; Rijcken et al., 2003; Laura et al., 2006), current guidelines for women with HNPCC recommend include annual screening by trans-vaginal ultrasound and endometrial sampling as early as 20 to 35 years of age.

Surgery management

Colo-rectal cancer

Among factors influencing management of newly diagnosed HNPCC, one may mention primary tumour location, the location of potential synchronous lesions, the magnitude of the disease, presence of co-morbidities, as well as patient awareness of respective risks and benefits and therapeutic alternatives. Most patients with HNPCC-related colo-rectal cancer display splenic flexure proximal tumours, which does not however exclude presence of rectal and left colon cancers as index lesions. In HNPCC, occurrence of synchronous CRC lesions has been reported in 6%-18% cases. At the same time, the estimate of metachronous CRC risk ranges from 40% to 72% at 10 and 40 years, respectively, after primary CRC tumour resection (Aarnio et al., 1995; Fitzgibbons et al., 1987; Box et al., 1999).

Other reports indicate a 16% risk of metachronous CRC at 10 years after segmental resection (de Vos tot Nederveen Cappel et al., 2002; Parry et al., 2011). Currently, diagnostic recommendations for colo-rectal cancer patients envisage complete assessment of tumour clinical stage prior to therapy, consisting of history and physical review, performance of colonoscopy/colonography (in case of difficult colonoscope passage and lack of acute obstruction); in addition, radiography of the chest and computed abdomen and pelvis tomography are also recommended. In case of rectum situated tumours, given the impact of screening results on the actual treatment (potentially offering neo-adjuvant therapy), assessment of rectal tumour stage with either MRI or endo-rectal ultrasound is very important.

In the context of superior incidence of metachronous and synchronous CRC and for lower morbidity and mortality (Madden et al., 1991), current recommendations envisage abdominal colectomy with IRA (ileo-rectal anastomosis), even though more extensive, as procedure of choice for HNPCC patients in whom colon cancer has been newly diagnosed as opposed to segmental resection.

However, as regards survival, benefits for patients undergoing IRA as compared to segmental resection have not been supported from retrospective and/or prospective studies. Research in that respect includes mathematical models comparing estimated values of life expectancy in HNPCC-related CRC patients undergoing segmental resections versus patients with the same diagnosis in whom more extended resections have been performed (Syngal et al., 1998; Maeda et al., 2010; de Vos tot Nederveen Cappel et al., 2003). Confirming expectations, younger early CRC patients with extended procedures showed higher life expectancy results in comparison to both older patients and every age patients with involvement of the lymph nodes (de Vos tot Nederveen Cappel et al., 2003).

In comparison with segmental colectomy however, abdominal resection with IRA has a disadvantage in higher bowel frequency, which is usually overcome by progressive adaptation.

Notwithstanding its demonstrated advantages, patients and physicians alike must be aware that the procedure is unable to prevent the occurrence of rectal cancer, estimated at 3%-12% and up to 20% (de Vos tot Nederveen Cappel et al., 2002; Lee et al., 2001; Rodriguez-Bigas et al., 1997; Baba et al., 1997; Kalady et al., 2012; Moslein et al., 1998). Therefore, patients of extended resection need to continue endoscopic surveillance of risk in the remaining rectum.

Approach of rectal cancer in HNPCC patients and sporadic patients is similar. In case of neo-adjuvant therapy, its administration is recommended.

The difference lies in the type of surgical procedure performed, the alternatives consisting of restorative procto-colectomy with IPAA (ileal pouch anal anastomosis), segmental resection with primary anastomosis such as LAR (low anterior resection) proctectomy with CAA (colo-anal anastomosis) or

APR (abdomino-perineal resection) for sphincters involvement, and local excision (very rare and only eligible for a selection of patients, in tumours allowing for local excision and in the absence of co-morbidities prohibitive of such procedures).

In theory, as far as restorative procto-colectomy is concerned, this removes the at-risk colon mucosa, but experience with this procedure in HNPCC practice is relatively limited. As in the case of patients of Familial Adenomatous Polyposis undergoing IPAA, monitoring of the pouch anal anastomosis is compulsory, given the possibility (even if very low) of a risk concerning development of neoplastic lesions in the anastomotic line, the anal canal or the ileal pouch.

The alternative is segmental resection with primary anastomosis, supported by results of two study reports suggesting a 15% and 18%, respectively, risk of metachronous cancer occurrence after proctectomy in HNPCC patients (Lee et al., 2001; Kalady et al., 2012). Accordingly, reports on 33 patients of the Cleveland Clinic in a median 101.7 months follow up context showed a 51% incidence of metachronous cancers or high-risk adenomas after proctectomy (Kalady et al., 2012).

Lee et al. (Lee et al., 2001) reported 3 of 18 patients to develop metachronous colon cancers at a 203 months median after proctectomy, whereas a German report and one of the Mayo Clinic indicated 6 of 11 patients developing metachronous colon cancers at a 88 months median post proctectomy (Moslein et al., 1998).

Restorative procto-colectomy is generally followed by construction of temporary loop ileostomy, resulting in a transitory faecal diversion for only ca. 3 months after IPAA performance in case no problems arise such as anastomotic stricture or a leak.

Theoretically speaking, because the IPAA addresses not only the primary tumour but also prevention of occurrence of other colon neoplastic lesions, this is recommended as procedure of choice in rectal cancer and LS patients. However, in 30% of the cases or more, patients undergoing IPAA have to adapt to certain disadvantages related to bowel activity, such as increased frequency (6–8 daily stools), occasional difficulty to distinguish gas from stool and consequent soiling (Meagher et al., 1998; Soravia et al., 1999). An additional problem to be considered is the morbidity of ileostomy closure. Segmental resection and primary colo-anal or colo-rectal anastomosis result in similar faulty bowel function. Regular screening colonoscopy after segmental rectal resection is mandatory as is pouchoscopy after performance of IPAA.

As already mentioned, extended procedures are generally the choice for managing newly colo-rectal cancer diagnosed HNPCC patients, which does by no means exclude the necessity for individualised approach.

Therefore, cases may arise when choice of more extended over less extended procedures is not recommended at the time of diagnosis for reasons such as primarily lack of data from retrospective or prospective studies indicating potential survival advantage.

Segmental and extended resections (subtotal or total colectomy) have been compared in two retrospective studies (Parry et al., 2011; Natarajan et al., 2010), both showing occurrence of less metachronous colo-rectal cancers in patients with extended procedure than in segmental resection. Neither study however demonstrated a survival benefit attached to performance of extended procedures.

Thus, the cumulative risk of metachronous CRC occurrence in patients with segmental colectomy in the study conducted by Parry et al. (Parry et al., 2011) was 16%, 41% and 62% at 10, 20 and 30 years, respectively, post primary procedure. The same study indicated a 31% reduction of CRC risk for each 10 cm portion of bowel length removed (Parry et al., 2011).

Choice of segmental over extended abdominal colectomy also requires consideration of function, which, even though adequate in most patients, may require administration of antidiarrheal medication for bowel regulation in some.

A different study by You et al. (You et al., 2008) focussed on comparison of short-term morbidity, long-term function and global quality of life in extended versus segmental colectomy performed over a 12 years time span. Results showed diminished short-term morbidity (25%) in patients with segmental resections as compared to 40 % in patients undergoing total abdominal colectomy and ileo-rectal anastomosis and 57 % in cases of sub-total colectomy and ileo-sigmoid anastomosis (You et al., 2008).

Concerning the disadvantage of bowel function, stools were less frequent in patients with segmental resection as compared to those with extended resections.

In this study, quality of life was measured with the irritable bowel syndrome instrument and scores recorded were relatively high in all patients; however, respective scores were lower in patients with ileo-rectal anastomosis than in segmental or ileo-sigmoid resections (You et al., 2008).

According to a Dutch registry study in HNPCC patients, comparing segmental with subtotal colectomy using two validated tools, the functional outcome was better after segmental procedure, with no difference however observed between the two in terms of generic quality of life (Haanstra et al., 2012), mainly due to patients' capacity to adapt to bowel problems and stool frequency after following abdominal colectomy.

There have been decision analysis models evaluating surveillance, segmental and extended resections in terms of survival benefit in HNPCC patients. Models have been designed for decision analysis from the perspective of the survival advantage in HNPCC patients, focussing on evaluation of extended vs. segmental resections as well as of surveillance. The models provided for such criteria as lifetime CRC risk, surveillance, surgical procedure type, stage-specificity in colo-rectal cancer mortality

and the quality of life. In that respect, two published decision analysis models consider the quality of life.

The model proposed by Syngal et al. relied on a comparison between prophylactic surgical resection and delayed colectomy based on CRC or adenoma, age as well as colonoscopic screening into a 25 years old mutation carrier. The risk reduction strategy proposed in this model was improved life expectancy vs. none. Advantages of colectomy diminished with ageing and became insignificant on colectomy at CRC diagnosis in comparison with to surveillance. Endoscopic screening resulted in superior quality adjusted life years (QALY) as compared to subtotal colectomy (0.3 years) and procto-colectomy (3.1 years), respectively (Syngal et al., 1998).

A different decision analysis model proposed both quality of life and survival for consideration. According to this model, 7 months mean survival advantage was reported in one 30-year old male patient with HNPCC, undergoing abdominal total colectomy, as compared to outcomes of segmental resection in the same individual (Maeda et al., 2010). As regards the quality of life, the authors reported theoretical 21.5 QALY in patients with abdominal colectomy as compared to 21.2 QALY in segmental resection (Maeda et al., 2010).

A third decision model disregarding the quality of life criterion showed higher life expectancy in younger CRC patients with more extended procedure versus patients with lymph node metastases and older patients, in whom similar procedures have been performed (de Vos tot Nederveen Cappel et al., 2002). According to this model, life expectancy depends on stage at diagnosis and age. As shown in the model, in a patient aged 67, no basic difference could be observed between segmental and extended procedures. The conclusion of the authors was that subtotal colectomy was the preferred surgical option in younger HNPCC patients, whereas segmental resection was the preferable option in older patients with HNPCC (de Vos tot Nederveen Cappel et al., 2002).

As mentioned above, individualised therapy is advisable for Lynch syndrome and colo-rectal cancer patients. When considering choice of a surgical procedure, either minimally invasive or open, tumour stage, age of diagnosis, as well as existing co-morbidities, surgical expertise and patient's wishes should also be considered.

The special issues arises of recommended approach of HNPCC patients encountered in surgical practice that have been treated with segmental resection because of either surgeon or patient choice or of HNPCC not having been recognised as such on diagnosis. Options for such patients' management include completion colectomy and ileo-rectal anastomosis, monitoring or chemo-prevention.

As regards completion colectomy, no data are available in support of its choice for this patient group. Should monitoring be opted for, general colonoscopy is advisable every year or every two years. As far as chemo-prevention is concerned, a daily dose of 600 mg of aspirin taken for a mean 25 months has been observed to reduce the incidence of cancer in mutation carriers following 57.7 months follow-up (Burn et al., 2011). An additional special case is that of abdominal colectomy preformed for prophylactic purposes in HNPCC patients still free from carcinomas or adenomas. Prophylactic abdominal colectomy with ileo-rectal anastomosis is advisable in such cases as poor patient compliance, instances of traumatic colonoscopy triggering patient refusal of further colonoscopic monitoring or in cases of fright of colo-rectal cancer development, with incapacitating psychological impact on the patient. As already mentioned, such patients as well necessitate endoscopic monitoring, which is less challenging to the patient than full colonoscopy.

In HNPCC patients, the adenoma to carcinoma succession has been observed to be accelerated than in cases of sporadic adenoma (Jass et al., 1994; Lanspa et al., 1994). Therapy options for such patients consist of surgical resection or endoscopic polypectomy with close monitoring, in the same manner as outlined for HNPCC and CRC patients. When monitoring versus surgery are considered, factors to be taken into account and reviewed with the patient refer to adenomas number and size, the frequency of metachronous or recurrent adenomas, the risk of developing interval cancer, endoscopic polypectomy related morbidity and risks associated with prophylactic surgery.

Endometrial cancer

In women, HNPCC diagnosis relates with increased risk of ovarian and endometrial cancer, which may be accounted for by the capacity of MSH6 mutation carriers to bear a higher risk of developing endometrial cancer than mutation carriers of other genes. However, extensive ranges (from 16% to 71% by age 70) have been reported in MSH6 carriers in terms of lifetime cumulative risk (Hendriks et al., 2004; Aarnio et al., 1995; Bonadona et al., 2011; Baglietto et al., 2010). The lifetime risk reported in women identified with MSH2 and MLH1 germline mutations has been 54% and 21% by age 70 (Bonadona et al., 2011).

In their study, Obermair et al. (Obermair et al., 2010) observed that ca. 25% of HNPCC and colo-rectal cancer female patients develop endometrial cancer within 10 years after being diagnosed with CRC. The mean age of diagnosis with endometrial cancer in MLH1, MSH2, and MSH6 mutation carriers has been observed to be 48, 49, and 54 years, respectively (Hendriks et al., 2004). Given the increased risk of developing endometrial and ovarian cancer, bilateral salpingoophorectomy and prophylactic hysterectomy should be presented to and discussed with HNPCC patients undergoing abdominal surgery who are either pre-menopausal but are not planning for other pregnancies or are post-menopausal, since both procedures decrease the respective risks (Schmeler et al., 2006).

Authors of a study performed on more than 300 females identified with mismatch repair gene

mutations reported 61 patients not developing endometrial or ovarian cancers after prophylactic surgery as compared to 33 women and 5.5% developing ovarian and endometrial on follow-up in the group not undergoing prophylactic surgery (Schmeler et al., 2006).

The efficacy of monitoring of endometrial cancer in HNPCC patients relies on no prospective study data, but expert panel recommendations have been published concerning surveillance of endometrial and ovarian cancers (Vasen et al., 2007; Lindor et al., 2006).

Potential Preventive Medication

Aspirin: One randomized controlled trial has found that aspirin has decreased long term risk of colo-rectal cancer occurrence in patients with family history positive for colon cancer. Similarly to NSAIDs however, aspirin is fraught with the risk of upper gastrointestinal ulcers and bleeding (Burn et al., 2011; Markowitz, 2007).

Calcium: According to a randomized control trial, calcium has decreased the risk of recurrent adenomas in patients at average risk and not in high risk patients genetically predisposed to develop colo-rectal cancer. A possible explanation may be that reduction of carcinogenetic effects is due to calcium binding to bile acids in the bowel (Baron et al., 1999; Grau et al., 2003; Wu et al., 2002).

Estrogen: Studies exist suggesting an association between estrogen and diminished incidence of colo-rectal tumours in patients at average risk and not in high risk patients genetically predisposed to develop colon cancer (Marino et al., 2008).

Folic Acid: Outcomes of an observational study involving usage for over 15 years showed that folic acid associates with inferior rates of colo-rectal cancer occurrence. It has been hypothesised that, due to folate being needed for DNA synthesis, sub-optimal levels of folic acid may result in DNA synthesis and repair of abnormalities (Cole et al., 2007; Giovannucci et al., 1998).

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs): Their administration may lead to shrinking of polyp size and decrease in their numbers. In spite of the fact that NSAIDs administration does not prevent polyp recurrence and polyps are best managed by surgical means, their use is still beneficial for patients with colectomy with ileo-anal anastomosis, for their capacity to reduce polyp size and decrease in their numbers in the rectum. Use of NSAIDs however is associated with risks of gastrointestinal ulcers and bleeding (Chan, 2002; O`Shaughnessy et al., 2002; DuBois et al., 1996).

COX-2 Inhibitors: Such medication is predominantly useful in familial adenomatous polyposis patients. As regards disadvantages to be considered, use of such medication affects the gastrointestinal system in a slighter adverse manner, and the risk of bleeding is also diminished. It is however associated with increased risk of coronary artery disease (Dubois et al., 1996; Sinicrope et al., 2004).

CONCLUSIONS

Planning management strategies for patients with HNPCC syndrome necessitates in-depth knowledge of the tumour spectrum, available through screening for CRC and endometrial cancer only. Use of immuno-histo-chemical determination of MMR proteins expression for pre-surgery identification of HNPCC patients may yield great and immediate clinical benefits, allowing for rigorous and accurate strategy for surgical procedure and global patient care.

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