Multimodal Approach to Familial Colorectal Cancer

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Take-Home Pearls

- Early referral to specialist centres improves patient outcome in familial CRC.
- Geneticists and counsellors have a key role in diagnosis.
- Management of polyposis syndromes can begin in childhood, involving paediatric and adolescent transition expertise.
- High-quality endoscopy and advanced endoscopic therapies are key in managing those with Lynch and polyposis syndromes.
- Most individuals with FAP, MAP and some with Lynch syndrome and hamartomatous polyposis syndromes require surgery, with well-informed and nuanced decision-making central.
- Lynch syndrome and all of the polyposis syndromes are associated with extraintestinal manifestations, necessitating involvement of a wide network of experienced clinicians.

10.1 Introduction

Colorectal cancer (CRC) development depends upon complex interaction between genetic predisposition and environment. Most tumours occur by chance, and environmental factors are thought largely responsible. Familial CRC arises in individuals where genetics plays a more influential role. This group may be categorised into low, moderate or high risk for CRC. This risk is higher in families with more relatives affected by cancer, and when tumours arise at a young age. About 5 % of CRC falls

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into the high-risk group, where genotype plays a fundamental role in the inheritance of bowel cancer. Lynch syndrome and polyposis syndromes fall into this group.

10.2 Evaluating Risk

Individuals should be risk stratified for CRC development to enable clinicians to determine appropriate surveillance and management (Fig. 10.1). It is imperative that an accurate family history is obtained detailing affected family members, sites of all tumours and the age at which they occurred (Houlston et al. 1990). A detailed personal history must be sought, including previous polyps, cancers or risk factors for CRC development (e.g. inflammatory bowel disease). This is best done in a specialist family cancer clinic where sufficient time can be given to gather accurate information and counsel patients (Lips 1998).

Evaluating cancer risk within a family is a dynamic process. Individuals may move to a higher-risk group as more cancers develop within the same family over time or as more information is gathered for existing relatives.

In the high-risk group of Lynch and polyposis syndromes, there is a one in two chances of inheriting a lifetime risk of bowel cancer of more than 50 %. The polyposis syndromes can usually be diagnosed without too much difficulty through a

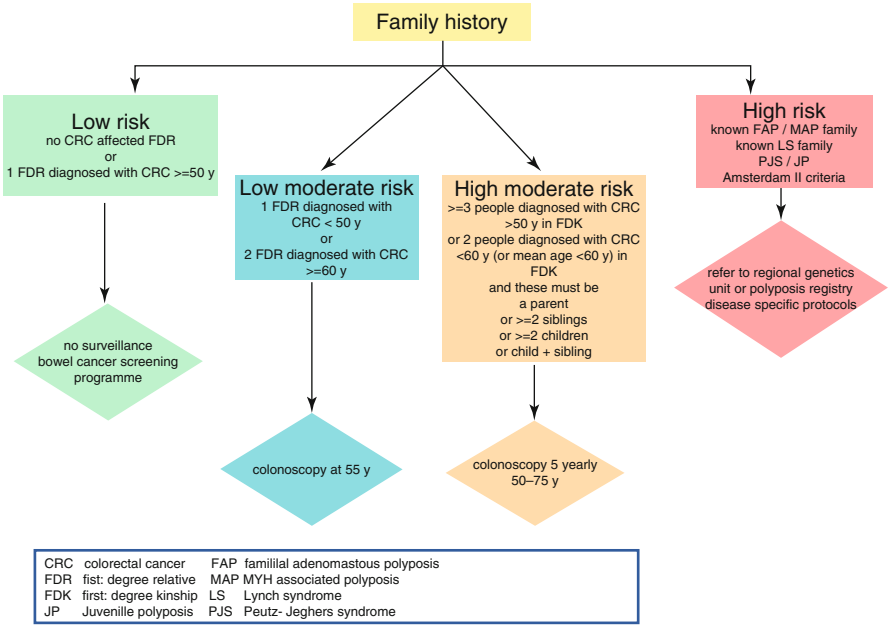

Fig. 10.1 Risk stratification for CRC according to family history (Based on Cairns et al. 2010)

recognisable phenotype, but Lynch syndrome can be more difficult because there is no distinguishing feature, only the presence of cancer.

10.3 Lynch Syndrome

This autosomal dominantly inherited condition accounts for approximately 2–4 % of all CRCs and the majority of inherited colonic tumours. Lynch syndrome was previously termed hereditary non-polyposis colorectal cancer (HNPCC), but as some adenomatous polyps can arise in this condition, this term has been largely discarded (Jass 2006).

Lynch syndrome typically presents with CRC in the fourth decade of life with a tendency towards right-sided, poorly differentiated, mucinous colonic tumours with lymphocytic infiltrates. There are often multiple cancers within the colon and elsewhere including the endometrium, stomach, ovaries, renal tract, pancreas, small bowel and brain (Aarnio et al. 1999).

10.3.1 Genetics

Lynch syndrome results from germline mutations in tumour suppressing mismatch repair (MMR) genes coding for proteins that either correct base pair mistakes during DNA replication or stimulate apoptosis when it is irreparable (Jass 2006). Affected individuals inherit a defective copy. MMR function is lost in a cell when the remaining normal gene becomes mutated. A lack of MMR proteins stimulates tumourigenesis by allowing rapid accumulation of mutations in other genes. Microsatellites, regions of short DNA sequence repeats, characteristically become mutated as a result of deficiency in MMR proteins, resulting in microsatellite instability (MSI). MSI is a key feature of tumours that lack MMR and is seen in approximately 15 % of sporadic CRCs as well as those arising in Lynch syndrome.

10.3.2 Diagnosis

A diagnosis of Lynch syndrome can be made using a combination of family history, tumour analysis (to detect MSI) and/or genetic testing. Whilst families fulfilling the Amsterdam II criteria (Box 10.1) may have Lynch syndrome, these will only identify half of those with the syndrome, as 50 % of those affected will fail to meet the criteria. Of those meeting the criteria, half will not have Lynch syndrome (Simmang et al. 1999). Nearly all Lynch syndrome tumours will be MSI high due to MMR mutation and show lack of MMR protein expression on immunohistochemistry (MMR-IHC). The Bethesda criteria (Box 10.2) help in deciding when to test tumours for MSI or MMR-IHC. This will usually identify up to 90 % of people with CRC due to Lynch syndrome (Umar et al. 2004).

Box 10.1. Amsterdam Criteria II (Vasen et al. 1999)

At least *three relatives* with a Lynch syndrome-associated cancer (colorectal, endometrial, small bowel, ureteral, renal pelvis). One should be a first-degree relative of the other two
At least *two successive generations* should be affected
At least 1 CRC should be diagnosed *<50 years*
FAP should be excluded
Tumours should be verified by pathological examination

Box 10.2. Bethesda Criteria

CRC diagnosed in a patient *<50 years old*
The presence of *multiple* colorectal or other Lynch syndrome-associated tumours, either synchronous or metachronous at *any age*
CRC with *high MSI* histology in a patient *<60 years* old
CRC diagnosed in *one or more* first-degree relatives with a Lynch syndrome-associated tumour, with one of the cancers diagnosed *<50 years* of age
CRC diagnosed in *two or more* first-degree or second-degree relatives with Lynch syndrome-associated tumours, at *any age*

MMR gene mutation detection is expensive, and the decision to test will depend upon individual circumstances. This requires a multidisciplinary team approach with specialist nurses and doctors working within the field of inherited bowel cancer and genetics (Scholefield et al. 1998; Burke et al. 1997). A histopathologist, specialising in inherited CRC, is important when determining which tumours require further testing to achieve an accurate diagnosis. Patients require appropriate counselling, informing them of the possible outcomes from genetic testing, from insurance to family and work life issues. If a mutation is found, appropriate surveillance can be arranged, and other family members can be offered predictive testing to establish whether they carry the abnormal gene. If they do not, they can be discharged from follow-up. In high-risk families where no mutation can be identified, individuals should continue with colonoscopic surveillance.

The complex nature of inherited CRC requires a multidisciplinary approach, particularly in cases of diagnostic difficulty. Regular meetings to discuss complicated cases will require contributions from specialist nurses/counsellors, gastroenterologists/endoscopists, paediatric services, geneticists, radiologists, histopathologists and surgeons. This creates a forum where team members can discuss cases amongst other specialists and consensus can be reached regarding diagnosis, appropriate investigations and management, supported where possible with evidence-based practice. A chairperson directs the team. Where further endoscopies may be required for tissue diagnosis/genetic testing, they can be arranged efficiently and results discussed within the same forum when available. Recommendations can then be communicated to the patient through specialist nurses, gastroenterologists or surgeons as appropriate. This ensures the delivery of a high-quality service where accurate diagnoses can be reached, appropriate surveillance can be arranged and optimal management instituted.

10.3.3 Surveillance

Where screening has been undertaken, significant benefits to life expectancy have been demonstrated in MMR mutation carriers. This is estimated to be an additional 13.5 years, and after prophylactic proctocolectomy, 15.6 years, when compared with no intervention (Syngal et al. 1998).

Colonoscopy is recommended for at-risk individuals every 1–2 years from 25 years of age or 5 years younger than the youngest affected family member, whichever is earlier. This continues until 75 years of age, or where a causative mutation found in a family is excluded from the individual (Vasen et al. 2007). There is no evidence to support surveillance for extracolonic cancers.

10.3.4 Medical Intervention

The Colorectal Adenoma/Carcinoma Prevention Programme 2 (CAPP2) study evaluated aspirin as a chemopreventative agent in Lynch syndrome and found a reduction in CRC rate. However, more data are required to determine optimal dose and treatment duration (Burn et al. 2011).

Some cytotoxic chemotherapy agents are of questionable benefit in Lynch syndrome-associated cancer. It is imperative that oncologists are aware of the underlying diagnosis (Vasen et al. 2007).

10.3.5 Surgical Intervention

Prophylactic surgery should be discussed with high-risk individuals. This may include prophylactic colectomy, hysterectomy and/or bilateral salpingo-oophorectomy. The options for addressing CRC risk include subtotal colectomy or total colectomy with restorative proctocolectomy (RPC).

There is a 16 % risk of metachronous bowel tumours after 10 years follow-up (Ruschoff et al. 1998). For those with a colonic tumour, the surgical options are segmental colonic resection or colectomy with ileorectal anastomosis (IRA). A segmental resection may result in a better function, but full colonoscopic surveillance is still required due to a risk of further CRC development. Colectomy with IRA reduces this risk. Because the rectum is retained, the morbidity associated with proctectomy is avoided and surveillance made easier. A proctocolectomy, in the form of an end ileostomy or RPC, is recommended for rectal cancers.

10.4 Familial Colorectal Cancer Type X

Lindor et al. introduced this term to describe individuals meeting the Amsterdam criteria with MSI negative colorectal cancers (Lindor et al. 2005). Family members meeting these criteria are at lower risk of developing CRC than in Lynch syndrome but will still require 3–5-yearly colonoscopic surveillance (Dove-Edwin et al. 2006).

10.5 Familial Adenomatous Polyposis (FAP)

FAP is a rare, autosomal, dominantly inherited condition characterised by the development of hundreds to thousands of colorectal adenomas. The population prevalence of FAP is between 1/7,500 and 1/13,000 with almost 100 % disease penetrance by 40 years of age (Bisgaard et al. 1994).

Without prophylactic colectomy, almost all individuals affected will develop CRC by the fourth decade of life (Petersen et al. 1991). Polyps also occur in the stomach and duodenum. Fundic gland polyps in the stomach pose no malignant risk (Wu et al. 1998b). Ninety per cent of those with FAP develop duodenal adenomas, and in 10 % of cases these can become malignant (Wallace and Phillips 1998). They are mostly peri-ampullary and associated with poor prognosis if they progress to cancer (Clark 2009).

Extra-intestinal manifestations of FAP include osteomas, dental abnormalities (e.g. supernumerary teeth), congenital hypertrophy of the retinal pigment epithelium (CHRPE), epidermoid cysts, adrenal adenomas, cancers (including thyroid, central nervous system tumours and hepatoblastoma) and desmoid tumours (Half et al. 2009).

10.5.1 Genetics

FAP is due to germline mutation in one of the copies of the tumour suppressing adenomatous polyposis coli (*APC*) gene.

10.5.2 Diagnosis

Traditionally, FAP was diagnosed by the presence of more than 100 colorectal adenomas, but this definition fails to incorporate all cases: i.e., in attenuated FAP only 10–100 polyps may occur, and CRC presents at a later age (Hernegger et al. 2002). In up to 80 % of cases, FAP can be confirmed genetically by identifying the *APC* mutation responsible. Most will originate from previously known FAP families but 20 % arise as a new mutation (Bisgaard et al. 1994).

An expert endoscopist is important in the accurate assessment and diagnosis of FAP. The use of chromoendoscopy (dye spray) can avoid under reporting of polyp burden and misdiagnosis (Wallace et al. 1999). An upper gastrointestinal (GI) endoscopy can be helpful in confirming the diagnosis of FAP as the majority will have duodenal adenomas and fundic gland polyps.

Registries play a fundamental role in ensuring the welfare of people with polyposis syndromes, from identifying at-risk family members through detailed family pedigrees to arranging regular follow-up and offering genetic testing and counselling where appropriate. When genetic testing is not appropriately delivered, there may be adverse consequences to patient care including inaccurate information giving and inadequate counselling (Giardiello et al. 1997). The affected individual should be

genetically tested, and where the mutation is identified, other family members can be offered predictive testing; if negative, they can be discharged from follow-up (Berk et al. 1999). Predictive testing is typically offered to children around the age of 12 years as it is rare for advanced colorectal adenomas to develop before this time. If no mutation is identified, then clinical surveillance is required for at-risk individuals.

10.5.3 Surveillance

Annual flexible sigmoidoscopy is recommended from 13 to 15 years but should be undertaken earlier should symptoms develop (e.g. change in bowel function, anaemia or bleeding per rectum). Screening for FAP at a younger age is not recommended due to ethical considerations and because intervention is rarely necessary in the asymptomatic (Tudyka and Clark 2012). Children should be followed up by a specialist paediatric gastroenterologist who will ensure they receive appropriate endoscopic assessment and management. Those developing more or larger polyps than expected for their age may require earlier referral for surgical intervention.

Provided no polyps are seen at flexible sigmoidoscopy, colonoscopy should commence from 20 years of age and continue at 5-yearly intervals with annual flexible sigmoidoscopy in the intervening periods. This algorithm also applies for at-risk individuals where no mutation can be identified.

10.5.4 Surgical Intervention

It is important to appreciate the genotype-phenotype correlation in FAP when planning surgery. The *APC* gene mutation site can affect phenotypic expression (Wu et al. 1998a). Mutations located between codons 1251 and 1309 predispose to a higher colorectal polyp burden, particularly in the rectum, and cancer often develops earlier. In contrast, mutations at the 3′ and 5′ ends of the gene tend to result in a milder 'attenuated' phenotype (Soravia et al. 1998; Nieuwenhuis and Vasen 2007). Some individuals with identical mutations exhibit different phenotypic expression which suggests that environmental factors or other genes are important in disease manifestation. Mutations 3′ of 1399 are associated with a higher risk of desmoid development, which can lead to significant morbidity (Sinha et al. 2010). This knowledge may impact upon surgical decision-making, influencing the timing and type of surgery offered.

Once a diagnosis is confirmed, prophylactic colectomy or proctocolectomy is usually offered. A thorough colonoscopy is required to determine polyp burden prior to surgery. Unless this is high or polyps cause symptoms, surgery can be planned for a convenient time, e.g. during school holidays, to minimise impact on education and other activities. For the majority, surgery will be undertaken around mid to late teens.

Until the late 1970s, the only surgical options were a total proctocolectomy (TPC) with end ileostomy or a colectomy with IRA. 1978 saw the advent of RPC with ileo-anal anastomosis (Parks and Nicholls 1978). More recently, a laparoscopic approach has become a surgical option, with the advantage of improved cosmesis.

10.5.5 Surgical Options

For the majority of people facing surgery, a permanent ileostomy will not be a real consideration, and so the decision regarding the type of surgery will come down to either RPC or colectomy and IRA. The advantages and disadvantages of these procedures are listed in Box 10.3.

10.5.5.1 TPC

The whole of the large bowel is excised and a permanent end ileostomy formed, completely removing the risk of CRC. This will rarely be performed prophylactically but is appropriate for very low rectal cancers.

Box 10.3. Comparing Advantages and Drawbacks of Colectomy and IRA and RPC

	Colectomy and IRA	RPC
Advantages	One-stage procedure, no ileostomy	Less frequent endoscopic surveillance
	Acceptable bowel frequency (×3/day). Incontinence rare	Lowered cancer risk
	Technically easier to perform laparoscopically/open	
	Lower perioperative morbidity	
	No effect on fertility/erectile function	
Disadvantages	Intensive endoscopic follow-up	Bowel frequency typically ×5/day. Impaired continence common
	Completion proctectomy sometimes needed	Usually two-stage procedure with temporary ileostomy. Complex surgery
	Rectal cancer risk (Nugent and Phillips 1992)	Higher perioperative morbidity (Björk et al. 2001)
		50 % reduction in female fertility (Olsen et al. 2003)
		2 % risk of erectile/ejaculatory dysfunction
		10 % risk pouch failure resulting in permanent ileostomy (Von Roon et al. 2007)
		Can develop cancer in the pouch/anastomosis (Van Duijvendijk et al. 1999a)

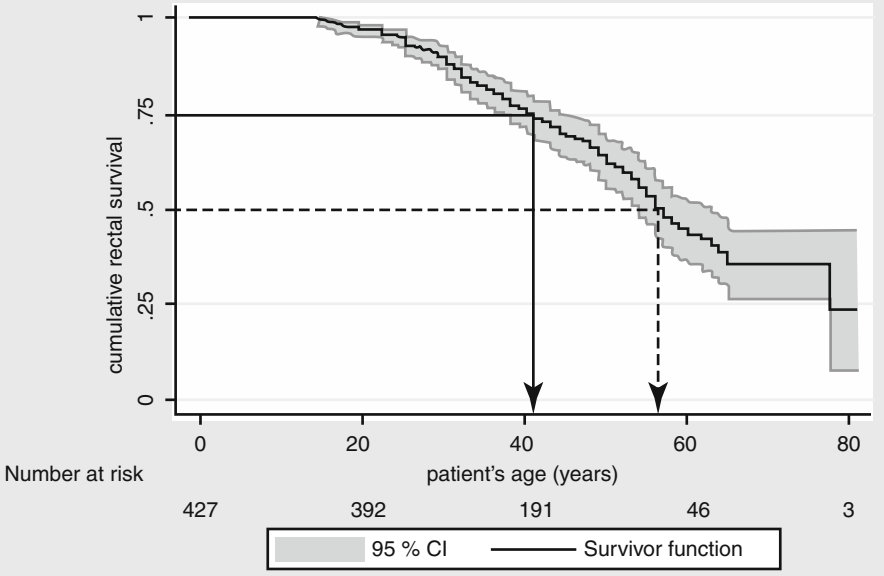

Fig. 10.2 Kaplan-Meier plot showing survival of a healthy rectum (i.e., not requiring removal because of cancer or high adenoma burden) plotted against patient age following IRA. St Mark's Hospital data 1948–2007. Tudyka and Clark (2012) (Reproduced with permission from Hellenic Society of Gastroenterology)

10.5.5.2 Colectomy and IRA

This can be a laparoscopic or open procedure. Defaecatory frequency and leakage are less when compared to RPC (Aziz et al. 2006). The major disadvantage is the carcinoma risk in the retained rectum, which rises sharply after 50 years of age (Fig. 10.2) (Tudyka and Clark 2012; Nugent and Phillips 1992; Nugent et al. 1993). For those requiring subsequent rectal excision, an ileo-anal pouch may be suitable or otherwise a completion proctectomy with end ileostomy will be necessary.

10.5.5.3 RPC

This operation is an attractive option as nearly the entire large bowel is removed. However, RPC can significantly reduce female fecundity and in 1–2 % of men lead to erectile or ejaculatory dysfunction (Aziz et al. 2006; Cornish et al. 2007). Controversy remains regarding the best technique for anastomosing the pouch and anus. Stapling leaves a small cuff of rectal mucosa where tumours can develop (Van Duijvendijk et al. 1999a). Performing a mucosectomy and a handsewn anastomosis instead is technically challenging, may affect functional outcome and does not abolish cancer risk. Adenomas and carcinomas can also occur in the pouch itself (Church 2005).

10.5.6 Other Considerations and Multidisciplinary Surgical Decision-Making

Historical data found a cumulative rectal cancer risk in the retained rectum after IRA of up to 30 % by 60 years of age. Before RPC, there was no alternative to permanent ileostomy following colectomy other than IRA, so many chose this, regardless of polyp burden. Managing the rectum post-surgery was difficult before flexible endoscopy became available.

It is known that some groups with FAP carry a higher risk of CRC development, e.g. those with codon 1309 mutation. RPC is recommended here rather than IRA, as the risk of developing significant rectal polyposis and requiring proctectomy is high. RPC is also recommended in severe phenotypes, e.g. over 500 colonic adenomas or more than 20 rectal adenomas (Church et al. 2003; Sinha et al. 2010).

It is vital that a multidisciplinary team (MDT) of specialists are involved in the surgical management of patients. In the first instance, it is important that the geneticist can identify the *APC* mutation where possible. Then, a skilled endoscopist is essential in determining the true extent of polyp burden in the colon and rectum. A pathologist must assess all histology accurately as this may influence the timing of surgery. Specialist nurses and paediatric gastroenterologists often build bonds with patients over years of clinic attendance and may act as patient advocates during MDT discussions. Finally, all available information is presented and discussed within the MDT meeting and surgical recommendations offered to the patient. In cases of attenuated polyposis, surgery may be deferred to a later stage if polyp burden remains small. Some can remain endoscopically manageable with annual surveillance. This may be particularly relevant for those with a desmoid prone mutation in whom trauma from surgery may stimulate desmoid development. Complex cases such as these highlight the importance of MDT discussion and the provision of patient-tailored care.

Patients are counselled about the advantages and disadvantages of each procedure in a specialist clinic setting so they can make an informed decision regarding their surgery. No significant difference has been demonstrated in bowel function and quality of life when comparing RPC and IRA (Aziz et al. 2006; Van Duijvendijk et al. 1999b; Ko et al. 2000; Günther et al. 2003; Hassan et al. 2005). A selective patient-tailored approach results in a better outcome following IRA (Church et al. 2003).

Lifelong follow-up is necessary for individuals with FAP, with endoscopic and clinical examination of the rectum or pouch. After colectomy, the major causes of morbidity and mortality are duodenal cancer and desmoid tumours (Nugent et al. 1993; Bertario et al. 1994), and it is important that these are monitored in a specialist, multidisciplinary setting too.

10.5.7 Managing Extra-colonic Manifestations of FAP

10.5.7.1 Duodenal Disease

Duodenal adenomas develop in nearly all people with FAP and become invasive in 10 % (Groves et al. 2002). Surveillance is recommended with endoscopy after 30 years of age in asymptomatic individuals (Cairns et al. 2010). Intervals between endoscopies will vary between 6 months and 5 years, determined by the Spigelman stage (Box 10.4) (Burke et al. 1999; Spigelman et al. 1989). Expert endoscopists using a side-viewing scope are essential in the assessment of the ampulla, and its surrounding area, that is at particular risk of tumour development. Thorough histological analysis by expert pathologists is necessary to determine the stage of disease. The cancer risk in stages I–II disease is minimal, but approaches one third with Spigelman stage IV disease over a 10-year period (Groves et al. 2002). Where cancer arises, prognosis is poor (Latchford et al. 2009). Expert endoscopic management using advanced techniques to control peri-ampullary polyps can be employed in severe diseases to delay definitive surgery, such as prophylactic pancreatico-duodenectomy or pancreas-sparing duodenectomy, that is associated with significant morbidity and mortality (Gallagher et al. 2004; Mackey et al. 2005). However, there are no data currently that show endoscopic therapies alter long-term cancer risk and the management of duodenal adenomatous polyps remains a challenge for clinicians.

Box 10.4. Spigelman Staging and Recommended Endoscopy Intervals

	Points allocated		
	1	**2**	**3**
Number of polyps	1–4	5–20	>20
Polyp size (mm)	1–4	5–10	>10
Histological type	Tubular	Tubulovillous	Villous
Degree of dysplasia	Mild	Moderate	Severe
Total points	**Spigelman stage**	**Recommended follow-up interval**	
0	0	5 years	
1–4	I	5 years	
5–6	II	3 years	
7–8	III	1 year and consider endoscopic therapy	
9–12	IV	6 monthly. Consider prophylactic duodenectomy	

10.5.7.2 Desmoid Disease

Desmoid tumours are benign, locally infiltrating, fibromatous tumours arising in connective tissue. They occur in approximately 15 % of patients with FAP, and although the majority are not associated with significant morbidity, there is an associated mortality rate of 10 % (Clark et al. 1999; Church et al. 1999). Most occur in the abdominal wall or mesentery, and associated complications include ureteric obstruction, bowel obstruction, perforation, fistulation, ischaemia and even death. Risk factors for desmoid development include trauma (e.g. surgery), female gender, particular germline mutations as well as other genetic factors (Sinha et al. 2010). Some desmoids grow and regress, whilst many remain in a stable state, and for these it is preferable to minimise surgical intervention that may otherwise stimulate further growth. Some grow relentlessly and remain a challenge to treat. The management of desmoid disease, particularly in severe cases, may require input from other disciplines. Expert radiologists are important in the identification and occasional radiological intervention of desmoids and their associated complications (e.g. intra-abdominal collections). Ureteric obstruction is not uncommon, and so regular radiological renal tract assessment with an ultrasound scan is recommended. Where obstruction occurs, ureteric stenting is required. For imaging assessment of abdominal desmoids, MRI is at least equivalent to CT and avoids radiation (Sinha et al. 2012).

Management options include nonsteroidal anti-inflammatory drugs, anti-oestrogens, cytotoxic chemotherapy and surgical excision. Good evidence for these is lacking due to desmoid rarity and variable course, but some specialist oncologists do provide chemotherapy for aggressively growing desmoids. Surgery may be considered as first-line treatment for actively growing extra-abdominal and abdominal wall desmoids, but recurrence is frequent. Desmoids growing on limbs may require specialist orthopaedic input if removal is necessary. Breast desmoids usually require referral to an expert breast unit so that lesions can be assessed and unnecessary removal avoided or significant lesions excised. For progressive mesenteric disease, referral to a specialist centre, where expert surgeons, gastroenterologists, urologists and intestinal failure specialists are available, should be sought. Surgery should only be considered in carefully selected cases due to high rates of obstructive complications, fistulation and short gut syndrome (Latchford et al. 2006). Referral to a small bowel transplant centre may be necessary when considering appropriate intervention in complicated cases.

10.6 MUTYH-Associated Polyposis (MAP)

This autosomal recessive adenomatous polyposis was described in 2002 after studying a family with FAP phenotype and no identifiable mutation (Al-Tassan et al. 2002). Similar to FAP, the development of colonic adenomas and carcinomas is the main feature of MAP. Approximately half of cases are phenotypically

similar to attenuated FAP, presenting with fewer colonic polyps, whilst the remainder resemble classic FAP. Interestingly, some develop cancer, with a tendency towards right-sided colonic lesions by middle age, despite having fewer than ten polyps (Cheadle and Sampson 2007). Fewer upper duodenal adenomas occur in association with MAP compared with FAP (30 and 90 %, respectively) (Kanter-Smoler et al. 2006).

10.6.1 Genetics

MAP is due to biallelic mutation of the mutY human homologue gene (*MUTYH*). As it is a recessive condition, there may be no significant family history.

10.6.2 Surveillance and Surgery

Both colonic and upper GI surveillance are the same as for FAP currently, although there may be a more attenuated phenotype in many with MAP. This can allow for some to be monitored and managed endoscopically for longer before considering a prophylactic colectomy. The risk of developing CRC in heterozygotes is not thought to be significantly higher than the general population, and surveillance is not currently recommended.

10.7 Peutz-Jeghers Syndrome (PJS)

This autosomal dominant condition classically features mucocutaneous pigmentation (95 % of affected individuals) and GI hamartomatous polyps, predominantly in the small bowel. In up to 94 % of cases, a mutation is found in *STK11* (Beggs et al. 2010). A diagnosis of PJS can be made when one of the features in Box 10.5 is seen.

Box 10.5. Diagnosing PJS

Diagnostic criteria for PJS
Two or more PJS polyps confirmed on histology
Any number of PJS polyps found and a family history of PJS in a close relative
Mucocutaneous pigmentation found and a family history of PJS in a close relative
Any number of PJS polyps and mucocutaneous pigmentation

Bowel obstruction is a common feature of PJS due to intussusception or adhesions from multiple laparotomies. This can be reduced by intra-operative enteroscopy to clear all polyps present at the time of surgery.

The cancer risk from PJS is significant, particularly for GI, pancreatic and breast tumours. The risk for CRC with advancing age is in the order of 40 % by the age of 70 years (Hearle et al. 2006). Surveillance is recommended from an early age both to identify and remove intestinal polyps before obstruction or cancer develops. A specialist paediatric gastroenterologist is imperative in the follow-up of children with PJS to identify and manage bowel polyps and PJS-associated cancers. Most centres undertake annual clinical examination (including breast and testicular examinations) with routine blood tests. A thorough baseline OGD and colonoscopy at the age of 8 should be considered. If polyps are present, upper and lower GI endoscopic surveillance continues 3 yearly. If no polyps are seen, 3-yearly surveillance should resume at 18 years. Capsule endoscopy or MR enterography should be performed 3 yearly from 8 years of age. Annual breast imaging is recommended from 25 years with mammography and/or MRI (Beggs et al. 2010).

10.8 Juvenile Polyposis

Juvenile polyposis is characterised by multiple hamartomatous juvenile polyps in the colon and upper GI tract and, for some, haemorrhagic telangiectasia. It is an autosomal dominant condition with germline mutations in *SMAD4*, *BMPR1A* or *ENG*. Regular upper and lower GI endoscopic surveillance is necessary, with polypectomy for larger polyps. Surgery is required when polyps are unmanageable endoscopically (Patel and Ahnen 2012).

10.9 Serrated Polyposis

In serrated polyposis (previously known as hyperplastic polyposis), multiple serrated colonic polyps are seen. The genetic basis is unclear and the CRC risk difficult to ascertain due to limited data but is so far thought to be between 37 and 69 % (Jass 2007). No consensus has been reached regarding surveillance intervals, but colonoscopic screening with polyp removal every 1–2 years is reasonable.

Conclusion

Familial CRC requires a multimodal approach in its management. A specialist service improves patient outcome through the provision of patient-tailored care, delivered by a team of dedicated experts able to identify, counsel and manage inherited bowel cancer syndromes. It requires skilled endoscopists, not only for diagnosis but for on-going surveillance and intervention. Specialist histopathology and genetic services are necessary for accurate diagnosis in this complicated patient cohort. Meticulous analysis of tissue for dysplasia and cancer is vital for successful surveillance and management. Finally, a decision

must be made regarding the need for surgery and, when it is required, the type and timing of it. It is through these measures that the outcomes from familial CRC have seen significant improvement in recent years and should continue to do so.

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