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Pathology of Staging of Early Colorectal Lesions During Surveillance Programmes

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1. Introduction

Colorectal carcinoma (CRC) is the second most common cancer in women after carcinoma of the breast and the third most common cancer in men after carcinoma of the prostate and lung with a lifetime risk in the UK of one in 16 for men and one in 20 for women (C-R-UK, 2011). In 2008, around 40,000 people in the UK were diagnosed with bowel cancer and approximately 16,000 died from the disease. In the same year, there were an approximately 334,000 new cases of CRC in the European Union (GLOBOCAN, 2008). The lowest rates for both men and women were in Greece and the highest rates for men were in Hungary and for women in Denmark. Rates for the UK for men and women were below the EU27 average (C-R-UK, 2011). Worldwide, every year, more than 1 million will develop CRC (Parkin et al., 2005).

Over 90% of CRC is sporadic in nature and affects 25 per 100 000 per year of individuals aged 45–55, but over 300 per 100 000 per year in individuals aged 75 and over (West et al., 2008). Internationally, the UK has an incidence of CRC close to the average for all EU countries, which is slightly lower than that for Australia, New Zealand and North America (Halloran, 2009).

Survival rates in individuals with CRC have increased substantially in the past few years, possibly as a result of early diagnosis and improved treatment. Although substantial information about risk factors exists, about 75% of diagnoses are in patients with no apparent risk factors other than old age (ACS, 2011), however, the 5-year survival is still less than 60% in most European countries (Verdecchia et al., 2007).

2. Why screen for bowel cancer?

In 1998 the NHS started to develop the Bowel Cancer Screening Programme (Hardcastle et al., 1996) and in 2006, the English CRC screening programme started a 2-yearly screening for individuals between the ages of 60 and 69 (extended to 74 years in 2010) (Halloran, 2009). The decision was based on the results of four large randomized controlled trials, including one in Nottingham (Hardcastle et al., 1996), where a 16% reduction in mortality was associated with the implementation of bowel screening. These trials showed that population screening with the faecal occult blood test (FOBT) every two years has the potential to

reduce colorectal mortality between 15% to 18% in people aged 45-74 (Hardcastle et al., 1996; Kronborg et al., 1996; Lindholm et al., 2008; Mandel et al., 1993). Individuals who attend screening have a 25% reduction in their risk of dying from CRC. These studies supported similar results from trials in Nottingham (Hardcastle et al., 1996; Steele et al., 2009; UK-Colorectal-Cancer-Screening-Pilot-Group, 2004).

The use of flexible sigmoidoscopy has also been investigated as a screening tool (Atkin et al., 1993; UK-Flexible-Sigmoidoscopy-Screening-Trial-Investigators, 2002) which showed that a once-only flexible sigmoidoscopy between the ages of 55 and 64 could reduce CRC incidence by 33% and mortality from CRC by 43% (Atkin et al., 2010). The test was also found to be safe and acceptable (Atkin et al., 1993). Several randomised trials and Cochrane reviews have provided high-quality evidence that this test, if offered every 2 years, has the potential to reduce mortality rates associated with CRC by 16% (Towler et al., 1998) and reduces incidence and mortality rates of distal CRC by 60-80% (Newcomb et al., 2003; Selby et al., 1992).

In general, the NHS Bowel Cancer Screening Programme (NHS BCSP) commenced in April 2006 and invites men and women aged 60-69 to participate via submission of faecal occult blood test every 2 years; those with a positive result will be offered colonoscopy (West et al., 2008).

As a marker of the success of the programme, at colonoscopy, the proportion of Duke’s stage A and B lesions is markedly higher than that diagnosed amongst the symptomatic population (Goodyear et al., 2008; Halloran, 2009).

3. Principles of screening

The aim of screening for CRC is to prevent the development of advanced disease through detection of early and premalignant adenomas, from which at least 80% of cancers are thought to arise (Cunningham et al., 2010). As outlined by Wilson and Jungner, (1968) the criteria for screening (Table 1), which have been adopted by the WHO, demonstrates that CRC is an ideal disease for screening. Population screening therefore continues to offer the best prospects for reduction in mortality rates (Cunningham et al., 2010).

WHO screening principles:

1. The condition sought should be an important health problem for the individual and community.
2. There should be an acceptable treatment or useful intervention for patients with the disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable screening test or examination.
6. The test should be acceptable for the population.
7. The natural history of the disease should be adequately understood.
8. There should be an agreed policy for referral for further examination and for whom to treat as patients.
9. The cost should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case finding should be a continuing process and not a once-only project.

Table 1. (Wilson and Jungner, 1968)

The programme uses faecal occult blood testing (FOBT) as the primary screening modality to select patients for colonoscopy (BCSP, 2011). Colonoscopy is the best means we have to detect CRC and it provides an opportunity for therapeutic intervention, which is not possible with virtual colonoscopy (computerized tomography colonography). CT colonography (virtual colonoscopy) is as sensitive as colonoscopy for the detection of cancers and large adenomas, but includes exposure to radiation, requires full bowel preparation, and, at the end, colonoscopy is necessary for definite treatment (Halligan et al., 2005; Whitlock et al., 2008). Whilst the morbidity and mortality associated with colonoscopy might be considered acceptable for patients with signs and symptoms of the disease, they are unacceptable as a first line population screening. Perforation and clinically significant bleeding occur after colonoscopic polypectomy in about 0.2% and 1% of cases, respectively (Bond, 2000).

Flexible sigmoidoscopy carries significantly lower risk but will miss some 30 to 40% of proximal lesions (Halloran, 2009). As a screening test, the guaiac FOBT (gFOBT) has significant limitations as it cannot detect low concentrations of blood and has a poor analytical specificity. Any blood that reaches the stool may give a positive test result such as in cases of ulcerative colitis, Crohn's disease, haemorrhoids, major dental surgery or upper gastrointestinal bleeds, as does a diet of large raw steaks and black pudding (Halloran, 2009). Evidence from randomized controlled trials designed to assess the impact of FOBT-based screening on mortality in the screened population have suggested that FOBT is more likely to detect distal colonic and sigmoid lesions rather than right-sided tumours (Thomas et al., 1992).

The sensitivity of FOBT varies but has been quoted as between 6.2% and 83.3% in a recent systematic review when considering all neoplasms (Burch et al., 2007).

Harmston et al. (2010) showed that the location of screen-detected cancers does not differ from that seen in the unscreened population which suggests that faecal occult blood test screening detects cancer irrespective of location within the colon. It should be stressed that patients with negative FOB negative should not be given the impression of being cancer free.

Hol et al. (2010) recently showed in a population-based CRC screening trial using immunochemical FOB (IFOB) randomized against guaiac-based FOB that the detection rate was far better in the former. The authors strongly suggest using the IFOB in screening programmes, however, these findings need to be validated before changing practice of screening.

As a result of bowel screening, there will be more cases of malignant polyps detected in the screening programme than in symptomatic patients. Furthermore, how should patients with positive FOB and negative colonoscopy be managed?

One review from Canada (McLoughlin and Telford, 2007) addressed the issue and showed that when there is positive FOB and the patient undergoes both upper and lower gastrointestinal endoscopy, the yield for upper tract pathology is significant. These authors, however, argue that in those patients with a positive FOB test and negative colonoscopy, it is not cost effective to perform routine upper endoscopy unless the patient is anaemic, symptomatic or has risk factors for gastric cancer.

What happens to the population outside the screening age group?

In an important study, Shellnut et al. (2010) looked at the appropriateness of restricting the screened age group and found that not screening individuals under 50 and over 75 years would miss around 49 to 50% of patients in their study. Harmston et al. (2010) looked at 100 patients with CRC in the NHSBCSP and analysed their symptoms. They found that 70% had

significant symptoms such as rectal bleeding, tenesmus, change in bowel habit and abdominal pain and they argued that with proper public awareness, these symptoms would have triggered referral. The study also showed that there was a significant increase in detecting Dukes A lesions in 28.5% of cases.

Ellul et al. (2010) again showed that with screening there is earlier detection of Dukes A over a non screened population of 45.3% compared with 10.1%. This is good evidence for the benefit of screening. It is remarkable, however, that the proportion of Dukes A stage tumours varied widely from 45.3% in the study of Ellul et al. to 28.5% in that of Harmston et al. with no apparent explanation for this variation. The screening programme is likely to be an effective and practical way of reducing CRC, but it does have its limitations, which can only be reduced by further research to maximize overall patient care (Haboubi, 2010).

4. Pathology and management of early (pT1) colorectal lesions in the NHSBCSP

Colorectal polyps are extremely common in Western countries and are found in up to 30% of autopsies performed in people aged more than 60 years (Williams et al., 1982). Histologically, colorectal polyps are divided into neoplastic or nonneoplastic and it is well known that more than 95% of CRC arise from neoplastic adenomatous polyps (adenomas) (Bond, 2000; Morson, 1966) through the well documented adenoma-carcinoma sequence (Muto et al., 1975).

By definition, all adenomas show dysplasia and is divided into either low or high grade (Quirke et al., 2007; Riddell et al., 1983) and architecturally into either tubular, tubulovillous or villous types according to the WHO classification (Hamilton and Aaltonen, 2000). High grade dysplasia shows complex glandular crowding and irregularity, prominent budding, cribriform architecture with 'back to back' glands and prominent cellular atypia (Quirke et al., 2007; Riddell et al., 1983). The latter includes loss of cell polarity or nuclear stratification, markedly enlarged nuclei with a dispersed chromatin pattern and a prominent nucleolus, abundant mitotic figures with atypical mitoses and prominent apoptosis.

A malignant colorectal polyp is a lesion in which cancer has invaded through the muscularis mucosae and into the submucosa (Cooper, 1983; Cooper et al., 1995; Lipper et al., 1983; Morson et al., 1984; Volk et al., 1995) and T1 adenocarcinoma is defined as invasion into the submucosa and not into the muscularis propria (Edge et al., 2010). The incidence of malignant colonic polyps amongst all removed colonic adenomas varies between 2.6% and 9.7%, with an average incidence of 4.7% (Coverlizza et al., 1989).

Increasing dysplasia and, presumably, malignant potential correlate with increasing adenoma size, villous component, and patient age (Konishi and Morson, 1982). The likelihood of invasive carcinoma also increases with increasing polyp size (Fenoglio and Pascal, 1982). Size is perceived to be one of the most important risk factor which put an adenoma into high risk category of malignant transformation. Amongst 5137 adenomas of diameter of less than 5 mm, none demonstrated malignant transformation (Nusko et al., 1997).

Generally, malignant colorectal polyps are divided into high and low risk lesions. High risk malignant polyps were defined as having one of the following: incomplete polypectomy, an involved resection margin, lymphatic or venous invasion, or are poorly differentiated histologically (Netzer et al., 1997). Adverse outcome in a malignant colorectal polyp was defined as residual cancer in a resection specimen and local or metastatic recurrence in the

follow up period (Netzer et al., 1998). In the high risk group, surgery is recommended when either of the two independent risk factors, such as incomplete polypectomy or a positive margin is present or if there is a combination of other risk factors. As lymphovascular invasion or poorly differentiated cancer did not have an adverse outcome when studied alone, operations in such cases should be individually assessed taking the risk of surgery into consideration (Netzer et al., 1998) as the risk for death from elective colonic resection averages about 2% (from 0.2% in the young to more than 5% in the elderly) (Greenburg et al., 1981).

An analysis of published series of malignant polyps estimated that the risk of residual cancer or nodal metastases from endoscopically resected pedunculated and sessile malignant polyps with favourable criteria was 0.3% and 1.5%, respectively (Cranley et al., 1986). Another review of endoscopically resected polyps with poor prognostic factors (poorly differentiated cancer, margin involvement, or presence of lymphatic or vascular invasion) reported residual cancer in 8.5% and 14.4%, for patients with pedunculated and sessile malignant polyps, respectively (Coverlizza et al., 1989). The American College of Gastroenterologist recommends no further treatment if the polyp is considered to be completely excised by the endoscopist, the cancer is not poorly differentiated and there is no vascular or lymphatic permeation and the margin of excision is free (Bond, 2000). Invasion of the stalk of a pedunculated polyp, by itself, is not an unfavorable prognostic finding, as long as the cancer does not extend to the margin of resection (Bond, 2000). In large sessile polyps which are not resectable endoscopically or that might contain invasive carcinoma with unfavorable prognostic features, it is useful to mark the polypectomy site (Shatz et al., 1997) to aid future identification of the site if necessary.

If the polyp is removed in one piece, the area of diathermy can be used as the histological landmark for the true transected margin of resection. If the polypectomy has been performed in piecemeal, it may be impossible to determine the true margin of resection, therefore precluding an accurate reporting on the status of completeness of excision (Cooper, 2007).

The presence of multiple adenomas in the same segment as the malignant polyp might be an argument for resection, particularly if the other polyps subsequently show high grade dysplasia (Haboubi and Scott, 2000). Similarly, the presence of a malignant adenoma in association with a strong family history of large bowel cancer would also be in favour of resection (Haboubi and Scott, 2000).

4.1 Factors against resection

Surgical resection is associated with a significant risk of mortality and morbidity with the risk of diarrhea after extensive colonic resection, particularly in the elderly (Haboubi and Scott, 2000) with an overall mortality of 5% (Scott et al., 1995). In practice, any individual patient with a histologically unfavourable malignant polyp has either a 10% chance of cancer-specific treatment failure or a 3-5% risk of postoperative death (Haboubi and Scott, 2000).

4.2 Margins of excision

Cancer at or near the resection margin is a histological finding that signifies the potential for an adverse outcome (Hackelsberger et al., 1995; Hassan et al., 2005; Ueno et al., 2004a). In one study, 21.4% of cases with cancer at or near the resection margin had an adverse outcome (Cooper et al., 1995). It is also important to record completeness of excision of the deep and mucosal margins as surgery is usually an indication when the former is involved and further local excision may be tempted if the mucosal margin is believed to be involved (Quirke et al., 2007).

An involved margin has many definitions in the literature. Cancer near the margin has been variously defined as cancer cells 1mm or less from the transected margin, (Cooper et al., 1995) cancer cells 2mm or less from the transected margin, (Netzer et al., 1997; Volk et al., 1995) and cancer within the diathermy and/or within one high-power field of the diathermy (Morson et al., 1984; Ueno et al., 2004b). However, most studies showed that the presence of cancer near the transected margin has the same clinical significance as cancer at the actual margin (Cooper et al., 1995; Hackelsberger et al., 1995; Netzer et al., 1997).

Presently, there is no consensus on what represents a 'negative margin'. A negative margin has been defined as one in which cancer is not within the actual diathermy, (Morson et al., 1984) more than one high-power field from the diathermy, greater than 1mm from the margin (Cooper et al., 1995) and more than 2mm from the margin (Netzer et al., 1997; Seitz et al., 2004). Incomplete local excision is not a judgement based on histology alone but a decision made jointly by the endoscopist and pathologist (Cooper, 2007).

4.3 Histological grade

Poorly differentiated (grade III) cancer, which has been classified as a poor risk factor in a malignant polyp, comprise 5–10% of cases and are associated with a significantly greater incidence of poor outcome than for better differentiated tumours (Kyzer et al., 1992; Nivatvongs et al., 1991).

4.4 Vascular invasion

Many studies showed that vascular invasion has been associated with an adverse outcome (Hassan et al., 2005; Ueno et al., 2004b). Muller et al. (Muller et al., 1989) demonstrated that vascular invasion on its own predicted an adverse outcome, but other studies have not supported these findings (Cooper et al., 1995; Volk et al., 1995):

4.5 Haggitt levels

Haggitt level of invasion in a pedunculated polyp is an important risk factor. In the Haggitt system (Haggitt et al., 1985) the level of invasion in a malignant pedunculated polyp is defined as follows:

Level 1: Carcinoma invading into the submucosa, but limited to the head of the polyp.

Level 2: Carcinoma invading to the level of the neck (the junction of the head and stalk) of the adenoma.

Level 3: Carcinoma invading any part of the stalk.

Level 4: Carcinoma invading into the submucosa of the bowel wall below the level of the stalk but above the muscularis propria.

According to these criteria, invasive cancer arising in a pedunculated adenoma could be classified as level 1 to level 4, but invasive cancer arising in a sessile adenoma is by definition a level 4 lesion. Studies have shown that level 4 invasion correlates with an adverse outcome and that patients with level 1–3 cancers and grade I or II cancers, and no lymphatic or venous invasion, can be successfully treated by polypectomy alone (Haggitt et al., 1985; Pollard et al., 1992).

Follow-up surgical resection has been recommended following polypectomy showing Haggitt level 4 invasion (Haggitt et al., 1985; Kyzer et al., 1992; Nivatvongs et al., 1991) or with any level polyp with grade III cancer, (Pollard et al., 1992) and/or lymphatic invasion (Haggitt et al., 1985).

4.6 Kikuchi's levels

In pT1 tumours, the frequency of lymph node metastasis in sessile tumours that involve the superficial, middle and deep thirds of the submucosa (so-called Kikuchi levels sm1, sm2 and sm3 respectively) (Kikuchi et al., 1995) has been reported to be 2%, 8% and 23% respectively (Nascimbeni et al., 2002). Invasion to level SM1 has been reported to have a significantly lower incidence of lymph node metastasis than level SM2 or SM3 invasion (Nascimbeni et al., 2002). However, neither the Kikuchi (for sessile tumours) nor the Haggitt (for polypoid tumours) system is easy to interpret, especially if there is fragmentation or suboptimal orientation of the polyp.

More recently, Ueno et al. (Ueno et al., 2004b) proposed that the depth of invasion measured in microns beyond the muscularis mucosae provides a more objective measure, and this system has been adopted in Japan. However, again this system is difficult to use in routine practice.

It has to be highlighted that each classification has advantages and disadvantages. The Kikuchi system cannot be used if there is no muscularis mucosa in the biopsy and the Haggitt system is of no value in sessile lesions and measurement depends on a recognisable submucosa and good orientation of the polyp (Quirke et al., 2007).

In an extensive review of the literature (31 studies involving 1900 patients), Hassan et al. (2005) reported good outcome in polyps showing favourable histological features (e.g. negative margin, grade I or II and absence of lymphovascular invasion), supporting the suggestion that endoscopic polypectomy alone is adequate treatment in these patients.

The treatment of patient with an endoscopically removed malignant colorectal polyp must be individualized for each patient, taking all factors into consideration. Guidelines endorsed by the American Gastroenterological Association (Bond, 2000) recommend no further treatment is indicated after colonoscopic resection of a malignant colorectal polyp if the following criteria are fulfilled:

- The polyp is considered by the endoscopist to have been completely excised
- The cancer is not poorly differentiated
- There is no vascular or lymphatic permeation
- The margin of excision is not involved.

The guidelines also comment that when a patient's malignant polyp has poor prognostic features, the relative risks of surgical resection should be weighed against the risk of death from metastatic cancer.

4.7 Tumour budding

Tumour budding is defined as isolated single cancer cells or small clusters (fewer than five cells) of cancer cells at the advancing edge of the tumour. Several studies have defined a tumour as positive for budding when there are five or more buds per 20 power field (Kaneko et al., 2007; Ueno et al., 2004b). Studies of T1 cancers have shown that the presence of tumour budding is significantly associated with lymph node metastasis and other adverse outcomes (Kaneko et al., 2007; Masaki et al., 2001a; Ueno et al., 2004b).

4.8 Cribriform histology

T1 CRC with a cribriform histology showed a high rate of lymph node metastasis when analyzed with multivariate analysis. In one of the studies, all the cases were all initially treated by surgical resection (Egashira et al., 2004).

4.9 Potential 'molecular' markers

Masaki et al. (Masaki et al., 2001b) showed that expression of MMP-7 (a matrix metalloproteinase) at the invasive margin of T1 cancers was significantly associated with other poor histological features and unfavourable outcome. Hirano and Minimoto (2000) reported that a high expression of p53 and a low expression of p27 were significantly associated with metastasis in cases of T1 CRC.

4.10 Pseudoinvasion/misplaced mucosa

Pseudoinvasion is misplacement of the whole mucosa into the submucosa and this herniated mucosa often mimics invasive cancer causing a diagnostic difficulty for pathologists. Even among experienced gastrointestinal pathologists, there is a lack of unanimity in differentiating invasive carcinoma from pseudoinvasion (Cooper et al., 1995; Muto et al., 1973). It is commonly seen in prolapsed polyps in the sigmoid colon and is perceived to be one of the most difficult areas in the interpretation of polyp and in the context of the bowel screening programme (Quirke et al., 2007).

In cases of pseudoinvasion, the rounded contour of the neoplastic glands and the cytological similarity of the herniated epithelium to the surface adenoma, continuity of the surface epithelium with the 'deep' epithelium and the presence of lamina propria around the submucosal are all indications of pseudoinvasion rather than invasive cancer (Cooper, 2007). The presence of haemosiderin deposits provides a clue to the presence of misplaced epithelium. The distinction between invasion and pseudoinvasion is made more difficult when the herniated epithelium is severely dysplastic (Pascal et al., 1990) and there are instances where the differentiation is difficult with 100% certainty and the pathology report should indicate this uncertainty.

4.11 Serrated lesions of the colorectum

Serrated lesions have only recently been highlighted as having distinct genetic features and a different architecture from classical adenomas. The family of serrated polyps comprises sessile serrated adenomas, also called sessile serrated polyps (SSA/Ps), traditional serrated adenomas, hyperplastic polyps, and mixed hyperplastic/adenomatous polyps or admixed polyps (Ensari et al., 2010).

It is estimated that SSA/Ps represent 8-20% of serrated polyps with a predilection for the right colon. The diagnosis is mainly based on architectural features and are usually larger than hyperplastic polyps, measuring from 5 mm to more than 10 mm. They are flat to sessile. The crypts are elongated and epithelial serration and dilatation are usually more prominent in the basal part of the crypts in a 'crescendo' fashion.

Traditional hyperplastic polyps that are large (>1 cm) and/or multiple and/or located in the proximal colon are associated with an increased risk for CRC, notably in the hyperplastic polyposis syndrome where they occur throughout the colon with a 50% risk of CRC (Leggett et al., 2001). From the management point of view they should be treated similar to conventional adenomas.

5. Conclusion

The histopathology reports on malignant colorectal specimens are of major importance regarding patient management, prognostic assessment, audit and research. It has been

shown that use of proforma greatly improves the quality of such reports (Quirke et al., 2007; Quirke and Morris, 2007).

The bowel cancer screening programme will generate many early cancers (pT1) for which there is poor management protocols as opposed to pT2 tumours which they need a definite surgical excision (Haboubi, 2010; Quirke et al., 2007).

The preferred care for patients with polypectomy specimens which contain invasive carcinoma is controversial (Haboubi and Scott, 2000). Taking into considerations all factors involved, the issue of polypectomy for malignant polyps versus surgical resection is best resolved by a multidisciplinary team involving the surgeon, pathologist and endoscopist, taking the patient's condition and wishes into account (Mitchell and Haboubi, 2008).

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To publish a book on colonoscopy suitable for an international medical audience, drawing upon the expertise and talents of many outstanding world-wide clinicians, is a daunting task. New developments in videocolonoscopy instruments, procedural technique, patient selection and preparation, and moderate sedation and monitoring are being made and reported daily in both the medical and the lay press. Just as over the last several decades colonoscopy has largely supplanted the use of barium enema x-ray study of the colon, new developments in gastrointestinal imaging such as computerized tomographic colonography and video transmitted capsule study of the colonic lumen and new discoveries in cellular and molecular biology that may facilitate the early detection of colon cancer, colon polyps and other gastrointestinal pathology threaten to relegate the role of screening colonoscopy to the side lines of medical practice. This book draws on the talents of renowned physicians who convey a sense of the history, the present state-of-the art and ongoing confronting issues, and the predicted future of this discipline.

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