Nitrite, commonly used in processed meats as preservation agents, as causes of human cancer. However, exposure is not specific to vegetables and a low consumption of meat and saturated fatty acids are associated with reduced colorectal cancer risk. However, there is some controversy surrounding these findings. For example, a meta-analysis of 13 prospective studies involving 3,635 cases of colorectal cancer and 459,930 participants found no association between total fat, saturated fat, monounsaturated fat and polyunsaturated fat consumption and colorectal cancer.

More than a decade ago, fruits and vegetables were strongly and widely considered to reduce risk of colorectal cancer, a message strongly supported by the media. Many anti-carcinogenic micronutrients, such as vitamin C, beta-carotene, folate, dietary fiber, flavonoids, selenium, phytosterols and other phytochemicals, have been proposed to contribute to this potential anticarcinogenic effect of fruits and vegetables.

In 1997, a World Cancer Research Fund/American Institute for Cancer Research report concluded that there was convincing evidence for a decreasing risk of colorectal cancer associated with increasing fruits and vegetable consumption. A decade later, in an updated report, the same organisation downgraded the protective effect of fruits and vegetables from convincing to probable. Between these reports, at the same time and using the same scientific evidence, an IARC Working Group declared a lack of association between consumption of fruits and vegetables and colorectal cancer.

Early cohort studies supported a protective effect for fruits and vegetables, which was not the case for more recent prospective research. Variations in results between cohort studies could be due to measurement error and to differences in adjustments. Most prospective studies used a single food frequency questionnaire to assess dietary exposition, which may not satisfactorily represent long-term intake.

In conclusion, the observed risk estimates in prospective studies between fruits, vegetables and colorectal cancer are very modest after adjustment for covariates.

Dietary fibre intake and colorectal cancer risk
Dietary fibre as an entity is difficult to separate from its dietary sources. Recent meta-analyses and pooled analyses have yielded null findings, that is no association between dietary fibre intake and colorectal cancer risk.

Red meat, processed meat and colorectal cancer
Prospective cohort and case-control studies have associated a daily intake of red and processed meat with an increased risk of colorectal cancer. The term red meat refers to beef, pork, lamb and goat; processed meat refers to meat preserved by smoking, curing, salting and/or addition of chemical preservatives. The results of meta-analysis support the hypothesis that high consumption of red and processed meat may increase the risk of colorectal cancer. However, the epidemiological association across the prospective studies is relatively weak with a 30% increased risk of colorectal cancer in high meat eaters compared to the lowest group of meat eaters.

Another hypothesis involves the potential role of nitrate and nitrite, commonly used in processed meats as preservation agents, as causes of human cancer. However, exposure is not specific to
CHAPTER 5
Screening for Colorectal Cancer
Julietta Patnick1 and Wendy S. Atkin2
1NHS Cancer Screening Programmes, Oxford University, UK
2Imperial College London, London, UK

OVERVIEW

• People living in the UK have a 1 in 20 chance of developing colorectal cancer.
• Survival is only 50% if diagnosed in people with symptoms but over 90% if detected at an early localised stage.
• Screening for early colorectal cancer can reduce colorectal cancer mortality. Finding and removing adenomas from which cancers slowly develop reduces incidence as well as mortality.
• Randomised trials have shown that colorectal cancer mortality can be reduced by 2-yearly faecal occult blood testing (FOBt) and by once only flexible sigmoidoscopy.
• Other methods for screening which have not been tested in randomised trials include faecal immunochemical testing, colonoscopy, CT colonography.
• The English Bowel Cancer Screening Programme offers 2-yearly screening by FOBt to people aged 60–74 and will shortly be introducing flexible sigmoidoscopy screening for those in their mid to late 50s. FOBt screening is currently available in Wales and Northern Ireland to those aged 60–69 and in Scotland to those aged 50–74.

Approximately 21,000 men and around 18,000 women are diagnosed with colorectal cancer each year in the United Kingdom. It is the third most common cancer after lung and breast cancer and the second most common cause of cancer death, killing over 16,000 people each year.

Survival rates have doubled over the past 30 years to about 50% for both colon and rectal cancer, although it is slightly higher in women than in men. How long a person is known that survival varies by stage, and at its highest for those with the earliest stage, Duke’s A colorectal cancer, which is greater than 90%. It is among those with Duke’s B colorectal cancer that survival drops to around 50%. The cancer has grown into other parts of the body (Duke’s D) — see Table 7.1 in Chapter 7. It is this survival differential that led to the initial interest in screening the large bowel. In addition, since colorectal cancers are thought to develop over a long period from adenomatous polyps in the bowel wall, it was suggested that finding and removing such polyps through screening could lead to a reduction in the incidence of colorectal cancer.

Many countries throughout the world have introduced colorectal cancer screening following publication of the results of faecal occult blood test (FOBt) trials in the 1990s. Most screening programmes therefore use the FOBt and a few use endoscopic methods.

How does the current colorectal cancer screening programme work in the UK?

England was the first of the UK countries to introduce a screening programme for people at average risk of colorectal cancer. Following an extensive pilot in England and Scotland, which operated from 2000, the screening programme in England started in 2006.

In England the programme initially targeted those aged 60–69, but now that it is operational across the country, it is extending to reach all people aged 60–74 inclusive. It uses the guaiac FOBt and is modelled on the Nottingham trial protocol which was replicated in the UK pilot.

The programme operates five ‘hubs’ which send invitations and literature to the target population, followed shortly afterwards by a FOBt kit. This comprises three cards of two windows each on to which the subject is asked to place a faecal smear sample from each of three bowel motions (Figure 5.1). This card is then returned by post to the hub in a plastic lined envelope. At the hub it is developed and the results are sent to the subject and his/her GP. Currently acceptance rates are just over 50%.

If the test is positive, the patient is sent an appointment to visit a screening centre. If the test is ‘weakly positive’, the subject is asked to repeat the test once or twice until a decision to refer to a screening centre or return to routine screening is made. About 2% of subjects who complete a test are referred.

The screening centres are accredited local endoscopy centres. After a positive FOBt the patient is first counselled and their health status checked. If appropriate, colonoscopy is offered and the need for careful bowel preparation explained. Around 10% of patients who have a positive FOBt test and undergo colonoscopy are found to have an invasive cancer present. Of the rest, half have adenomas found and of the remainder some will have other bowel pathology. Around one third will have a normal colon.
Chapter 8
Imaging of Colorectal Cancer
Andrew Slater
John Radcliffe Hospital, Oxford, UK

Overview
- Diagnosis of colorectal cancer can be by Colonoscopy or CT Colonography, which have equal sensitivity. Minimal preparation CT of the Colon is a less accurate test that is very easy to tolerate.
- Staging of colorectal cancer is by CT of the whole body. MRI is also used to stage rectal cancer, and endoscopic ultrasound is useful for early rectal tumours. MRI of the liver and PET/CT are not used routinely, but are helpful in staging complex cases.
- Follow up of metastatic disease, and surveillance in cured patients is usually carried out with CT scanning.
- Liver metastases can be treated successfully with Radiofrequency ablation as a percutaneous procedure.
- Bowel obstruction from colon cancer can be treated successfully with self-expanding metal stents placed endoluminally under radiological guidance.

Diagnosis of colorectal cancer
Optical colonoscopy (OC) and Computed Tomography Colonography (CTC) have equivalent very high sensitivities for detecting colorectal cancer of around 98%. The terms Virtual Colonoscopy and CT pneumocolon are synonymous with CTC. OC requires full laxative bowel preparation and sedation. It is expensive, occasionally causes bowel perforation, but has the advantage of immediate biopsy of detected lesions and can detect non-malignant process such as colitis.

There has recently been a UK National Patient Safety Agency (NPSA) initiative regarding laxative bowel preparation (Picolax, Citrafleet, Fleet Phospho-Soda, Klean Prep, Moviprep). This was stimulated by reported incidents of harm from use of these drugs, including one death. It is no longer acceptable for UK Radiology departments to send patients laxative bowel preparation in the post based upon the very limited clinical information usually available on a radiology request card. In future all requests for examinations that use laxative bowel preparation (Colonoscopy, CT Colonography and Barium Enema) must state explicitly that the patient is safe to take these medicines, for example stating ‘patient fit for laxative bowel prep’.

Information regarding cautions and contraindications to these drugs is available in the British National Formulary (BNF), but the main risks are of bowel perforation in patients with acute diverticulitis, and electrolyte imbalance in patients who are also taking diuretic medication or have renal impairment. Information regarding safe use of laxatives is provided for patients when these drugs are dispensed, and referring clinicians are asked to emphasise to patients the importance of following these instructions.

CTC was first described using laxative bowel preparation, but techniques have been developed that use oral contrast agents for 24–48 hours and a modified diet instead. This technique is called faecal tagging. Faecal material that remains in the colon will be ‘tagged’ with oral contrast and so can easily be distinguished from pathology (Figure 8.1). The NPSA regulations described above do not apply to this type of preparation. When the patient attends for the CT scan, a small tube is placed in the back passage and CO₂ is insufflated until the colon is distended. CO₂ is absorbed much more rapidly by the bowel than air, and so greatly reduces the gas content of the colon before scanning.

Figure 8.1 CT Colonography with faecal tagging. This axial CT image shows some residual faecal fluid within the colon, but this is high attenuation due to the tagging material (black arrow). A small polyp is easily distinguished from this fluid (white arrow).

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The Role of Primary Care

of relatives. The primary care doctor may also advise patients with diagnosed colorectal cancer about practical considerations, including access to social security benefits. In the United Kingdom eligibility for attendance allowance may be immediately available in the exceptional circumstance of cancer with a short terminal prognosis of less than six months.

For some patients, especially those with rectal tumours, the diagnosis of cancer is also accompanied by the necessity for either colostomy or ileostomy. Such patients will often require further specialised support, and liaison between the primary care team and specialist stoma nurses is important (see Chapter 15).

As colorectal cancer is the sixth most common cause of mortality in the United Kingdom, a general practitioner will on average care for a patient dying from colorectal cancer every 18 months. As the disease progresses, management will shift towards palliative care. Ideally, this would be delivered jointly by the primary care team and specialist palliative care services, such as those based at a hospice or provided by specialist palliative care nurses. Few data exist to guide on the most effective models for palliative care in colorectal cancer. However, non-randomised studies have shown high satisfaction among patients when they are kept fully involved in understanding the progression of their disease and their treatment options, when shared care cards are used, and when home care teams are provided. Complex symptomatic care in some cases can be enhanced by admission to a specialist unit when specialist care is not available or manageable at home.

A shared (between healthcare sectors) end of life pathway is in use in most parts of the UK. The patient and carer preference for where the patient wishes to die should be documented and updated as part of the pathway and primary care clinicians, as part of the palliative care team, will realise those wishes where at all possible.

Conclusion

Whilst it was often perceived that the key role of primary care was limited to a gatekeeper function, ensuring appropriate cases are referred for secondary care investigation, it is now acknowledged that it has a significant contribution to make in all stages of the cancer pathway. Indeed with the governmental changes in England only, primary care will lead the commissioning and provision of healthcare. Heath promotion, advice concerning genetic risk and encouraging participation in screening will assist in the prevention of disease and in early diagnosis. Early recognition of symptoms that warrant further investigation remains an important part of the primary care role. There are also key functions after diagnosis: encompassing the coordination of continuity of care; providing ongoing support for patients, carers and families; providing palliative care to patients; and supporting families and carers, including the provision of bereavement care. At all these stages, primary care plays an important role not only in the management of disease but also in the provision of information to assist in decision making.

Further reading


digitalassets/documents/digitalasset/dh_123394.pdf [accessed 10 April 2011].


of a wedge, are inserted into the radiotherapy beam to produce an even dose of radiation across the treatment volume (Figure 10.5). Standard radiotherapy doses are 45–50 Gy in 25 daily fractions over 5–6 weeks, giving between 1.8 Gy and 2 Gy per fraction to the ICRU reference point when combined with chemotherapy. When patients refuse general anaesthesia, or refuse surgery, then higher total tumour doses may need to be considered, ideally attempting to deliver over 70 Gy. However, rectal cancer cannot be treated at this dose with standard external beam radiotherapy and conventional volumes, because rectal and small bowel toxicity would be unacceptable. Endocavitary or interstitial brachytherapy irradiation may be combined with external beam treatment to achieve doses in excess of 100 Gy. A few groups have demonstrated reasonable results with acceptable acute and long term toxicities using these techniques.

**Pre- and postoperative radiotherapy**

Despite 15 major prospective randomised trials comparing surgery alone with surgery plus various radiotherapy regimens, the precise role of radiotherapy has yet to be defined. Recent trials using preoperative radiotherapy in patients with rectal cancer have shown significant reductions in local recurrence although only one has shown a clear benefit in terms of improved survival.

The German trial by Saur et al. randomised over 823 patients with locally advanced (T3/T4) or node positive rectal cancers to pre- or postoperative chemoradiotherapy. The 5-year local relapse was 6% in the preoperative group versus 13% in the postoperative group \( (p = 0.006) \). Both acute (27% vs 40%) and late toxic (14% vs 24%) effects of treatment were significantly increased in those patients receiving postoperative therapy. These results contributed to a paradigm shift, such that preoperative chemoradiotherapy has been widely adopted as the standard of care for locally advanced rectal cancer with postoperative therapy being rarely used in this setting.

Radiotherapy courses given preoperatively may be short course (5 fractions) or long course (20–30 fractions). Short course therapy may be given for mobile operable tumours while long course therapy is required for the more locally advanced and fixed tumours in order to downstage them. The Swedish Rectal Cancer Trial (1997) reported a reduction in overall recurrence at 5 years from 27% following surgery alone to 11% when short course radiotherapy was given prior to surgery. This trial was the first to show an overall improvement in survival (5-year survival 58% for radiotherapy plus surgery compared with 48% for surgery alone \( p = 0.004 \)). Surgery is undertaken within 1 week of completing short course preoperative radiotherapy. While this short course therapy may produce some reduction in tumour bulk, a downstaging effect is not seen. Whether a longer interval between completion of radiotherapy and surgery would lead to a meaningful downstaging effect on the tumour remains unanswered.

Disadvantages of short course preoperative therapy the fact that high radiotherapy doses per fraction (5 Gy per fraction) may result in more severe late (long term) side effects. Preoperative radiotherapy is not selective and there is little information on which subgroups of patients may benefit e.g. do patients with T1–T2 N0 tumours benefit as much as patients T2–T3 N1 tumours? Table 10.3 outlines some of the early and late side effects which may be experienced by patients undergoing radiotherapy.

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Short courses of radiotherapy (up to 10 fractions) may be used to palliate symptoms such as rectal bleeding or bone pain.

**Chemotherapy**

Recent years have seen key advances regarding the addition of chemotherapy to preoperative radiotherapy. Concomitant chemotherapy with a fluorouracil (5-Flurouracil or Capecitabine)
Figure 11.1 Circulating tumour cells isolated from the peripheral blood of a preoperative patient with colorectal cancer. The left of the panel shows the composite images at high magnification (×100) of cells stained with AUA-1 (green fluorescence, EpCAM specific antibody), CAM 5.2 (Cy5 fluorescence, epithelial keratin specific antibody), DAPI (nuclear stain) followed by FISH, with CEP 7/aqua (sentromeric probe for chromosome 7) and CEP 8/aqua (sentromeric probe for chromosome 8). This demonstrates that these cells are epithelial with a total of 7 aqua dots present in each nucleus, indicating polysomy for at least one of the chromosomes 7 or 8 (the middle panel shows cell images in the aqua channel). A pseudo coloured composite image of the nucleus, in which chromosomes 7 and 8 appear as aqua dots, is shown on the right of the panel (dot count). (Courtesy of Dr. Triantafyllia G. Ntouroupi, Weatherall Institute of Molecular Medicine, Oxford.)

Figure 11.2 A photomicrograph of a colorectal cancer cell line (SKCO-1) established in culture. The line was derived from a human metastatic colorectal cancer. (Courtesy of Sir Walter Bodmer, Weatherall Institute of Molecular Medicine, Oxford.)

Speaking, surgery is the first option in colonic lesions. For stage II or III rectal cancer, preoperative radiotherapy with or without chemotherapy is considered prior to resection (Chapter 10). Factors such as the ability of the patient to manage a stoma also need to be considered prior to surgery.

**Clinical assessment**

It is important to evaluate the stage of the cancer and to exclude synchronous tumours. This will influence whether the tumour is suitable for local or segmental resection. The presence of metastases will influence whether systemic therapy is considered.

Prior to rectal surgery, anorectal function needs to be assessed. In patients with poor function, sphincter preservation will be less of an issue. Past history is also of importance, for example previous radiotherapy for urogenital organs precludes the use of peri-operative radiotherapy. Box 11.2 summarises an example of a medical clinical assessment.

**Box 11.2 Clinical assessment**

- Establish stage
- Are there synchronous lesions?
- Evaluate operative risk
- Assess preoperative anorectal function
- Level of tumour from anal verge
- Imaging (CT/MR/US)
- PET scan in cases of recurrence

**Preoperative evaluation**

Imaging for preoperative staging is detailed in Chapter 8. Routine investigations include the use of blood tests (including FBC, renal function and liver function tests as well as serum CEA) ECG, CXR, chest function and the detection of metastases (CT, CT-PET and MRI).

**Assessment of peri-operative risk**

A thorough preoperative evaluation in order to minimise the risk of death and morbidity is essential. Patients with chronic diseases such as ischaemic heart disease, congestive cardiac failure, hypertension, asthma and diabetes mellitus need to be optimised prior to surgery. Warfarin, clopidogrel and aspirin need to be stopped and adequate DVT prophylaxis instituted. Transanal excision for rectal cancer is associated with decreased stress on the cardiovascular and respiratory systems and may be a suitable option in patients with significant co-morbidities.

**Preoperative preparation**

Standard practice is now to omit mechanical bowel preparation. Patients have oral dietary restriction to fluids only and a phosphate enema for rectal and left colonic operations. DVT prophylaxis is important with the use of LMWH and graded compression
### Table 13.4 Common chemotherapy schedules.

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Clinical Setting</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capcitabine</td>
<td>First line</td>
<td>Tablets taken orally days 1–14 every 21 days</td>
</tr>
<tr>
<td>Oxaliplatin +</td>
<td>First or subsequent line</td>
<td>Oxaliplatin as a 2-hour infusion on day 1 with oral capcitabine taken on days 1–14. Repeated every 3 weeks</td>
</tr>
<tr>
<td>Capcitabine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxaliplatin +</td>
<td>First or subsequent line</td>
<td>Oxaliplatin + LV as a 2-hour infusion followed by 5-FU bolus and 46-hour 5-FU infusion. Repeated every 2 weeks</td>
</tr>
<tr>
<td>5-FU/LV (FOLFOX)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irinotecan +</td>
<td>First or subsequent line</td>
<td>Irinotecan + LV as a 2-hour infusion followed by 5-FU bolus and 46-hour 5-FU infusion. Repeated every 2 weeks</td>
</tr>
<tr>
<td>5-FU/LV (FOLFIRI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irinotecan</td>
<td>Second or subsequent line</td>
<td>Intravenous infusion given every 3 weeks</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>First or subsequent line</td>
<td>Intravenous infusion given every 2 or 3 weeks. Given in conjunction with cytotoxic chemotherapy</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>First or subsequent line</td>
<td>Intravenous infusion given every week either as a single agent (3rd line) or in conjunction with cytotoxic chemotherapy (1st, 2nd and 3rd line)</td>
</tr>
</tbody>
</table>

### Table 13.5 Pivotal clinical studies in advanced colorectal cancer.


### Oxaliplatin

Oxaliplatin is a platinum-based cytotoxic agent that inhibits DNA replication by the formation of interstrand and/or intrastrand adducts. It is given as a 2-hour infusion with 5-FU and a leucovorin bolus. Common toxicities include diarrhea, cramps and diarrhoea. Hair loss is unusual.

### Irinotecan

Irinotecan inhibits topoisomerase I, an enzyme that is essential for DNA replication. It may given as a single agent or in combination with 5-FU. Common toxicities include diarrhea, myelosuppression, acute cholinergic symptoms (sweating, stomach cramps and diarrhoea) and alopecia.

### Other conventional cytotoxic agents

Raltitrexed inhibits the enzyme thymidylate synthase. Its use is largely limited to patients who are intolerant of 5-FU. Mitomycin C is an alkylating agent with activity in colorectal cancer. It is used in combination with 5-FU.

### Targeted chemotherapeutics

Over recent years the focus of drug development has moved away from conventional cytotoxic agents towards the development of agents that selectively target the molecular pathways involved in cancer growth. Molecular targeted agents currently approved for use in advanced colorectal cancer are: cetuximab and panitumumab, monoclonal antibody agents that target the epidermal growth factor receptor (EGFR) and bevacizumab, a monoclonal antibody that targets vascular endothelial growth factor (VEGF). The targeted chemotherapy agents have distinct side effect profiles which differ from the conventional cytotoxic drugs. The targeted chemotherapeutics for advanced disease are summarised below and discussed in detail in the following chapter.

### Bevacizumab

Bevacizumab is given in combination with conventional cytotoxic chemotherapy schedules and has been shown to provide a survival benefit in both the first- and second-line setting. The main toxicities are: hypertension, slow wound healing, bleeding, increased risk of thromboembolic events. There is also a risk of perforation of the GI tract which occurs in 1.5–3.9% of patients.

### Cetuximab (Chimeric IgG1) and Panitumumab (Fully humanised IgG2)

Clinical studies have demonstrated that the activity of these agents is limited to patients whose tumours express the wild-type KRAS
Innovative Treatment for Colorectal Cancer

Figure 14.1 Angiogenesis as a target for anti cancer therapy.

Table 14.1 Results of phase 3 trial comparing IFL to IFL and bevacizumab (from Hurwitz et al.).

<table>
<thead>
<tr>
<th></th>
<th>IFL/Placebo</th>
<th>IFL/Bevacizumab</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median survival (mo)</td>
<td>15.6</td>
<td>20.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Progression-free survival (mo)</td>
<td>6.24</td>
<td>10.6</td>
<td>0.001</td>
</tr>
<tr>
<td>Overall response rates</td>
<td>34.7%</td>
<td>44.9%</td>
<td>0.004</td>
</tr>
<tr>
<td>Duration of response (mo)</td>
<td>7.1</td>
<td>10.4</td>
<td>0.001</td>
</tr>
</tbody>
</table>

of the VEGF receptor. Future studies with this drug are likely to incorporate twice daily dosing.

Other novel agents targeting the VEGF signalling pathway are currently being investigated in combination with chemotherapy are AZD2171 (cedinib) and sunitinib. Alfiblercept, a humanised soluble VEGF receptor protein designed to act as a "VEGF trap" is being tested in combination with 5-FU and irinotecan in second-line treatment of metastatic CRC.

Inhibitors of the epidermal growth factor receptor

The epidermal growth factor receptor (EGFR, also known as HER-1) is a cell-surface receptor which binds to various ligands and cytokines leading to cell division via the tyrosine kinase cascade EGFR, is over-expressed by 25–77% of colorectal cancers and is associated with a poor prognosis. The K-RAS protein is a key component of the EGFR pathway (Figure 14.2). Approximately 35% of colorectal cancers express an abnormal mutated form of K-RAS which results in the pathway being permanently ‘switched-on’ leading to increased tumour cell proliferation, migration, angiogenesis and decreased apoptosis (programmed cell death) (Figure 14.2).

Cetuximab (Erbitux\textsuperscript{®}) is a chimeric monoclonal antibody which binds to the EGFR preventing ligand-binding and receptor activation. This has been shown to have response rates in the region of 8–10% when given as a single agent in patients with irinotecan refractory CRC. When given in combination with irinotecan to patients with EGFR-expressing tumours who had irinotecan refractory disease the response rates are improved to 23% vs 11% with cetuximab alone. There was no evidence of a survival benefit due to crossover between the two arms of the study.

A study in Canadian and Australian patients with metastatic colorectal cancer showed a survival advantage in those treated with cetuximab compared to those treated with best supportive care, and on further analysis this was shown to be confined to those patients expressing the wild-type K-RAS protein. In a large multi-centre phase III study, response rates to treatment with cetuximab in combination with chemotherapy were significantly higher than those for chemotherapy alone (47% vs 39%), but more significantly this improvement was shown only in those patients who expressed wild-type K-RAS (RR 59% in this group). Cetuximab was of no clinical benefit in patients expressing the mutated K-RAS protein.

Panitumumab (Vectibix\textsuperscript{®}) is a fully humanised monoclonal antibody which also targets the EGFR pathway. Although no formal comparisons between cetuximab and panitumumab have been made, it appears to be similar to cetuximab in mode of action and
with BCG as an immunomodulatory adjuvant. These vaccines presumably contain a wide spectrum of tumour antigens and also have the advantage of being "tailored" to the individual as biopsies of their own tumour are used as the basis of the vaccine. When trialled in the adjuvant setting there was some evidence of an immune response following vaccination, and in one study there was evidence of prolonged survival in a subset of early stage patients. However these trials did not include adjuvant chemotherapy, nor considered the standard of care, and this approach has not entered widespread clinical use.

**Virally encoded vaccines**

This is a technique whereby a gene of interest is inserted into the genome of a viral vector that is injected as a vaccine with the aim of infecting host cells. This causes production of the protein of interest which is then presented to the immune system via the MHC by the patient’s own antigen presenting cells. CEA (carcinoembryonic antigen) is a foetal protein expressed by the majority of colorectal cancers and it has been used as a target gene in trials using vaccinia virus. Although specific anti-CEA T cell immune responses were identified, and the vaccines were well tolerated, no tumour responses were seen.

ST4 is a glycoprotein expressed by more than 85% of colon cancers. Expression by normal gut cells is minimal. A vaccine has been developed to the ST4 antigen (Trovax®), which in early phase studies has been shown to be safe and to produce an anti-ST4 immune response. When given in combination with chemotherapy the overall response rate was 60% vs 40% response rates to chemotherapy alone in historical controls. Further work is being carried out with this vaccine in the adjuvant setting.

**Matrix metalloproteinase inhibitors**

The matrix metalloproteinases (MMPs) are a family of 24 enzymes which degrade the extracellular matrix and are involved in the early stages of tumour invasion and metastasis. Some have been shown to be over-expressed in colorectal tumour types and are associated with poor clinical outcome. Inhibitors of MMPs (e.g. marimastat) have been developed, and one study in patients with early disease showed a dose-dependent reduction in CEA when treated with marimastat, but no obvious clinical benefit. It is thought the different MMPs have overlapping substrate specificity and the drugs inhibit only some of the isoenzymes, and therefore new generations of MMP inhibitors have wider specificities than their predecessors.

**Cyclooxygenase 2 inhibitors**

Cyclooxygenase 2 (COX2) is an intracellular enzyme that converts arachidonic acid into prostaglandins. High levels of COX2 and prostaglandin E2 are commonly found in colorectal tumour cells and there is laboratory evidence suggesting that the COX2 pathway plays an important role in colorectal carcinogenesis during the transition from adenoma to carcinoma and subsequently during invasion and metatasis. Epidemiologic studies have indicated that the incidence of colorectal cancer is reduced by 30–70% in patients taking NSAIDs. A large randomised UK phase III study was therefore initiated in patients who had undergone potentially curative surgery for colorectal cancer to determine the relative benefit of rofecoxib (Vioxx®) in preventing tumour recurrence. Follow-up of the trial patients showed a moderate increase in serious cardiovascular events in patients on the treatment arm (1% for rofecoxib vs 0.5% for placebo) after rofecoxib was withdrawn from the market. The study (with only around a third of the target number of patients enrolled), was a negative one, showing no significant differences in outcomes with respect to overall, disease-free, or recurrence-free survival. The results of a similar large US study are awaited.

**Gene therapy**

Gene therapy is the transfer of genetic material via a vector into a patient’s cells with the aim of directly or indirectly causing the demise of the cancerous cells.

One approach is gene-directed enzyme pro-drug therapy (GDEPT) where the gene for an enzyme, which can convert a pro-drug into an active metabolite, is transferred via a viral vector into tumour cells. This is a way of delivering tumour cells to avoid systemic side effects of chemotherapy (Figure 14.5). The major obstacle with this approach is the limited gene transfer efficiency with the currently available vectors, and therefore there is increasing interest in developing replication-competent viruses

**Table 14.2 Biological targets for novel therapies.**

<table>
<thead>
<tr>
<th>Antigen type</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heat shock protein</td>
<td>Cellular protein</td>
</tr>
<tr>
<td>Microenvironmental factors</td>
<td>VEGF, MMPs</td>
</tr>
<tr>
<td>Growth factor receptors</td>
<td>EGFR, Her-2</td>
</tr>
<tr>
<td>Mutated proteins</td>
<td>Ras, p53</td>
</tr>
<tr>
<td>Carbohydrate antigens</td>
<td>MUC-1</td>
</tr>
<tr>
<td>Glycoprotein antigens</td>
<td>CEA, ST4</td>
</tr>
</tbody>
</table>
Table 15.3 General principles for management of side effects of chemotherapy for colorectal cancer.

(Evidence-based management guidelines to be used in everyday practice)

- A comprehensive assessment prior to initiation of chemotherapy to be undertaken
- Reduce dose or stop relevant drug(s) as indicated in guidelines

Be aware and be on hand to immediately treat any hypersensitivity with oxaliplatin and cetuximab infusions.

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Principle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>Assess patient for risk of neutropenia in pre-chemotherapy check; Use ASCO, NCCN or EORTC Guidelines on Prevention and Management of Neutropenic Sepsis/Cancer-Related Infections.</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Patient instructions must stress starting loperamide at the first sign of diarrhoea (change in consistency or frequency of stools) and to begin with 4 mg (2 tablets), followed by 2 mg every 2 hours until they have had no bowel movement for 12 hours.</td>
</tr>
<tr>
<td>Mucositis</td>
<td>Assess for neutropenic sepsis; promote good oral hygiene and use analgesia and antifungals and/or antibiotics for overlying infection.</td>
</tr>
<tr>
<td>Nausea and vomiting (N&amp;V)</td>
<td>Assess risk of types of N&amp;V in pre-chemotherapy check. Optimal emetic control in the acute phase is essential to prevent nausea and vomiting in the delayed phase; prophylaxis is better than treatment. Always commence anti-emetics before chemotherapy and give oral doses at least 30 minutes before chemotherapy. Anti-emetic therapy should be administered regularly and reviewed with each cycle of chemotherapy; initiate anti-emetics at lowest level appropriate for chemotherapy prescribed.</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>Oxaliplatin – reduce doses for chronic chemotherapy-induced neuropathy and discontinue the drug for persistent grade 3 neuropathy. Safety measures include wearing gloves when outdoors in cold weather, using potholders when cooking, wearing shoes when outdoors in both cold and warm weather to avoid frostbite or burns and using assistive devices (e.g. handrails and bathmats) as required.</td>
</tr>
<tr>
<td>Palmar-Plantar Erythrodysesthesia (PPE)/Hand-Foot Syndrome</td>
<td>Patients’ shoes should be removed to examine feet properly. Patients should be instructed to stop capecitabine immediately if they develop grade 2 PPE or have manifestations that interfere with ADL. Symptomatic management e.g. using emollients to decrease skin drying. Patients should be asked to examine their skin and promptly report PPE manifestations to their keyworker and to avoid increased pressure to hands and feet from exercise and avoid increased exposure to heat.</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>For patients receiving bevacizumab, monitor blood pressures, assess for bleeding and thrombosis and test urine for proteinuria routinely. Refer to specialist in area of concern.</td>
</tr>
<tr>
<td>Rash Paronychia</td>
<td>Cetuximab – local comfort measures (i.e. warm soaks or compresses) may partially relieve discomfort, moisturisers and emollients may relieve dry skin and topical steroids may diminish erythema. Treat any overlying infection with antibiotics.</td>
</tr>
</tbody>
</table>


Dehydrogenase deficiency may experience potentially fatal toxicity from 5-FU or severe stomatitis, diarrhoea, neutropenia and neurotoxicity with capecitabine.

New care pathway and technologies for monitoring the side effects of chemotherapy

We are currently testing and developing novel services for monitoring side effects of chemotherapy in patients with colorectal cancer who are receiving capecitabine. The service provides a specially programmed mobile phone (or they can use their own should they wish) to aid those individuals receiving chemotherapy in patients with colorectal cancer who are receiving capecitabine. The service provides a specially programmed mobile phone (or they can use their own should they wish) to aid those individuals receiving chemotherapy in patients with colorectal cancer who are receiving capecitabine. The service provides a specially programmed mobile phone (or they can use their own should they wish) to aid those individuals receiving chemotherapy in patients with colorectal cancer who are receiving capecitabine. 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Locoregional and peritoneal recurrence

Although incidences of cure are reported in patients who developed local or regional recurrence from colorectal cancer, this is uncommon. Most patients who develop such recurrence will die of disease. Although it may be treatable with cytotoxic chemotherapy or, in the pelvis, radiotherapy, there is no real evidence to support the contention that finding such disease before it becomes apparent symptomatically is of benefit. Hence follow-up directed towards detecting locoregional recurrence may not be justified at present.

Peritoneal metastasis carries a bad prognosis. Radical surgical approaches have been applied to peritoneal disease, similar to that which are employed for pseudomyxoma peritonei. In general terms although a subgroup may benefit there is little evidence to support cytoreductive surgery and intraperitoneal chemotherapy in this group. Therefore at present this approach probably does not have a place outside of clinical trials.

Surgical approaches have been employed for local recurrence from rectal cancer. However, if original treatment of the rectal cancer has been of good quality, including appropriate chemoradiotherapy and a good surgical technique, the results from a re-resection are not good. It would therefore be logical to look for a symptom follow-up to detect this disease at a potentially curable stage.

Luminal recurrence and metachronous polyps and cancer

If the original surgical treatment has been adequate an actual luminal recurrence should be very rare. Luminal manifestation of locoregional recurrence certainly occurs but follow-up to detect this alone is not justified. By contrast, metachronous polyps and cancer are of considerable importance. Patients with colorectal cancer are predisposed to develop further polyps (Figure 16.2) and ultimately metachronous cancer and there is therefore clear evidence to support surveillance of the colon in this setting (see the Association of Coloproctology and SIGN guidelines). It is firstly critical that synchronous polyps and cancer are excluded at the time of the original resection. This is something that can be overlooked as the presenting malignancy may preclude detailed examination of the remainder of the colon. This is particularly the case when the patient presents as an emergency. Therefore, before a follow-up strategy is implemented, the entire colon must be examined to determine whether there are any other polyps or missed synchronous cancers. Assuming this is done the evidence at present would support a further colonoscopy at around 5 years.

Other sites of recurrence

Bone, skin and brain metastases from colorectal cancer are all recognised. They reflect systemic disease and are not commonly curable. There is no suggestion a follow-up strategy might be devised to detect these.

Follow-up techniques

A number of techniques have been used to follow-up patients who had colorectal cancer with different levels of success.

Clinical follow-up with examination

In brief, there is no evidence to suggest that simple clinical follow-up with clinical examination has any place in the detection of treatable recurrent disease. It may serve to reassure a patient, falsely in many cases. It may aid data collection but at a significant cost in healthcare terms. It is, however, important to separate clinical review for follow-up from review of a clinically symptomatic patient. For instance, patients who have had rectal excisions often complain of a variety of symptoms which may need advice or treatment. This is not follow-up in the context of this article.

CT imaging

CT is currently the best form of follow-up imaging overall in patients who have had colorectal cancer. Whether CT should be


