Global Summaries

Clinical Review
A Middle-aged Woman With Morbid Obesity – How to Treat?

In Focus
Colorectal Cancer: Prevention & Early Diagnosis

Colorectal Cancer: Features & Investigation

Can Metastatic Colorectal Cancer Be Cured?

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Colonisation by gut microflora is essential

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The source of the infant formula product is of cow’s milk origin.

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Rivaroxaban after acute coronary syndrome

Rivaroxaban is a direct, selective inhibitor of factor Xa. A preliminary trial showed that rivaroxaban therapy reduced the risk of death, myocardial infarction, or stroke in patients who had recently had an acute coronary syndrome. Now, a phase III trial has been reported.

At 766 sites in 44 countries, a total of 15,526 patients were randomized, within 7 days of hospital admission for myocardial infarction (ST-segment elevation or non-ST-segment elevation) or unstable angina, to rivaroxaban 2.5 mg twice daily, rivaroxaban 5 mg twice daily, or placebo, for up to 31 months (mean, 13 months). The rate of the primary efficacy end point (cardiovascular death, myocardial infarction, or stroke) was 9.1% (2.5 mg dose), 8.8% (5 mg dose), and 10.7% (placebo), a significant reduction at either dose compared with placebo. The lower dose, but not the higher dose, reduced all-cause and cardiovascular mortality. Rivaroxaban was associated with significantly increased rates of non-coronary-artery-bypass-grafting-associated major bleeding (2.1% vs 0.6%) and intracranial haemorrhage (0.6% vs 0.2%), but not of fatal bleeding (0.3% vs 0.2%). There were fewer fatal bleeds with the lower dose (0.1%) than the higher dose (0.4%).

Rivaroxaban reduced the cardiovascular risk but increased the risk of major bleeding but not of fatal bleeding.


Vorapaxar in acute coronary syndromes

Vorapaxar is an oral drug that inhibits thrombin-induced platelet aggregation by acting as an antagonist of protease-activated receptor 1, an activator of such platelet aggregation. It has been compared with placebo in patients with acute non-ST-segment-elevation coronary syndromes in a multinational trial.

A total of 12,944 patients with a non-ST-segment-elevation acute coronary syndrome were randomized at 818 sites in 37 countries to vorapaxar (40 mg loading dose, then 2.5 mg daily) or placebo, in addition to standard therapy. The trial was stopped early after a safety review. After an average follow-up of 502 days, the rate of the primary end point (cardiovascular death, myocardial infarction, stroke, rehospitalization for recurrent ischaemia, or urgent coronary revascularization) was 1,031/6,473 (16%) in the vorapaxar group and 1,102/6,471 (17%) in the placebo group, with Kaplan–Meier 2-year rates of 18.5% vs 19.9%, a non-significant difference. The composite outcome of cardiovascular death, myocardial infarction, or stroke occurred in 14.7% vs 16.4%, a significant 11% reduction in the vorapaxar group. There was a highly significant increase of 35% in moderate or severe bleeding in the vorapaxar group compared with the placebo group. There was a 3.4-fold increase in risk of intracranial haemorrhage in the vorapaxar group.

The addition of vorapaxar to standard therapy increased the risk of major bleeding and did not reduce the rate of the primary end point significantly.


Stroke risk with sub-clinical atrial fibrillation

About 15% of strokes are attributed to known atrial fibrillation (AF), but AF may be asymptomatic and undetected. In about 25% of cases of ischaemic stroke, the cause remains unknown. The results of a multinational study have suggested that in some of these cases, the cause may be undetected AF.

The study, in 23 countries, included 2,580 patients aged 65 years or older with hypertension and no history of AF. They had all recently received an implanted pacemaker or defibrillator. Patients were monitored for 3 months for episodes of subclinical atrial tachyarrhythmia (atrial rate >190 beats per minute for > 6 minutes) indicative of AF. Mean follow-up was for 2.5 years. At 3 months, subclinical atrial tachycardia had occurred in 261 patients (10%). The occurrence of subclinical atrial tachyarrhythmia was associated with a 5.6-fold increase in risk of clinical AF and a 2.5-fold increase in risk of ischaemic stroke or systemic embolism. Fifty-one patients had an ischaemic stroke or systemic embolism, and 11 of them had had subclinical atrial tachyarrhythmia on monitoring in the first 3 months. None had had clinical AF during that time. The population attributable risk of stroke or systemic embolism associated with subclinical atrial tachyarrhythmia was 13%.

Subclinical AF may explain many strokes of which the cause is not apparent.


Diabetes risk models and scores

A systematic review has assessed risk models and scores for the prediction of risk of type 2 diabetes.

Medical Progress June 2012
The review included 43 papers with details of the development and/or validation of 145 models and scores, of which 94 were assessed in detail. They had been based on data from almost 7 million people with follow-up for up to 28 years. Meta-analysis was not possible because of the heterogeneity of the data. The mean number of components per score was 8 (3–14), and some, but not all, models and scores were statistically robust and had been externally validated on a different population. Seven risk scores were chosen as having a high potential for use in practice, and ten mechanisms were outlined whereby the assessment of risk of type 2 diabetes might lead to improvement in outcomes.

There are many risk scores for the development of type 2 diabetes, but few are used routinely. Seven risk scores were considered to be highly suitable for clinical use.


**Intensive glucose control to preserve renal function**

An impaired glomerular filtration rate (GFR) increases the risk of end-stage renal disease in patients with diabetes. Intensive blood glucose control reduced the risk of developing both microalbuminuria and macroalbuminuria in patients with type 1 diabetes in the Diabetes Control and Complications Trial (DCCT) reported in 1993. Now, 22-year follow-up data from that trial have been used to assess the effect of intensive glucose control on glomerular filtration rate deterioration.

A total of 1,441 patients aged 13–39 with type 1 diabetes were randomized in the DCCT to intensive diabetes therapy (target glycated haemoglobin, < 6.05%) or conventional therapy for 6.5 years. Over a median of 22 years, impaired GFR (estimated GFR [eGFR] < 60 mL·min/1.73 m² on two successive visits) occurred in 24 patients (intensive group) versus 46 (conventional group), a significant 50% risk reduction with intensive therapy. End-stage renal disease occurred in eight patients vs 16. Intensive therapy slowed the rate of decrease in eGFR. The effect on eGFR was fully explained by the control of diabetes (glycated haemoglobin levels) and of proteinuria.

Intensive glucose control preserves renal function in type 1 diabetes.


**New drugs for chronic HCV genotype 1**

Treatment of chronic hepatitis C virus (HCV) infection with pegylated interferon (peginterferon) alpha and ribavirin for 48 weeks achieves a sustained virological response in 4 weeks after stopping treatment in 40–50% of patients. Adding a protease inhibitor to treatment for non-responders after 12 weeks of treatment produces a sustained virological response in 14–33%. Now, a multicentre phase II study in the USA has shown that the use of two new antiviral agents may improve results. Daclatasvir is an HCV NS5A replication complex inhibitor and asunaprevir is an HCV NS3 protease inhibitor.

The trial included 21 patients with chronic HCV genotype 1 infection unresponsive to treatment with peginterferon and ribavirin for 12 weeks. Randomization was to daclatasvir plus asunaprevir with (DAPR) or without (DA) peginterferon plus ribavirin. In the DA group, four of 11 patients achieved a sustained virological response at 12 and 24 weeks after treatment. In the DAPR group, all 10 patients had a sustained virological response at 12 weeks and nine at 24 weeks. In the DA group, six patients had viral breakthrough on treatment, and in all six cases there were resistance mutations to both daclatasvir and asunaprevir. Diarrhoea was common in both groups, and six patients had transient rises in alanine aminotransferase levels.

Adding daclatasvir and asunaprevir to peginterferon and ribavirin achieved sustained virological response in patients who had not responded initially to peginterferon and ribavirin alone.


**Gene therapy for haemophilia B**

Haemophilia B (Christmas disease) results from a mutation in the gene for coagulation factor IX (FIX). In severe haemophilia B, functional FIX levels are < 1% of normal. Current therapy with FIX protein concentrate is not curative, and it is associated with inhibitor formation as well as being expensive. Gene therapy offers the prospect of a cure. Researchers in the UK and the USA have assessed a new gene therapy—a serotype-8-pseudotyped, self-complementary adenovirus-associated virus (AAV) vector expressing a codon-optimized human factor IX (FIX) transgene (sc AAV2/8-LP1-hFIXco) given intravenously.

Six patients with severe haemophilia B received a single gene therapy dose via a peripheral vein: two given a high dose, two
an intermediate dose, and two a low dose. Follow-up was for 6–16 months. All patients benefitted: the two given the low dose were able to increase the intervals between injections of FIX and the other four were able to stop FIX prophylaxis and remained free of spontaneous bleeding. One patient who received the high dose had a transient asymptomatic increase in serum aminotransferase levels with detection of AAV8-capid-specific T cells in peripheral blood. The other high-dose patient had a transient increase in aminotransferase. Both had normal aminotransferase levels after a course of steroids. Their FIX levels were 3–11% of normal values.

This gene therapy at intermediate or high dosage was successful in raising FIX levels sufficiently to stop spontaneous bleeding without prophylactic FIX. The investigators express concern about immune-mediated clearance of AAV-transduced hepatocytes but point out that the process can be controlled with a short course of steroid without loss of transgene expression.

Farzadfar F et al. Effectiveness of diabetes and hypertension control. Farzadfar F et al. Effectiveness of diabetes and hypertension control. Farzadfar F et al. Effectiveness of diabetes and hypertension control. From the Non-communicable Disease Surveillance Survey (NCDSS) of 2005, data for systolic blood pressure (SBP) were available for 64,694 adults (11,521 in rural areas) and for fasting plasma glucose (FPG) for 50,202 (9,337 in rural areas). Overall, 39% of people with diabetes and 36% with hypertension were receiving treatment (more likely in women and in urban areas). On average, treatment in rural areas lowered FPG by 1.34 mmol/L and SBP by 2.5 mm Hg. In urban areas, the corresponding reductions were 0.21 mmol/L and 3.8 mm Hg. A single additional BW per 1,000 adults was associated with a significant 0.09 mmol/L lowering of district-level average FPG but did not reduce SBP significantly.

These researchers conclude that primary care systems with trained community health-care workers and well-established guidelines can be effective in non-communicable disease prevention and management.
Gene changes and resistance of colorectal cancer to chemotherapy

Gene alterations, both genomic and epigenetic, are common in human cancers, and some of them may affect response to chemotherapy. Researchers in Germany have concentrated on the gene encoding transcription factor AP-2 epsilon (TFAP2E) and its potential downstream target, DKK4, the gene encoding Dickkopf homologue 4 protein. Tumour samples were obtained from 74 patients treated for colorectal cancer and, later, another four cohorts (total, 220 patients) undergoing chemotherapy with or without radiotherapy. The expression, methylation, and function of TFAP2E was analysed in colorectal cancer cell lines in vitro and in patients with colorectal cancer. The gene was hypermethylated in 38 of the initial 74 samples, and this was associated with decreased gene expression. Cancer cell lines with overexpression of DKK4 had increased resistance to fluorouracil but not to irinotecan or oxaliplatin. In the four later cohorts, hypermethylation of TFAP2E was significantly associated with resistance to chemotherapy. Hypomethylation was associated with a sixfold increase in likelihood of chemotherapy responsiveness. Epigenetic alterations in TFAP2E were independent of key regulatory cancer gene mutations, microsatellite instability, and other genes affecting fluorouracil metabolism.

Hypermethylation of TFAP2E is associated with chemotherapy resistance in patients with colorectal cancer, and this resistance is mediated through DKK4. Targeting of DKK4 could potentially reverse this resistance.

Ebert MPA et al. TFAP2E-DKK4 and chemoresistance in colorectal cancer. NEJM 2012; 366: 44–53.

Denosumab for prostate cancer

Bone metastases are common in prostate cancer. Tumour cells in bone secrete growth factors that induce RANKL production by stromal cells and osteoblasts, and RANKL induces osteoclastic activity. Such activity is suspected to promote the establishment of metastases. Prostate cancer cells might themselves express RANKL and that too might increase the likelihood of metastases in bone. Denosumab is a human monoclonal antibody that inactivates RANKL. It has been shown to be better than zoledronic acid in the prevention of bony metastases in breast or prostate cancer. Now, a multinational trial has shown that denosumab delays the development of bone metastases in men with prostate cancer.

At 319 centres in 30 countries, a total of 1,432 men with castration-resistant prostate cancer but without, though at high risk of, bone metastases were randomized to subcutaneous denosumab 120 mg, or placebo, every 4 weeks. Median bone-metastasis-free survival was 29.5 months (denosumab) vs 25.2 months (placebo), a significant difference. Time to first bone metastasis was 33.2 vs 29.5 months. There was no significant difference in overall survival (43.9 vs 44.8 months). Osteonecrosis of the jaw occurred in 33 patients (5%) in the denosumab group but in none of the placebo group. Hypocalcaemia occurred in 12 (2%) vs 2 (<1%).

Denosumab may delay the development of bone metastases in men with high-risk prostate cancer. The optimal clinical use of denosumab has yet to be determined.


Prostate cancer gene mutation

Prostate cancer may be familial, but the genetic basis is unclear. Genome-wide association studies have identified > 30 single nucleotide polymorphisms associated with increased risk, but the increase in risk from each of them has been low. An intensely studied locus has been at chromosome 17q21-22. Now, a US study has identified a new variant in the gene HOXB13 that is associated with increased risk of hereditary prostate cancer.

More than 200 genes in the 17q21-22 region were screened by sequencing germline DNA from 94 unrelated patients with prostate cancer from families with familial prostate cancer linked to the 17q21-22 region. Four of these subjects had a mutation (G84E) in HOXB13 (rs138213197), a homeobox transcription factor gene important in prostate development. In these four families, there were 18 men with prostate cancer and available DNA, and all of them carried the mutation. This mutation was present in 72 of 5,083 unrelated men of European descent with prostate cancer (1.4%) and 1 of 1,401 controls without prostate cancer (0.1%), a highly significant difference. It was significantly more common in men with early-onset, familial prostate cancer (3.1%) than in men with late-onset non-familial prostate cancer (0.6%).

The new variant accounts for a small proportion of prostate cancers but may provide increased understanding of the disease.

A Middle-aged Woman With Morbid Obesity – How to Treat?

Sharon Marks, MB BS, FRACP

An individual approach should be taken when treating morbidly obese patients, with multidisciplinary input.

Case Scenario

Shirley is 41 years of age and has presented in despair about her huge weight gain since the birth of her sixth child, who is now 10 years old. She is 165 cm tall and weighs 179 kg. She is dyspnoeic on even minimal exertion, has painful knees and has recently developed a large inguinal hernia. She reports that she is uncomfortable in bed at night and sleeps poorly.

A full blood check finds no major problems, although she reports a very strong family history of diabetes (she is of South Sea Island descent).

Shirley enjoys all the cooking she does for her large extended family and reports eating frequently and voraciously.

What strategies or treatments would have the best chance of success for a patient with this level of morbid obesity?

Commentary

This level of obesity (body mass index [BMI] of 65.7 kg/m²) is referred to as extreme morbid obesity or super obese (BMI of more than 50 kg/m²) and is difficult to treat. In most cases, specialist intervention is required because...
many GP offices are not adequately equipped. Many patients (and their GPs) are unable to find scales to give an accurate weight, and hospital clinics need industrial type scales. (Some patients use weighbridges to weigh themselves.) Waiting room chairs as well as examination couches need to be able to support extremes of body weight.

The problems for this particular patient are not so much the metabolic disorders that are usually connected with obesity, but more the physical effects of her extreme body weight hindering mobility through breathlessness and joint problems. However, Shirley’s family history suggests an increased risk of diabetes. She needs initial rapid and substantial weight loss prior to the initiation of an exercise routine. Starting exercise too early can lead to further joint damage and thus limit ongoing weight maintenance.

It is important to exclude any other factors that may be contributing to immobility, such as obstructive sleep apnoea, which is commonly seen in this group of patients. A sleep study is essential, particularly if excessive tiredness limits weight loss attempts or increases snacking behaviour. Nightly use of a continuous positive airway pressure pump should be considered if the patient has periods of hypoxaemia overnight or if the obstructive sleep apnoea is considered to be moderate to severe.

Another issue to consider is the medications the patient is taking. Diabetic medications such as insulin, sulfonylureas and glitazones can contribute to increasing body weight and may need to be altered or ceased. Other medications, particularly high-dose corticosteroids and some of the antipsychotic and antiepileptic treatments, can markedly increase appetite. Although the patient in this scenario is taking no medications, she is the exception rather than the rule.

Patients should also be assessed for depression and obsessive–compulsive behaviour as these conditions can contribute to increased snacking behaviour.

**Treatment**

The energy required for initial weight loss in this situation usually needs to be achieved by calorie restriction rather than by increasing physical activity. More substantial weight loss can be achieved and maintained by introducing a very-low-calorie diet. Once weight loss (even a small amount) has occurred, increased incidental activity such as walking can help potentiate further weight loss. Surgical intervention may give the best outcome for patients who have little chance of long-term maintenance.

**Medications**

Some of the selective serotonin reuptake inhibitors (SSRIs; eg, fluoxetine and sertraline) and some of the serotonin and noradrenaline reuptake inhibitors (SNRIs; eg, duloxetine and reboxetine) used to treat depressive and obsessive–compulsive disorders have effects on satiety. The balance between increased satiety and overstimulation (insomnia and anxiety) needs to be found. These medications are not weight-loss drugs in their own right (and are not Therapeutic Goods Administration [TGA]-approved for the management of obesity), but they can be helpful if a patient is demotivated and struggling with frustration about their weight. It should also be noted that many patients find long-term diets to be very depriving and actually show signs of depression and anger if food is restricted. These patients benefit from being ‘primed’ prior to altering their food intake.

Until recently, it was possible to use sibutramine to induce satiety and help patients eat smaller portions while maintaining a higher metabolic rate. However, sibutramine was withdrawn from sale in mid-October 2010 and is no longer an option. The recently published SCOUT study showed an increased risk of non-fatal cardiac events in high-risk patients, most of whom were treated ‘off-licence’. Most of the patients recruited had type 2 diabetes and had known cardiovascular disease with either a previous myocardial infarction or episodes of angina and so were at high risk of recurrent cardiac events. The weight loss achieved in the study group did not meet the minimum (5% of initial body weight) set by the Food and Drug Administration for a weight loss product. However, sibutramine’s efficacy and safety in a low-risk population was not evaluated.

In some individuals, sibutramine was an effective medication that enabled greater adherence to a long-term diet, and in patients with morbid obesity it was possible to see significant weight losses in ‘responders’, although not in all cases. There is very little to use in its place as, apart from orlistat (discussed later), the only other drug approved by the TGA for the management of obesity is phentermine. This medication has been around for many years and has not undergone a similar rigorous study to prove efficacy and safety in this group of patients. It is approved only for short-term weight loss (less than 3 months) and has a very limited role in the management of extreme morbid obesity, which requires a long-term approach.

Orlistat is a lipase inhibitor that may be of some benefit in producing a weight loss effect as it reduces the absorption of about 30% of ingested dietary fat. In the ‘diet-naïve’ patient,
who may not have a good comprehension of the fat content of food, it can help identify high-fat foods. The medication causes diarrhoea, abdominal pain and oil incontinence if a high-fat diet is consumed, thus encouraging adherence to a low-fat diet.

Orlistat may help commence the weight loss process but is unlikely to cause substantial weight loss (ie, of more than 12 to 20 kg) in this group of patients. It may also have a place in the ongoing management of obesity because it can be used intermittently and has few side effects other than the effect of the drug to cause fat malabsorption. Supplementation with fat-soluble vitamins is not usually required unless the patient has a nutrient-poor diet overall. The cost of this over-the-counter treatment, about A$120 for a packet of 84 capsules (1 month’s supply) or A$70 for 42 capsules, needs to be placed in perspective with the outcome of the intervention. It is not available on the Pharmaceutical Benefits Scheme but is available on the Repatriation Pharmaceutical Benefits Scheme on authority for a once per lifetime treatment of obesity (BMI of 30 kg/m² or greater with specified comorbidities, including type 2 diabetes, or BMI of 35 kg/m² or greater without associated problems).

**Diet**

In patients with extreme morbid obesity, an energy-restricted diet should be used in the first instance. Some patients do respond to a well-balanced, low-fat, calorie-reduced diet, particularly if satiety is increased. Thus, initial substantial weight loss can be seen with the use of low glycaemic foods and regular meal times plus the altering of other factors such as tiredness (related to obstructive sleep apnoea) or medications causing increased appetite. The assistance of a qualified dietitian can be of great benefit, and weight losses of up to about 20 kg can occur fairly rapidly using a food-based dietary approach.

In patients who are unable to modify their food intake because of excessive hunger or uncontrollable snacking behaviour, a very-low-calorie diet (VLCD) programme can achieve an energy deficit even in those with extreme immobility. Once weight loss has occurred, the patient can become more mobile as joint pain and obstructive sleep apnoea benefit greatly from relatively small weight losses. A VLCD programme (a diet of 800 calories [about 3,350 kJ] per day or less) can be expected to achieve a weight loss of 15 to 30 kg in the first 3 months, with ongoing weight loss if the intensive programme is continued.

Patients need blood tests including liver and renal function testing as well as a lipid profile and diabetes screening before starting a ketogenic programme. Other investigations should include thyroid function test and a full blood count as well as iron studies. Medications such as insulin, sulfonylureas and glitazones may need to be adjusted or ceased during the weight loss phase to avoid episodes of hypoglycaemia, which may prevent the patient adhering to the strict ketone-inducing regimen. Blood pressure medications may also need to be reduced to avoid hypotension. If a diuretic is being used, electrolytes should be monitored on a regular basis as weight loss occurs.

I encourage all patients to follow the intensive regimen using the VLCD as a complete three-meal per day replacement for at least the first 2 weeks. During this initial phase, only a large bowl of steamed low-starch vegetables is allowed in addition to the three meal replacements. Once ketone bodies are produced, appetite usually reduces dramatically, which enables the continuation of the intensive programme (ie, three meals per day) for at least 3 months. Some people are able to continue further, particularly if motivated by initial weight loss.

A gradual reintroduction of a low-fat and carbohydrate-reduced diet together with increasing exercise tolerance helps with ongoing weight maintenance. It is not unusual to see some weight regain when normal meals are introduced as the low carbohydrate content of the intensive phase contributes to an early diuresis. It is almost inevitable that some fluid regain will occur, and so it helps if the patient is prewarmed. Weight maintenance needs to be encouraged although there should be a low threshold to returning to the intensive phase (replacing three meals
a day) if needed. Patients need to be encouraged to be proactive with regard to weight regain and not see it as a failure of a particular programme.

Regular follow-up is essential during the VLCD programme. Other health professionals, such as clinical psychologists, dietitians and exercise physiologists, can help lighten the load as it is fairly time-intensive to monitor these patients. A multidisciplinary team approach is of great value with regard to goal setting and provides useful feedback as many patients with extreme morbid obesity cannot weigh themselves at home or be weighed at the local doctor’s surgery.

Surgery
For some patients, the task of initiating and then continuing weight loss is overwhelming. Those with severe sleep apnoea (and associated tiredness) as well as those with debilitating joint disease may achieve initial weight loss but have little chance of maintaining the loss in the long term. A surgical intervention may give the best outcome in these patients.

Laparoscopic gastric banding has become the most common bariatric surgery procedure in Australia as it is relatively non-invasive and adjustable and provides a long-term weight maintenance strategy. Other options include the gastric sleeve procedure and the Roux-en-Y gastric bypass. These procedures have their own complications, including risk of nutritional inadequacy and wound breakdown, but their suitability must be assessed in the light of the severity of the obesity and its complications. For instance, a patient with an insatiable appetite or a ‘sweet tooth’ may be a poor candidate for a lap band, which requires food restriction. These patients may take in excess energy in the form of frequent small portions or by drinking high-calorie drinks that may pass around the band. Gastric bypass, which causes malabsorption by reducing the absorptive area of the small bowel, may be the best option to achieve significant weight loss even though life-long monitoring of nutritional indices is required.

Generally, any intervention will be most successful if it reduces appetite and increases satiety. The gastric sleeve procedure is thought to achieve this by removing the portion of the stomach that produces ghrelin, the hormone that stimulates appetite. Long-term data is not yet available for this procedure. With the lap band, however, weight losses of more than 50% of excess body weight have been maintained over a 5-year period. Again, patients who have had lap bands need lifelong monitoring to ensure ongoing compliance and weight maintenance.

Summary
Successful treatment of patients with extreme morbid obesity is very complex. Patients vary greatly in their expectations and in their physical ability. It is imperative that an individual approach is taken with as much input from a multidisciplinary team as possible. Often the simple problem of weighing a patient who is more than 150 kg means that the treatment cannot be undertaken by the local doctor alone. Access to public hospital bariatric clinics is severely limited, with waiting lists of up to 12 months for initial assessment. The opportunity to obtain a lap band or gastric bypass procedure is similarly problematic, with even longer waiting lists. Those patients with private health insurance fare better although the out-of-pocket expenses are sometimes prohibitive. Although there is much discussion about the obesity epidemic and the need for better bariatric assessment clinics with greater access to surgery, very little has changed in this regard over the past 10 years.

For the individual patient presenting at this level of obesity, the first interaction with a doctor will often dictate the long-term outcome. First attempts at long-term weight loss and maintenance are often unsuccessful, and the doctor needs to avoid expressing disappointment because it will only confirm the patient’s belief that the problem is insurmountable. A positive approach, balanced by a clear understanding of the physical and emotional barriers inherent in patients with extreme morbid obesity, will at least facilitate compliance. Obviously, the prevention of weight gain in at-risk patients is a vital component as it is easier to treat obesity in a mobile patient than in one unable to be active due to osteoarthritis, breathlessness or obstructive sleep apnoea.

Declarations of Interests
Dr Marks has been a member of medical advisory boards for Optifast, sibutramine and orlistat and has been involved in clinical trials of these products. She has also received honoraria from Nestle, Abbott and Roche for talks on obesity management.

Reference


About the Author
Dr Marks is a Consultant Physician in Clinical Nutrition at Monash Medical Centre, Melbourne, Victoria, Australia.
Colorectal cancer is one of the most common cancers worldwide and is a disease of 'Westernized' populations. With early detection, diagnosis and treatment, the morbidity and mortality associated with this cancer can be prevented.

How much do you know about colorectal cancer?

1. It is estimated that among those with colorectal polyps, 95% will develop invasive colorectal cancer (CRC).  
2. Central obesity is a risk factor for CRC.  
3. Colonoscopy is the gold standard investigation for CRC and polyps.  
4. The liver is the most common metastatic site.  
5. Metastatic CRC is potentially incurable, even when limited to a specific organ site.

See page 292 for answers
Colorectal Cancer: Prevention and Early Diagnosis

Robert Dennis, MSc, FRCS; Samson Tou, MSc, FRCS; Richard Miller, MSc, FRCS

Colorectal cancer (CRC) is a curable disease; over 90% of patients who have surgical resection of a Dukes’ A tumour will still be alive after 5 years. This is direct evidence that an early diagnosis will reduce mortality from CRC. Despite this, CRC is the second most common cause of cancer-related death in the UK. The discrepancy suggests that outcomes can be improved by a better understanding of the causes of the disease and its early detection and treatment. In this article, prevention and early diagnosis are discussed.

Colorectal cancer (CRC) is a major cause of cancer morbidity in the UK, and in 2006 there were more than 37,500 new cases and 16,000 deaths from the disease. After lung cancer, it is the second most common cause of cancer-related death.1

Pathogenesis

The pathogenesis of the majority of CRC is well understood in terms of the ‘adenoma–carcinoma sequence’. This describes the progression of CRC as an accumulation of mutations in key genes, for example, tumour suppressor genes, such as the adenomatous polyposis coli (APC) and TP53 genes, and in proto-oncogenes such as K-ras. In macroscopic terms, these molecular changes contribute to the development of polyloid lesions and, later, invasive carcinoma. In polyps, the normal architecture of colonic crypts is disrupted by disturbances in the sequence of basal proliferation, migration, and differentiation. Many individuals have polyps, but it is estimated that only 5% will develop invasive cancer.
estimated that only 5% will develop invasive cancer. Prevention of colorectal cancer, therefore, depends on early elimination of these polyps and/or the factors that predispose the colonic epithelium to become transformed.

Aetiology

Eighty-five percent of CRC cases fall into the category of ‘sporadic’ disease, where the primary cause of polyp formation is unknown. The remaining 15% of cases are accounted for by less common causes of CRC, for example familial CRC (ie, where one first-degree relative aged < 45 years old is affected by CRC or there are two affected first-degree relatives), dominantly inherited CRC syndromes and inflammatory bowel disease (IBD). In the latter two groups, the molecular events of polyp formation are understood. The hereditary CRC syndromes (eg, hereditary non-polyposis colorectal cancer (HNPCC), familial adenomatous polyposis (FAP), Peutz–Jeghers syndrome, and juvenile polyposis) have germ-line mutations that predispose the epithelium to develop multiple polyps. A germ-line mutation of APC is responsible for the colorectal polyps that develop in FAP, whereas mutations in mismatch repair genes, which usually detect, excise and replace any inadvertent nucleotide mismatches during DNA replication, result in HNPCC. Compared with the large number of polyps in FAP, there are markedly fewer polyps in HNPCC. The HNPCC polyps are predominantly located in the right side of the colon, but their rate of transformation is high compared with FAP (see Figure). In IBD, such as ulcerative colitis and colonic Crohn’s disease, the predisposition to CRC arises from the increased proliferation of colonic epithelium during inflammatory episodes.

Polyp formation in sporadic disease is not well understood; consequently, numerous studies on external factors such as diet, obesity and other lifestyle parameters have been and are being undertaken to identify causal relationships with CRC. Some of these studies are discussed below and are an important source of evidence-based preventative measures.

Prevention

Diet

In the 1960s, Burkitt proposed that ‘the relationship between diet and bowel disease’ should be investigated. His hypothesis was that low-fibre diets slowed colonic transit and thereby increased the opportunity of carcinogens, generated by bacterial activity on faecal constituents, to exert their effect on the colonic epithelium. The effect of diet (as well as metabolic, genetic and environmental factors) on the development of cancer is now being explored in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. EPIC is the world’s largest prospective study and involves over half a million people recruited from 23 different regions of 10 European
countries. The advantage of obtaining data from multiple regions is that a clearer relationship between different dietary habits and the development of cancer may be seen.2

The first completed data sets from the ongoing EPIC study have now been analysed; these show that dietary patterns are regional and that diet does have an impact on the development of CRC. For example, it has been demonstrated that dietary fibre is likely to be protective against colorectal cancer; comparison between the lowest daily fibre intake of 12 g and the highest intake of 30 g showed a 40% reduction in the risk for CRC after calibration.3 The source of fibre was not significant.3 As a result, it has been suggested that about eight portions of fruit and vegetables and the equivalent of five slices of wholemeal bread should be eaten daily if the benefits of dietary fibre are to be realized.2

Linked studies have also shown that a high intake of red or processed meat is associated with a 35% increase in colorectal cancer if more than 160 g are consumed per day (two or more portions) when compared to less than one portion per week.4 In contrast, a high fish consumption of 80 g or more is protective.4 The increased risk of CRC with a high consumption of red and processed meat may be related to the association of these foodstuffs with increased amounts of N-nitrosocompounds in the faeces. These compounds bind to the epithelial DNA and may act as mutagens to initiate the adenoma–carcinoma sequence.

The US prospective National Institutes of Health–AARP Diet and Health Study6 analysed 293,615 men and 198,767 women aged 50–71 years with self-administered food-frequency questionnaire at baseline in 1995–1996 and then 5 years of follow-up. Men with high scores on the fruit and vegetable factor were at decreased risk of colorectal cancer (relative risk, RR, 0.81; 95% confidence interval, CI, 0.70–0.93; \( P \) for trend = 0.004). High scores on the red meat factor were associated with increased risk (RR, 1.17; 95% CI, 1.02–1.35; \( P \) for trend = 0.14 for men; and RR, 1.48; 95% CI, 1.20–1.83; \( P \) for trend = 0.0002 for women).

Not all studies have demonstrated that a high-fibre diet reduces the risk of CRC. A pooled analysis of 13 prospective cohort studies found that dietary fibre was not associated with a reduced risk of colorectal cancer after adjusting for other dietary risk factors. A Cochrane collaboration systematic review7 has analysed five studies of over 4,000 subjects for the effect of intervention with soluble and insoluble dietary fibre or a comprehensive dietary intervention with high-fibre whole food sources. Over the 2- to 4-year period of the studies, combined data showed no outcome difference between the intervention and control groups in the number of subjects with at least one adenoma or a new diagnosis of colorectal cancer.

A more recent analysis within the EPIC study has shown a possible relationship between pre-diagnostic, serum 25(OH)-vitamin D concentration and risk of colorectal cancer.8 After correcting for dietary and other possible confounding factors, serum 25(OH)-vitamin D concentration showed a strong inverse linear dose-response association with risk of colorectal cancer \( (P \) for trend < 0.001), although subgroup analyses showed this association for colon but not rectal cancer \( (P \) for heterogeneity = 0.048). Greater dietary intake of calcium was also associated with a lower colorectal cancer risk. The authors noted that further randomized trials are needed to assess whether increases in circulating serum 25(OH)-vitamin D concentration can effectively decrease the risk of colorectal cancer.
Obesity and Exercise
There is accumulating epidemiological evidence that central obesity is a risk factor for CRC. The biological mechanisms still need to be elucidated, but hyperinsulinaemia appears to play a role. With further research, it may emerge that weight loss is an important preventative measure against CRC, as it is against endometrial cancer, heart disease, and type 2 diabetes mellitus.

Regular exercise also protects against CRC.9,10 Furthermore, there is evidence that CRC patients have an absolute improvement of 14% in their 5-year survival if they had active lifestyles before presenting with symptoms of CRC.9 An active patient is defined as someone who exercises vigorously for 20 minutes at least once a week or participates in weekly general health and fitness.9 The Swedish study showed differing distributions of colon cancer between the sexes, and no association between physical activity and rectal cancer.10

Alcohol and Smoking
The link between alcohol and CRC remains equivocal. Some evidence suggests that there is a dose–risk relationship that is particularly pertinent to rectal cancer. The evidence for tobacco is slightly stronger in rectal cancer, with a relationship to smoking even after adjustment for alcohol.11 This epidemiological evidence is also supported by other studies that have shown that smokers have a higher incidence of colorectal polyps.

Chemoprevention
Non-steroidal anti-inflammatory drugs may inhibit progression and development of CRC. A recent Cochrane meta-analysis analysed four randomized controlled trials that compared aspirin with a placebo in ‘average’-risk populations.12 No significant reduction in the incidence of adenomas was noted in the primary prevention trial, but data from the three secondary prevention trials showed a statistically significant reduction in the recurrence of sporadic adenomas in the ‘treatment’ groups. The overall results (which included trials treating FAP patients with aspirin) showed a trend in favour of treating with aspirin to prevent colorectal adenomas.12

However, this may be a type I error, since the subgroup taking 325 mg of aspirin did not see the benefit of the subgroup receiving 81 mg.13 A prospective study of 47,363 male health professionals aged 40–75 years followed up for 18 years showed that men who regularly used aspirin (≥ 2 times/week) had a multivariate RR for colorectal cancer of 0.79 (95% CI, 0.69–0.90), compared with non-regular users.14 However, this potential benefit necessitates at least 6 years of consistent use with maximal risk reduction at doses greater than 14 tablets/week. As noted by the authors, the risks of gastrointestinal bleeding and haemorrhagic stroke must be weighed against the benefit of treatment.

Table 1. Recommendations to reduce risk of developing colorectal cancer

<table>
<thead>
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<th>Recommendation</th>
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<tr>
<td>Diet contains high fibre/fruit and vegetables/fish</td>
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<tr>
<td>Reduce intake of red or processed meat</td>
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<tr>
<td>Stop smoking and reduce alcohol consumption</td>
</tr>
<tr>
<td>Reduce obesity</td>
</tr>
<tr>
<td>Regular exercise</td>
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<tr>
<td>Patient education/screening</td>
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Patient Education
Symptoms of CRC include a change in bowel habit (particularly loose stools for more than 6 weeks) and rectal bleeding (characteristically, dark blood that may or may not be mixed with stool). Bright red rectal blood in the absence of other anal disease (e.g., haemorrhoids, tags and fissures) is also a high-risk symptom. Efforts to educate patients about the importance of these symptoms, together with information about screening programmes, are likely to lead to earlier patient presentation, particularly as there is evidence that patients do ignore symptoms (for years in some cases), and express fears about unpleasant examinations and not wanting ‘to waste the doctor’s time’. A summary of the recommendations to reduce the risk of developing colorectal cancer is shown in Table 1.

Early Diagnosis Through Screening
There is evidence that polypectomy reduces the incidence of CRC.15,16 Population screening for premalignant or early disease in the form of polypoid lesions is, therefore, likely to reduce the incidence of sporadic CRC in the longer term. For an average-risk individual (e.g., no family or personal history of CRC), the lifetime cumulative incidence of CRC is 6%,17 but the risk of developing sporadic CRC doubles every 10 years after 40 years of age.17 To achieve the maximum benefits of a screening test, it should be undertaken when the patient is most likely to have pre-invasive or very early invasive disease. Since the average age of patients who receive a diagnosis of adenomatous polyps is around 60 years, the Department of Health guidelines in the UK advise that biennial screening should be offered to everyone between...
In focus respectively (see Table 2 for definitions). Estimates of the sensitivity for CRC range from 12.9% to 50%, and for large adenomas as low as 12%. The English Bowel Cancer Screening Pilot invited 480,250 individuals to take part in FOBT screening. There was a 56.8% uptake with an overall positive test rate of 1.9%. The cancer detection rate was 1.62/1,000 individuals screened. This gave a positive predictive value of 10.9% for cancer and 35.0% for adenomas. It is predicted that for every 1,000 individuals screened in the National Health Service (NHS) Bowel Cancer Screening programme, approximately 20 will be offered colonoscopy, 16 of whom will take up the offer. Half of these colonoscopies are expected to be normal, six are expected to detect adenomas, and two to detect cancer. The normal colonoscopies are the most significant cost to screening. They impose a financial burden to patients and the health service as well as the associated morbidity and mortality rates of the procedure, even though these are low.

Despite the criticisms, FOBT is still a viable screening test; it is non-invasive and cheap, but more importantly it reduces mortality from CRC. Several trials have independently shown a significant reduction in mortality from CRC in the individuals randomized to undergo FOBT. In the FOB-tested groups, the reduction in mortality was 15–18% for biennial screening and 33% for annual screening. Furthermore, 18 years of follow-up from the Minnesota trial has demonstrated a significant reduction in the incidence of CRC in patients randomized to FOBT.

Flexible Sigmoidoscopy

A large, multicentre, randomized, controlled trial has recently been published assessing once-only flexible sigmoidoscopy in people aged from 55 to 64 years as an effective means for the prevention of colorectal cancer. The rationale for this screening tool is that approximately two-thirds of colorectal cancers are located in the rectum and sigmoid colon, and most have arisen from adenomas. In

Table 2. Definitions of sensitivity and specificity

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>Definition: probability of a positive test when the disease is present</th>
<th>Application: if the test has a high sensitivity, it will identify patients with the disease, and therefore a negative result indicates that the patient does not have the disease</th>
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<tbody>
<tr>
<td>Specificity</td>
<td>Definition: probability of a negative test when the disease is absent</td>
<td>Application: if the test has a high specificity, a negative result identifies people who do not have the disease, and therefore a positive result indicates that the patient has the disease</td>
</tr>
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</table>

Faecal Occult Blood Test

The principle behind FOBT is that polyps and malignant lesions bleed, and blood from these lesions is shed into the faecal stream. The guaiac-impregnated test cards detect the peroxidase activity of haem. However, not all colonic lesions bleed, and the principal criticism of FOBT is its low sensitivity and inadequate specificity, which can translate into high false-negative and false-positive rates,
the majority of cases, people who develop a distal colon cancer will have developed an adenoma by 60 years of age, so removal of adenomas by sigmoidoscopy would provide long-term protection against the development of distal colorectal cancer.

Recruitment and screening were started in 1994 and completed in 1999. An initial 170,432 patients were randomized to either flexible sigmoidoscopy (40,621 screened) or a control group (112,939 analysed) and followed up for a median of 11.2 years. Participants underwent flexible sigmoidoscopy with polypectomy for small polyps and referral for colonoscopy if they had polyps meeting the following criteria: 1-cm diameter or larger; three or more adenomas; tubulovillous or villous histology; severe dysplasia or malignant disease; or 20 or more hyperplastic polyps above the distal rectum. Those with low-risk polyps were discharged from further follow-up. In the screened group, colorectal cancer incidence was reduced by 33% for all colorectal cancer sites and by 50% for the distal colon. Mortality from colorectal cancer was reduced by 31%. The authors estimated that 191 patients needed to be screened to prevent one colorectal cancer diagnosis over the course of the study. The authors concluded that flexible sigmoidoscopy is a safe and practical test, and provides substantial benefit when offered once only for patients aged between 55 and 64 years.

At odds with these findings of the UK trial, the Norwegian Colorectal Cancer Prevention (NORCCAP) trial, assessing the effects of once-only flexible sigmoidoscopy in 55–64-year-olds, has reported no reduction in colorectal cancer incidence at 7 years.25 The Italian SCORE trial (similar protocol to the UK trial) and US PLCO trial (screening every 3–5 years between ages 55 and 74) are due to be reported soon.

**CRC Prevention Through the Surveillance of Screened Patients With Early Disease**

The number of patients found to have adenomas and early CRC will increase as a result of the screening programme. These patients need regular follow-up or surveillance because of their increased risk of recurrent adenomas. The interval between surveillance colonoscopies is timed to balance the risk of repeat colonoscopies against the
In focus

for patients with ‘at risk’ symptoms/signs, but delays still exist where, for example, the doctor gets ‘locked’ into the wrong diagnosis or makes a routine referral because TWR criteria are either not met or not included. In practice, therefore, it may be necessary for all patients with suspicious symptoms, not just those who meet TWR criteria, to have rapid investigation. This could be via GP direct-access colonoscopy or the ‘direct to test’ approach, where a consultant receives a referral and arranges investigation before a clinic visit. Clearly, this would require a significant improvement in colonoscopy services, especially since hospital waiting times, particularly for colonoscopy and computed tomographic scans, are significant in many units.

The common factor to improve the efficiency of the TWR is rapid access to high-quality colonoscopy, the current gold-standard investigation.

Prevention and Early Diagnosis – The Future

Screening promises to improve the detection of early CRC and ultimately contribute to its prevention. The value of FOBT as a single test is currently limited because of its low sensitivity and inadequate specificity, but if FOBT were complemented by another non-invasive test, sensitivity could be significantly improved. Various potential ‘complementary’ non-invasive tests are currently being developed, such as faecal DNA tests and molecular tests on isolated colonicocytes. However, the availability of these tests for clinical investigation is still in the future. Consequently, continuing patient education about lifestyle, symptoms of CRC and screening, as well as promoting and funding initiatives to expedite diagnosis, staging and treatment of CRC associated with this syndrome.

Furthermore, surveillance frequency for HNPCC is based on the early age of presentation with the disease (median age, 40–45 years) and the likelihood that progression from adenoma to invasive carcinoma is more rapid than sporadic CRC – sometimes within 3 years of a clear colonoscopy. In contrast to HNPCC, the disease profiles and risks for FAP, IBD and familial CRC are all different, and so different surveillance guidelines are required. These guidelines are summarized in Table 3, but they remain flexible and practice standards will evolve as new data are published.

Prevention Through Surveillance of Patients at Above-average Risk of CRC

For patients with a higher risk of CRC compared with the general population (eg, inherited CRC syndromes and IBD), early detection of CRC depends on appropriate surveillance programmes. Strong evidence (level II) has shown that surveillance of HNPCC patients reduces both the incidence of CRC and the risk of mortality from

"The number and size of the adenomas often predict the polyp findings at subsequent follow-up colonoscopies"
CRC, are vital to help prevent the mortality and morbidity associated with the disease.

Declaration of Interests
None.

References

Further Reading

About the Authors
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Colorectal Cancer: Features and Investigation

Nigel Hall, BA, DM, FRCS

Colorectal cancer, also known as bowel cancer, is a common malignancy and is common in 'Westernized' populations, owing largely to dietary factors. Bowel cancers are thought to arise through a combination of hereditary predisposition, exposure to environmental agents (eg, diet), lifestyle, and chance.

Epidemiology

Colorectal cancer is generally a disease of advancing age.

Colorectal cancer, often known simply as bowel cancer, is a common solid organ malignancy affecting 35,000 patients a year in the UK, about half of whom will die from it. At all ages, it is more common in males (especially rectal cancer), but because of the greater longevity of women the overall sex distribution is equal. It is generally a disease of advancing years, with a peak age at diagnosis of 70 years; the lifetime risk by the age of 80 years is about 5–10%.

Factors. Europe, the USA and Japan have high rates compared with Africa and Asia. Bowel cancers are thought to arise through a combination of hereditary predisposition, exposure to environmental agents (eg, diet), lifestyle, and chance. Dominantly inherited strongly penetrant syndromes, such as familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (Lynch syndrome), are responsible for a small percentage of colorectal cancers, often developing before the age of 40 years. A much greater proportion may be the result of weakly penetrant but more common susceptibility genes, which are yet to be identified. Other known risk factors include diets high in red meat and low in...
fibre, lack of exercise, obesity, alcohol and (probably) smoking, personal history of adenomatous polyps or previous colorectal cancer, and long-standing colonic inflammatory bowel disease. Aspirin and non-steroidal anti-inflammatory drugs are thought to be protective against polyps and cancer, but their use as chemopreventative agents is not currently recommended.

**Pathology and Pathogenesis**

**Adenoma–Carcinoma Sequence**

Analysis of the histological and molecular changes of colorectal polyps and malignancies has led to the adenoma–carcinoma hypothesis that now underpins our understanding of carcinogenesis in many other malignancies. There are two common molecular pathways — the ‘classical’ or chromosomal instability pathway and the microsatellite instability pathway. The majority of sporadic cancers follow the classical pathway in which large segments or whole chromosomes may be lost or duplicated; but about 15% follow the other pathway in which small changes in DNA, often at repeated nucleotide sequences (microsatellites), result in cancer-causing genetic mutations. These pathways have their counterparts in hereditary syndromes — FAP cancer follows the classical pathway whereas Lynch syndrome follows the microsatellite instability pathway. Detailed genetic analysis of individual tumours is becoming a reality with ever-decreasing costs and improved technology. This will help to predict behaviour and response to therapy.

The large majority of colorectal cancers are adenocarcinomas arising from the mucosa. Rare tumours include carcinoids, lymphoma, and melanoma.

**Distribution**

About two-thirds of sporadic cancers arise distal to the splenic flexure, with about 40% arising in the rectum. In patients with Lynch syndrome, this proportion is reversed with caecal cancer being the most common site.

**Spread**

Like many cancers, colorectal carcinoma spreads locally, via lymphatics and through the bloodstream. The liver is the most common metastatic site, via the portal venous system, followed next by pulmonary seedlings. Rarer sites include the skin, brain, and bone. Trans-coelomic spread leads to the development of multiple peritoneal nodules, though ascites is usually minimal.

**Pathological Staging**

Histological staging of colorectal cancers is performed postoperatively. Dukes’ and TNM staging (Figure 1) are widely used to inform decisions about
Dukes’ staging: node-negative tumours are staged A if they have not penetrated the muscularis propria, B if they have. If there is lymph node spread, the tumour is automatically a Dukes’ C.11 A C2 tumour is one in which there is lymphatic invasion at the node furthest away from the tumour – at the ‘high tie’. Although not described by Dukes, it is now conventional to label any metastatic spread as stage D.

TNM staging is more precise than Dukes’ staging but clinically less useful because there are so many subgroups.

Malignant polyps: with the advent of screening programmes, earlier detection of cancers has led to an increased detection of ‘polyp cancers’, which are T1 lesions. Many of these are cured by polypectomy alone. Use of other staging methods that take into account the depth of penetration, such as the Haggitt12 and Kikuchi13 classifications, is helpful in judging the risk of lymph node metastasis and thus in deciding whether a formal resection is indicated.

Circumferential margin: for surgery to be potentially curative, especially for rectal cancers, it is important to remove a margin of normal tissue around a cancer. Measurement of whether the circumferential resection margin is involved with cancer can be a very useful predictor of local and even distant recurrence.14,15

Diagnosis

Symptoms

Gastrointestinal symptoms are common, even in the absence of pathology, and there is a wide overlap of symptomatology for malignant and benign causes. Based on a large clinical database in Portsmouth, referral criteria have been developed that identify patients with colorectal cancer most reliably (Table 1),16 but only about 10–14% of patients meeting such criteria harbour a malignancy.

Obstructive symptoms: as tumours enlarge, they tend to narrow the bowel lumen. This commonly leads to a more frequent stool rather than constipation, although any persistent change in bowel habit should be investigated. Distal tumours are more likely than proximal tumours to lead to an alteration in bowel habit, as the stool consistency is more solid. Proximal tumours may produce no symptoms at all until they obstruct completely. In the rectum, the mass effect of a cancer leads to tenesmus (a feeling of incomplete evacuation).

Bleeding: rectal bleeding, especially if associated with a change in bowel habit, is a worrying symptom. Low rectal tumours can bleed bright red and mixed in with the stool. Although right-sided tumours bleed, this is not visible in the stools, and so these cancers classically present with iron-deficiency anaemia because there is no warning sign to the patient.

Symptoms not usually associated with colorectal malignancy: bowel cancers are biologically inert and do not display paraneoplastic features. Weight loss and anorexia are very uncommon unless there is widespread metastatic disease. Pain is also unusual unless a tumour is so advanced that it is nearly obstructing the bowel lumen or invading bone or nerves.

Acute presentation: about 20% of patients with colorectal cancer present as emergencies – usually with obstruction but occasionally with perforation or abscess formation. Most of these will require emergency surgery.

Signs

Patients with symptoms suggestive of colorectal pathology should undergo abdominal examination, rectal examination and a rigid sigmoidoscopy in the clinic.

Palpable mass: many colorectal cancers are palpable – typically, a right colon cancer gives rise to a firm mass in the right iliac fossa. Rectal cancers can often be felt on digital examination, and a rolled edge or circumferential nature can easily be appreciated. If a tumour is found, the surgeon will be greatly helped by information about the height of tumour from the anal verge, whether it is mobile, tethered, or fixed, and which quadrants are involved.

Sigmoidoscopic findings: a rigid sigmoidoscope will be able to examine most of the rectum and sometimes the distal sigmoid, so it can easily identify rectal tumours in the clinic. Equally important, it may reveal bleeding and inflamed mucosa from inflammatory

Table 1. Criteria for referral to fast track colorectal clinic

- A change in bowel habit (looser and/or more frequent stools) persisting > 6 weeks without rectal bleeding in a person aged 60 years or older
- Rectal bleeding persisting > 6 weeks without a change in bowel habit and without anal symptoms, in a person aged 60 years or older
- Rectal bleeding with a change of bowel habit towards looser stools and/or increased stool frequency persisting for 6 weeks or more, in a person aged 40 years or older
- A palpable right lower abdominal mass or a palpable rectal mass (intraluminal and not pelvic)
- Iron-deficiency anaemia with a haemoglobin of 11 g/dL or less in a man, or of 10 g/dL or less in a non-menstruating woman

Adjuvant therapy.

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<th>Diagnosis</th>
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bowel disease as an alternative explanation of the patient’s symptoms. The presence of streaks of blood in the lumen of the rectum is strongly indicative of pathology in the sigmoid above the reach of the rigid scope – usually a large polyp or cancer.

Differential Diagnosis
There is a wide differential diagnosis: alteration in bowel habit may be caused by irritable bowel syndrome, diverticular disease, infections, thyroid dysfunction, coeliac disease or inflammatory bowel disease; rectal bleeding may be caused by haemorrhoids, anal fissure, inflammatory bowel disease or polyps; iron-deficiency anaemia may be caused by gastric or small bowel pathology, poor diet, celiac disease or bleeding from other organ systems (eg, renal or genital tract).

Investigations

Diagnosis
Biochemical tests: no blood test will confirm or refute the diagnosis of colorectal cancer. A full blood count is useful to detect anaemia. Although carcinoembryonic antigen is commonly assayed, its value is more in follow-up than diagnosis. Faecal occult blood testing is a screening tool and is not indicated in persons with colorectal symptoms – such individuals need full colonic evaluation as described below.

Colonoscopy: it is the gold standard investigation for colorectal cancer and polyps. Completion rates should be over 90% in good centres with a perforation rate less than 0.1%. Colonoscopy will identify cancers and enable biopsy, and has therapeutic potential for removing polyps distant from the cancer to prevent metachronous malignancy developing during follow-up. A tattoo can be placed to allow the site of a tumour to be recognized at subsequent lapa-

Figure 3. Magnetic resonance imaging of a locally advanced rectal cancer.
Pre-operative Clinical Staging

Once a colorectal cancer has been diagnosed, clinical staging investigations should be performed to detect synchronous polyps and cancer, local spread, and metastatic disease. CT of the chest, abdomen, and pelvis is used for all patients to detect distant spread. Rectal cancers should be discussed at a multidisciplinary meeting before surgery; all tumours are discussed postoperatively.

Rectal cancer: the extent of local spread determines pre-operative therapy, and so pelvic imaging is very important. Transrectal ultrasound can accurately stage bowel wall invasion but is less good at detecting lymph node involvement. Magnetic resonance imaging is probably the most useful method for determining tumour invasion and nodal status. For colorectal cancer, this is less important as the treatment is decided. For colonic disease, this is less important as the endoscopic appearances usually indicate the need for surgery.

Computed tomography (CT) scans: particularly for elderly patients, a CT of the abdomen and pelvis is a useful diagnostic tool and is non-invasive. Occasionally, spasm on the right side of the abdomen can mimic the appearances of cancer on CT: if there is no clinically palpable mass in this situation, a colonoscopy is required to visualize the right colon and corroborate the CT findings.

CT colography: with multislice volume acquisition CT, excellent views can be obtained by insufflating air into a prepared colon. CT colonography is almost as accurate as colonoscopy and can visualize bowel proximal to an obstructing tumour.

Biopsy: all rectal cancers require biopsy proof of malignancy before treatment is decided. For colonic disease, this is less important as the endoscopic appearances usually indicate the need for surgery.

References


Further Reading


About the Authors

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Can Metastatic Colorectal Cancer Be Cured?

David L. Bartlett, MD; Edward Chu, MD

Significant advances have been made in the treatment of metastatic colorectal cancer. Development of the targeted biologic agents and their integration with cytotoxic chemotherapy regimens has led to improvements in clinical efficacy. A multimodality team-based approach involving medical oncologists, surgical oncologists, radiologists, and other health-care providers is absolutely critical for the success of this therapeutic approach. This article reviews the main issues that must be considered from the surgical oncology and medical oncology perspectives, respectively.

Introduction

In 2012, colorectal cancer (CRC) continues to be a major public health problem. In the United States this year, there will be an estimated 147,000 new cases diagnosed and nearly 50,000 deaths resulting from this disease.1 Worldwide, approximately 1 million new cases of CRC are diagnosed each year, with nearly 500,000 deaths attributed to this disease annually. About 25% of patients present with metastatic disease, and of this group, 50% to 75% will have disease confined to the liver.2–4 In patients who present initially with early-stage disease, up to 50% will eventually develop metastatic disease, with the liver being the most common site. Another 10% to 20% of patients will present with disease involving the lung and other less common sites of metastatic involvement, including the peritoneum, ovaries, adrenal glands, bone, and brain.5,6

When metastatic disease is limited to an
organ-specific site, an important consideration is whether the disease is resectable at the time of initial diagnosis or whether it is initially deemed to be unresectable but may become resectable with the up-front use of chemotherapy. With the integration of chemotherapy and surgical resection, overall 5-year survival rates on the order of 30% to 40% can now be achieved. A multidisciplinary, team-based approach involving surgeons, medical oncologists, radiologists, and other health-care professionals is required to determine the optimal timing and sequence of surgery and chemotherapy.

This article reviews the multidisciplinary approach to patients who have organ-limited metastatic CRC (mCRC), with the main focus being on liver-limited disease. In particular, the surgical and chemotherapy aspects of disease management will be discussed.

### Surgical Considerations for Patients With Metastatic Disease

Historically, the setting of liver-limited metastases from CRC has been one of the few examples of curative metastasectomy in oncology. Even before the development of effective chemotherapy agents, surgical resection of limited hepatic metastases was associated with prolonged survival and cures. Several important prognostic factors, such as disease-free interval, number and size of metastases, presence of extrahepatic disease, and stage of the primary cancer, have all helped to define the expected cure rate for hepatic metastasectomy. For patients with metastases defined by the most favourable prognostic categories, cure rates of 24% have been achieved with surgery alone. The indications for surgical metastasectomy were for patients with disease limited to the liver, a total of four or fewer metastases, unilobar involvement, tumours of less than 5 cm in their greatest diameter, and a disease-free interval of at least 6 months. It is, therefore, not surprising that the development of more effective chemotherapy has led to a significant improvement in overall survival (OS) and cure rates, as well as an expansion of the indication for metastasectomy. This indication has evolved into resection of any disease that allows for adequate hepatic residual volume for liver regeneration and survival, assuming there has been a response to neoadjuvant chemotherapy. In the past, surgeons were appropriately concerned that resection of visible disease would be followed by rapid recurrence from microscopic metastases in the residual liver. However, incorporation of effective neoadjuvant and/or conversion chemotherapy, as will be discussed in this article, provides greater confidence that micrometastatic disease can be eliminated and that removal of gross disease can lead to long-term cure. In addition, as hepatic surgery has become safer and easier for the patient, there is now wider acceptance of incorporating hepatic resection into a multimodality strategy to prolong survival.

The options for local and regional treatment of hepatic metastases have become broad, and include surgical resection, local ablation therapy, hepatic arterial infusion therapy, transarterial chemoembolization, radiomicrosphere therapy, and isolated hepatic perfusion. Each of these approaches has been associated with long-term cures, although surgical resection and local ablation strategies have been the most effective. The goal for surgical resection is to achieve a negative microscopic margin. Given the concern about microscopic extension beyond the visible tumour, a 1-cm margin around the tumour is ideal. Numerous coagu-

### Table 1. Prognostic factors for cure after surgical resection

<table>
<thead>
<tr>
<th>Category</th>
<th>Factors reported in multivariate analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary tumour characteristics</strong></td>
<td>Tumour grade</td>
</tr>
<tr>
<td></td>
<td>Lymph node involvement</td>
</tr>
<tr>
<td><strong>Liver metastatic burden</strong></td>
<td>Tumour-free interval</td>
</tr>
<tr>
<td></td>
<td>Tumour size (&gt; 5 cm)</td>
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<tr>
<td></td>
<td>Tumour number (&gt; 3)</td>
</tr>
<tr>
<td></td>
<td>Preoperative CEA (&gt; 60)</td>
</tr>
<tr>
<td></td>
<td>Extrahepatic disease (including hepatic lymph nodes)</td>
</tr>
<tr>
<td></td>
<td>Unilobar vs bilateral involvement</td>
</tr>
<tr>
<td><strong>Surgical factors</strong></td>
<td>Major resection</td>
</tr>
<tr>
<td></td>
<td>Positive margin</td>
</tr>
<tr>
<td></td>
<td>Blood transfusion</td>
</tr>
<tr>
<td></td>
<td>Resection of adjacent structures</td>
</tr>
<tr>
<td></td>
<td>Postoperative morbidity</td>
</tr>
<tr>
<td><strong>Chemotherapy</strong></td>
<td>Response to neoadjuvant/conversion chemotherapy</td>
</tr>
</tbody>
</table>

CEA = carcinoembryonic antigen.
lation devices exist to enhance the safety of parenchymal transection by limiting blood loss. Minimally invasive approaches, such as laparoscopic and robotic assistance, have become commonplace, and they are associated with reduced blood loss, shortened hospital stay, and decreased narcotic usage postoperatively.\textsuperscript{16,17} For patients undergoing multimodality therapies, minimally invasive surgery may also improve quality of life during treatment and decrease the recovery time necessary before adjuvant chemotherapy is administered. The options for resection include extended lobectomy, lobectomy, segmentectomies, and non-anatomic wedge resections. Many surgeons remove the least amount of liver tissue feasible to preserve the anatomy for future resections, if necessary, while others prefer formal anatomic resections in order to provide the best chance of a negative margin. These two approaches have not been directly compared in a randomized trial; however, retrospective data suggest that the ability to achieve a negative margin, as opposed to the specific type of resection, determines long-term prognosis.\textsuperscript{18}

Local ablative approaches have provided an alternative to surgical resection for patients with mCRC. These approaches include radiofrequency ablation (RFA), microwave ablation, cryotherapy, and focused radiotherapy (eg, using the CyberKnife). RFA is a reliable technique to ablate metastases up to 5 cm in size. However, it has limited efficacy in centrally located tumours in which proximity to the main portal triads or hepatic veins may cause bile duct injury, extensive hepatic necrosis, or inadequate tumour cell death adjacent to the vessels. The potential advantages of these local strategies over surgical resection include enhanced safety, outpatient percutaneous treatment options, and the ability to preserve hepatic parenchyma. The local recurrence rate after local ablative procedures is clearly higher than with surgical resection, with rates as high as 34% having been reported.\textsuperscript{19} The local recurrence rate at the site of ablation is influenced by the size and location of the metastatic lesions, as well as the use of percutaneous vs laparoscopic approaches. Although local recurrence can often be salvaged with repeat ablation or resection, for patients with limited comorbidities in whom the goal is curative intent, surgical resection is the preferred and most reliable method for actual cure. A meta-analysis of non-randomized studies comparing RFA with surgical resection demonstrated an improvement in 5-year survival for patients treated with hepatic resection.\textsuperscript{20}

The curative potential of surgical resection for hepatic metastases from CRC varies depending on a number of important prognostic factors (Table 1). Nomograms for predicting cancer-related survival have been developed and may be helpful when considering the utility of resection.\textsuperscript{21} A patient’s risk for morbidity and mortality also plays a significant role in defining the eventual treatment strategy. Surgical resection is still associated with a defined mortality rate of 2.8% (0% to 6.6%), which is influenced, in large part, by the health of the background liver.\textsuperscript{22,23} Liver failure is the most common cause of death after hepatectomy, and as discussed below, this complication is influenced by the specific type and cumulative dose of chemotherapy received. The indications for surgical resection are currently based on feasibility and safety in patients who have responded to chemotherapy. It is critically important for the surgical resection to leave 20% to 25% of functioning liver volume (future liver remnant) in patients with a normal background liver, and 40% of liver volume in patients whose background liver is diseased from previous chemotherapy.\textsuperscript{24} Preoperative planning computed tomography scans, including residual volume calculations, are essential when planning an extended or bilobar resection.\textsuperscript{25}

To date, more than 750 series of hepatic metastasectomy for metastatic CRC have been reported in the literature. The actuarial 5-year survival rate for patients who underwent R0 resections (negative margins) was 30% when combining 16 well-reported series of more than 100 patients with follow-up greater than 2 years (15% to 67%).\textsuperscript{22} While 5-year survival was historically considered a cure for this disease, because of advances in systemic chemotherapy an increasing number of patients are now living with their disease beyond 5 years. A single-institution study of 455 patients revealed a median OS of 33 months, with 5- and 10-year actuarial survival
rates of 34% and 25%, respectively.26 In that study, 124 patients were identified as actual 5-year survivors (27%), and of this group 59 were found to be 10-year survivors. This finding suggests ongoing disease-related mortality beyond the 5-year timeframe, with actual cure rates of 10% to 15%. Randomized clinical data suggest an improvement in disease-free survival (DFS) when systemic chemotherapy is incorporated as part of a combined neoadjuvant and postoperative adjuvant approach, as will be discussed in detail in this article.

With the extended indications for hepatic metastasectomy in the presence of active systemic chemotherapy, larger resections can now be safely and effectively performed. Commonly used techniques include staged resections for bilobar disease and preoperative portal vein occlusion to achieve compensatory hypertrophy and safer extended resections.27,28 While there appear to be impressive actuarial 5-year survival rates in these series of extensive surgical resections, it is expected that the true cure rate will be much lower. When looking at patients with initially unresectable colorectal liver metastases who were treated with chemotherapy and then resected, 16% of this group were considered cured, with a disease-free interval of more than 5 years after metastasectomy.29 On multivariate analysis, the main predictors of cure included maximum size less than 3 cm, no more than three metastatic lesions, and complete pathologic response.

**Systemic Chemotherapy**

Long-term cures are exceedingly rare when patients with organ-limited mCRC are treated with chemotherapy alone. In a retrospective review of 2,751 patients with metastatic CRC, during a median follow-up of 10.3 years, only six (0.24%) were found to be free of disease after having received chemotherapy alone.30 It is now well established that a multimodality strategy results in a much higher chance of long-term cure. In patients with organ-limited disease, chemotherapy is administered in three main settings, which include neoadjuvant therapy, conversion therapy, and adjuvant therapy. Neoadjuvant therapy refers to chemotherapy given to patients with potentially resectable disease, while conversion therapy refers to chemotherapy given to patients deemed to have initially unresectable disease. Adjuvant chemotherapy is the use of chemotherapy following an R0 surgical resection, with the intent of preventing disease recurrence.

**Neoadjuvant Chemotherapy**

Up to 20% to 30% of patients with liver-limited mCRC may have potentially resectable disease at the time of initial presentation. However, because a large proportion of patients experience recurrence of their disease either in the liver or systemically, chemotherapy has been integrated in their up-front care to improve upon the potential benefit of surgery. Several clinical trials have specifically evaluated the role of neoadjuvant therapy for patients with potentially resectable liver metastases. In a single-arm trial involving 20 patients, neoadjuvant therapy with a weekly administration of FOLFOX (fluorouracil [5-FU], leucovorin/folinic acid [LV], and oxaliplatin) resulted in a partial or complete response in all patients enrolled.31 A total of 16 patients underwent a potentially curative resection, with seven developing recurrence during the median follow-up period of 23 months. A phase II trial of neoadjuvant therapy investigated bevacizumab plus the combination of capecitabine and oxaliplatin.32 In this study, 56 patients received six cycles of therapy prior to surgical resection, and a remarkably high objective response rate of 73% was observed. A total of 52 of the 56 patients were able to undergo an R0 resection, with complete pathologic response occurring in nearly 10% of patients. Given concerns over the potential risks of bleeding or wound-healing complications, bevacizumab was not given with the last cycle of chemotherapy prior to surgery. This study is important as it showed that bevacizumab could be safely administered to patients with no increased risk of intraoperative bleeding or wound-healing complications. Moreover, it was estimated that normal liver regeneration occurred in all but one patient.

The European Organisation for Research and Treatment of Cancer (EORTC) randomized phase III trial 40983 investigated use of perioperative FOLFOX4 chemotherapy in patients with up to four resectable liver metastases. In this study, patients were randomized to surgery alone or to receive six cycles of FOLFOX4 before surgery and six cycles of FOLFOX4 after surgery.33 The overall response rate was 43% in patients receiving chemotherapy. Of note, surgery was performed in 83% of patients randomized to chemotherapy and in 84% of patients randomized to surgery alone, providing evidence that use of initial chemotherapy did not compromise the ability of patients to undergo surgical resection. While there was an increased risk of postoperative complications in patients receiving neoadjuvant chemotherapy, these events were reversible and not associated with an increased risk of
mortality. When the entire group of randomized patients was considered, a 7.3% increase in progression-free survival (PFS) at 3 years was observed in patients receiving chemotherapy, although this difference did not reach statistical significance. However, in the group of patients who underwent surgical resection, a significant 9.2% improvement in 3-year PFS was, in fact, observed.

Adam et al examined the influence of the response to neoadjuvant chemotherapy on the eventual outcome in patients following surgical resection of multiple liver metastases. In this retrospective analysis of 131 patients, 44% underwent hepatectomy after achieving an objective tumour response, 30% went to surgical resection after tumour stabilization, and 26% were surgically resected after tumour progression. Five-year survival was significantly lower in the group of patients who had evidence of tumour progression, compared with patients who had evidence of tumour response (8% vs 37%). Of note, patients with stable disease on neoadjuvant chemotherapy had only a slightly worse prognosis with respect to 5-year survival, compared with responders (30% vs 37%). DFS in patients who progressed on neoadjuvant chemotherapy was only 3%, compared with rates of 21% and 20% for patients with tumour response or stable disease, respectively. Based on this study, it is clear that tumour progression before surgery is associated with extremely poor clinical outcome, and in this setting, hepatic resection should be avoided in patients who are deemed to be non-responders to pre-operative chemotherapy.

Neoadjuvant chemotherapy may be associated with complete disappearance of some or all of the hepatic metastases on imaging studies (approximately 18% of tumours will disappear completely). Pathological complete response is associated with a high rate of long-term cure after surgical resection (5-year survival of 79%). Controversy exists regarding the need to resect patients with complete radiographic responses, to achieve long-term cure. Up to 70% of these sites of complete radiographic response are associated with pathologic complete response or failure to recur at these sites. The remaining 30% of patients are at risk of disease recurrence if resection is not performed. Thus, curative therapy should include resection of these regions, although the potential risk of disease recurrence at other sites must also be taken into consideration.

### Table 2. Select trials reporting conversion of unresectable metastatic CRC to resectable metastatic disease

<table>
<thead>
<tr>
<th>N</th>
<th>Regimen</th>
<th>Response</th>
<th>Conversion</th>
<th>R0 rate</th>
<th>Disease-free survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adam (2004)40</td>
<td>FOLFOX or FOLFIRI</td>
<td>NR</td>
<td>12.5%</td>
<td>11.6%</td>
<td>22% 5-year DFS</td>
</tr>
<tr>
<td>Alberts (2005)42</td>
<td>FOLFOX4</td>
<td>25%</td>
<td>40%</td>
<td>33.3%</td>
<td>19 mo median DFS</td>
</tr>
<tr>
<td>Barone (2007)43</td>
<td>FOLFIRI</td>
<td>47.5%</td>
<td>33%</td>
<td>33%</td>
<td>Median DFS &gt; 5 years</td>
</tr>
<tr>
<td>Falcone (2007)44</td>
<td>FOLFIRI or FOLFIRI</td>
<td>34% 60%</td>
<td>12% 36%</td>
<td>12% 36%</td>
<td>NR</td>
</tr>
<tr>
<td>Souglakos (2006)45</td>
<td>FOLFIRI or FOLFIRI</td>
<td>33.6% 43%</td>
<td>4% 10% &amp;</td>
<td>3.4% 8% &amp;</td>
<td>NR</td>
</tr>
<tr>
<td>Masi (2009)46</td>
<td>FOLFIRI</td>
<td>70%</td>
<td>24%</td>
<td>19%</td>
<td>29% 5-year DFS</td>
</tr>
<tr>
<td>Van Cutsem (2009)54</td>
<td>FOLFIRI or FOLFOSIRI</td>
<td>39% 47%</td>
<td>3.7% 7% &amp;</td>
<td>1.7% 4.8% &amp;</td>
<td>NR</td>
</tr>
<tr>
<td>Bokemeyer (2009)55</td>
<td>FOLFOX</td>
<td>36%</td>
<td>NR</td>
<td>2.4% 4.7% &amp;</td>
<td>NR</td>
</tr>
<tr>
<td>Folprecht (2010)56</td>
<td>FOLFIRI + cetuximab</td>
<td>68% 57%</td>
<td>NR</td>
<td>38% 30% &amp;</td>
<td>NR</td>
</tr>
</tbody>
</table>

DFS = disease-free survival; FOLFIRI = folinic acid, fluorouracil (5-FU), irinotecan; FOLFOSIRI = folinic acid, 5-FU, oxaliplatin, irinotecan; NR = not reported.

Denominator is entire cohort of patients with metastatic colorectal cancer and not limited to only liver-limited disease.
Conversion Therapy

The majority of patients will present with liver metastases from CRC that are unresectable or not optimally resectable based on their size, number, or location at the time of initial assessment. In this setting, conversion therapy is used in appropriately selected patients. The primary focus, therefore, is on achieving downsizing of the metastatic disease that is sufficient to allow surgical resection to be performed, but not with the goal of achieving a complete or even maximal response.

Adam and colleagues in France have had the largest experience in this area to date, and their work has provided important insights into the potential role of conversion therapy. In their original series of 701 patients with initially unresectable liver metastases, treatment with oxaliplatin-based chemotherapy resulted in downsizing in nearly 15% of patients, and subsequent surgery. Based on 5-year follow-up after surgery, 22% of patients had no evidence of residual or recurrent disease. When stratified according to the underlying reasons for initial unresectability, the 5-year OS rates were 60% for patients with large tumours, 49% for those with poorly located tumours, and 34% for patients with multinodular tumours. In an expanded series of 1,439 patients treated with a broader range of cytotoxic chemotherapy, the conversion rate was 12.5%, with a 5-year survival rate of 33%.

Folprecht and colleagues conducted an interesting analysis of all published/presented clinical trials and retrospective studies of the rate of objective response and the subsequent rate of resection of initially unresectable metastases. They observed a strong correlation \((r = 0.96)\) between response rates and the subsequent resection rate in patients with isolated liver disease. Moreover, their analysis confirmed that patient selection and efficacy of preoperative chemotherapy were strong predictors of potential resectability of liver metastases. Since this analysis, several prospective clinical trials incorporating systemic chemotherapy plus surgery have been performed. In these studies, use of oxaliplatin- vs irinotecan-based chemotherapy has shown similar clinical outcomes. Of note, approximately 20% to 30% of patients were able to undergo R0 surgical resection. Two trials have directly compared the clinical efficacy of FOLFOX plus irinotecan (FOLFOXIRI), an aggressive regimen that incorporates the three active cytotoxic agents, against that of FOLFIRI (5-FU, LV, irinotecan). Falcone et al randomized patients with mCRC to receive either FOLFOXIRI or FOLFIRI, and they reported a significant increase in R0 resection for the subgroup of patients with liver-only metastases who were randomized to the FOLFOXIRI arm. The R0 resection rate was 36% in the FOLFOXIRI arm vs 12% in the FOLFIRI arm \((P = 0.017)\). Despite the increased clinical activity of FOLFOXIRI, patients receiving this regimen experienced a significantly higher incidence of grade 3/4 toxicity in the form of myelosuppression and neurotoxicity. In contrast to the positive findings of the Falcone study, Souglakos et al observed a non-significant increase in overall response rate (43% vs 33.6%), conversion rate (10% vs 3.4%), and R0 resection rate (8.8% vs 3.4%). A pooled analysis of the Falcone phase III study and two phase II studies reported an overall response rate of 70% with the FOLFOXIRI regimen and a 19% R0 resection rate. The 5-year DFS and OS were 29% and 42%, respectively.

Is there an optimal cytotoxic chemotherapy regimen for conversion therapy? To date, there has been a significant absence of randomized trials directly comparing the various che-
motherapy regimens in patients with liver-limited disease. In reviewing the literature, it appears that irinotecan- and oxaliplatin-based regimens yield approximately the same rate of conversion, on the order of 20% to 30%. While FOLFOXIRI appears to result in higher conversion rates in the 40% to 60% range and higher R0 surgical resections, this treatment regimen is clearly associated with increased toxicity and should be used only in certain select patient populations. Upon review of the recent National Comprehensive Cancer Institute (NCCN) guidelines, several regimens are currently recommended, and they include FOLFIRI, FOLFOX, the combination of capcitabine and oxaliplatin, and FOLFOXIRI.47

The introduction of targeted therapies with either the anti-angiogenic agent bevacizumab or the epidermal growth factor receptor (EGFR) inhibitors cetuximab and panitumumab has improved the clinical efficacy of chemotherapy in patients with mCRC. As a result, combination regimens incorporating these agents have now been evaluated in clinical trials for patients with liver-limited metastases. Upon review of the recent National Comprehensive Cancer Institute (NCCN) guidelines, several regimens are currently recommended, and they include FOLFIRI, FOLFOX, the combination of capcitabine and oxaliplatin, and FOLFOXIRI.47

The addition of the anti–vascular endothelial growth factor (VEGF) antibody bevacizumab to either FOLFOX or to capcitabine and oxaliplatin vs the cytotoxic chemotherapy regimens alone was investigated in a randomized phase III trial in advanced mCRC.46 Unfortunately, there was only a slightly higher incidence of R0 surgical resection with bevacizumab (8.4%) vs chemotherapy alone (6.1%).

The anti-EGFR antibodies cetuximab and panitumumab have been approved for use in patients with mCRC.49 Subsequent studies have shown that these agents are active only in patients with wild-type KRAS tumours. KRAS mutations occur in up to 30% to 40% of patients with CRC, and they typically involve codon 12 or 13. In general, KRAS mutations lead to resistance to antibody therapy. However, recent studies have suggested that the G13D mutation in codon 13 may still allow for sensitivity to anti-EGFR antibody therapy, in sharp contrast to mutations in codon 12.

Retrospective analyses of clinical trials in mCRC have provided insights into the potential role of cetuximab in the treatment of liver-limited disease. In a phase II trial of FOLFOX plus cetuximab, 37 of the 43 patients enrolled had liver involvement, and in 17 of these patients, the liver was the only site of metastatic disease.50 An objective response was seen in 34 of the 37 patients; 10 of these patients underwent surgical resection of their metastases, including eight patients with liver metastases. In a series of 151 patients with unresectable mCRC liver metastases refractory to systemic chemotherapy, the addition of cetuximab to combination chemotherapy allowed 27 patients to undergo surgical resection, and of this group, 25 underwent potentially curative hepatectomy.51 Of note, this group included a majority of patients who were deemed to have either technically unresectable or marginally resectable disease. Moreover, the incorporation of cetuximab with chemotherapy conferred significant clinical benefit, with median PFS and OS of 13 and 20 months, respectively.

Several single-arm phase II trials have investigated the combination of cetuximab with either irinotecan- or oxaliplatin-based regimens. Min et al reported a radiologic response rate of 39%, with 30% of patients treated with FOLFIRI plus cetuximab able to undergo resection of their liver metastases.52 Nearly identical results were observed with the combination of FOLFOX and cetuximab, which yielded an R0 resection rate of 29%.53 Two recent randomized studies have investigated the safety and efficacy of cetuximab in combination with either FOLFIRI54 or FOLFOX.55 The addition of cetuximab to FOLFIRI significantly increased the overall response rate (59% vs 43%; P = 0.004) in patients with wild-type KRAS when compared with FOLFIRI alone, and this resulted in a higher number of patients able to undergo R0 surgical resection (4.3% vs 1.5%). An exploratory analysis revealed a twofold higher rate of R0 surgical resection in patients with liver-limited disease (9.8% vs 4.5%).54 Similar findings were reported by Bokemeyer et al55 with the combination of cetuximab plus FOLFOX4. The overall response rate increased from 37% to 61% in patients with wild-type KRAS and in those treated with the combination vs FOLFOX4 alone. This improvement in response rate in patients treated with the combination was associated with an increase in the R0 resection rate from 2.4% to 4.7%.

A trial of 114 patients with initially non-resectable liver-limited metastases randomized patients to receive cetuximab in combination with either FOLFOX6 or FOLFIRI. R0 resection rates of 38% and 30% were observed, respectively, with an overall R0 resection rate of 34%.56 In a retrospective analysis of response according to KRAS status with the two arms of the trial combined, the clinical response rate in patients with wild-type KRAS was 70% compared with 41% for those with mutant KRAS. This study provides further evidence of the strong association between high tumour response rate and increased rate of liver metastasectomy.

PRIME (the Panitumumab
Randomized Trial in Combination With Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy was designed to evaluate the efficacy and safety of panitumumab plus FOLFOX4 vs FOLFOX4 alone as initial treatment for mCRC. The addition of panitumumab to FOLFOX4 chemotherapy significantly improved the overall response rate (57% vs 48%; \( P = 0.02 \)) and median PFS in patients with wild-type KRAS tumours (9.6 vs 8.0 months; \( P = 0.01 \)), which translated into a non-significant increase in median OS from 19.7 to 23.9 months.

In terms of surgical resection, metastasectomy of any site was attempted in 10.5% of patients treated with the combination regimen as opposed to 9.4% of patients treated with chemotherapy alone. However, the R0 resection rate was higher in patients with wild-type KRAS tumours and liver-limited disease (28% vs 18%) who were treated with panitumumab plus FOLFOX4. At the time of the most recent analysis, median OS had not been reached in patients who underwent R0 liver resection, in contrast to a median OS of 23.6 months in those who were unable to undergo complete surgical resection.57

**Adjuvant Chemotherapy**

To date, only a limited number of clinical trials have investigated the role of adjuvant chemotherapy following surgical resection of organ-limited metastases. Two randomized phase III trials were conducted to determine the potential role of adjuvant chemotherapy with 5-FU/ LV vs surgery alone.58,59 Both trials showed a non-significant trend for improvement in DFS. Unfortunately, both studies closed prematurely due to slow patient enrolment. As a result, neither study had sufficient statistical power to demonstrate the predefined difference in OS. A pooled analysis of the individual data from these two trials was subsequently conducted by Mitry et al to improve the statistical power of the survival analysis. This analysis showed a marginally significant trend toward improved PFS for patients receiving chemotherapy (27.9 vs 18.8 months).60

What should the recommendations be for adjuvant chemotherapy following surgical resection? Although definitive clinical data are lacking, the current approach would be to offer adjuvant therapy with an oxaliplatin-based regimen, whether it be FOLFOX or XELOX, for a defined 3- to 4-month period. As is the case for the adjuvant treatment of early-stage colon cancer, there is presently no role for a biologic agent, such as bevacizumab or the anti-EGFR antibodies cetuximab and panitumumab, in oxaliplatin-based chemotherapy. Further support for this approach comes from the recently published NCCN clinical practice guidelines for adjuvant therapy of resected metastatic disease, which recommend a shortened course of cytotoxic chemotherapy, as would be offered for patients with resected stage III colon cancer.67

**Limitations of Chemotherapy**

The role of chemotherapy is to enhance the outcomes of surgery and/or permit potentially curative resection to be performed. Unfortunately, chemotherapy has potential disadvantages, which relate to direct toxic effects on the liver, leading to an increased risk of potential postoperative complications. There is now a large body of evidence showing that systemic chemotherapy can result in non-alcoholic fatty liver disease and sinusoidal injury. The chemotherapy-associated liver disease ranges from steatosis to steatohepatitis (CASH).62 Steatosis resulting from chemotherapy and/or any other etiology has been shown to lead to a higher rate of complications following hepatic resection. However, the development of CASH appears to hold greater significance.63 Of note, CASH appears to be more closely associated with the use of irinotecan-based chemotherapy and to occur more commonly in patients with higher body mass index.64 The development of CASH has been associated with a higher postoperative mortality rate related primarily to postoperative liver failure. In one series, the 90-day...
mortality rate in patients with steatohepatitis was 14.7% vs 1.6% for those who did not have steatohepatitis. In contrast to treatment with irinotecan, oxaliplatin-based chemotherapy has been typically associated with liver sinusoidal injury. In more severe cases, perisinusoidal fibrosis, sinusoidal obstruction, and portal hypertension have been observed. In contrast to CASH, the development of sinusoidal dilation has not been associated with an increased risk of perioperative morbidity and mortality.

Peritoneal Carcinomatosis

While this review has focused on liver-limited metastatic disease, cures have also been reported after pulmonary metastasectomy, isolated nodal recurrences, and ovarian metastases. While these are highly selected cases, they are worthy of consideration for patients with favourable tumour biology and/or for those who are responsive to chemotherapy. A growing field of interest has been the surgical management of peritoneal metastases from CRC, using cytoreductive surgery and intraoperative chemoperfusion with mitomycin C or oxaliplatin, combined with hyperthermia (HIPEC). This interest stems from early randomized trials with this treatment strategy in gastric cancer and a randomized trial in mCRC from the Netherlands. This mCRC carcinomatosis trial demonstrated an improvement in median survival in patients receiving intraoperative HIPEC, compared with systemic 5-FU/LV (22.3 months vs 12.6 months). Patients whose tumours could be completely resected from the peritoneum followed by HIPEC had an actuarial 3-year survival of 95%. A follow-up report on this trial demonstrated an overall actual 5-year survival of 45% in the HIPEC arm for patients with all disease resected. A recent report from France noted a 5-year survival of 26% in patients receiving HIPEC with oxaliplatin for colorectal peritoneal carcinomatosis. A number of series have compared surgical cytoreduction and HIPEC for peritoneal carcinomatosis vs surgical resection of hepatic metastases from mCRC, demonstrating similar survival curves. This finding suggests that an aggressive combined-modality approach for peritoneal carcinomatosis may have a defined cure rate. Presently, most centres combine surgical cytoreduction and HIPEC with neoadjuvant and postoperative adjuvant systemic chemotherapy, such as has been described for liver-limited metastatic disease.

Conclusions

When limited to a specific organ site, mCRC is potentially curable. To date, nearly all of the clinical studies have focused on liver-limited disease, but similar results are now being reported for patients with disease limited to the lungs, ovaries, and peritoneum. It is clear that a multidisciplinary team-based approach is required for the optimal care of this particular subset of patients. The development of an individual treatment plan comes from a careful discussion and ongoing communication among a multidisciplinary team of specialists, including surgeons, medical oncologists, and radiologists. With the appropriate integration of chemotherapy plus biological agents and surgery, up to 30% to 40% of patients with organ-limited metastatic disease can be cured. While the costs of the three biological agents— cetuximab, panitumumab, and bevacizumab—are not insignificant, the clinical evidence is now well-established that their incorporation with cytotoxic chemotherapy regimens in the neoadjuvant and conversion settings has greatly facilitated curative resection of liver-limited metastatic disease. However, further improvements are needed to enhance the clinical outcome of the remaining 60% to 70% of patients. Further refinements in whole-body and hepatic imaging should provide for a more accurate selection of the subset of patients who would benefit most from resection and would identify the presence of minimal residual disease following surgery. Finally, clinical trials are needed to develop novel cytotoxic agents and biologic/targeted agents that can be used in both the preoperative and postoperative settings to reduce the risk of local and systemic recurrence.

Declaration of Interest

None.

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A complete list of references can be obtained upon request from the editor.


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Roflumilast—Last But Not Least?
Tan Tze Lee, MBChB(Edin), MRCP(UK), FRCP(Edin); Ong Kian Chung, MBBS, MRCP(UK), FRCP(Edin), FCCP(USA)

Roflumilast, a novel phosphodiesterase-4 inhibitor, has demonstrated efficacy in improving lung function in severe chronic obstructive pulmonary disease (COPD). Its anti-inflammatory properties appear to address COPD’s underlying chronic inflammatory process, and it has been shown to improve the forced expiratory volume in the first second of expiration and quality of life, and reduce exacerbations, especially in the chronic bronchitis subgroup.

Introduction

Chronic obstructive pulmonary disease (COPD) is an increasing problem in the world today, with an estimated 64 million having moderate to severe disease in 2004. By 2020, it is estimated to be ranked fifth worldwide in terms of burden of disease based on a World Bank/World Health Organization study, and is expected to become the third ranked cause of death by then. The predominant cause is cigarette smoking, although exposure to biomass and occupational pollution also play a role, in some cases significantly.

This chronic inflammatory disease of the lungs and airways is a major cause of morbidity and mortality. It is well recognized to be a progressive chronic inflammatory disease, and early detection, smoking cessation and therapeutic intervention are key to optimizing COPD management.

Until recently, there has been no available treatment that alter the progression of COPD, and current therapies have, to date, focused on symptom relief and improvement of quality of life (QOL). Inhaled short-acting β2-agonists, long-acting β2-agonists (LABA), short-acting muscarinic antagonists (SAMA), long-acting muscarinic antagonists, and LABA–inhaled corticosteroids (ICS) combinations have all been used to manage COPD.

Theophylline has been used for
over 100 years in clinical practice. Concerns about its narrow therapeutic window and drug interactions can limit its use in COPD. A weak bronchodilator, it nevertheless remains popular because it is inexpensive and widely available.

**Background**

Cyclic adenosine monophosphate (cAMP) plays an important part in regulating inflammatory cell activity and is degraded by the phosphodiesterase enzymes. The phosphodiesterase 4 (PDE4) enzyme is the main cAMP-metabolizing enzyme in inflammatory cells, and its inhibition leads to accumulation of cAMP levels in the cell, which reduces the cell’s inflammatory activity.

**Pharmacology**

PDE4 is a primary regulator in most inflammatory and immune cells. By inhibiting PDE4, various pro-inflammatory processes are suppressed, and this has shown, in some studies, to benefit animal models of pulmonary inflammation.

PDE4 inhibitors have demonstrated many anti-inflammatory properties, including inhibition of inflammatory mediators and immune cell activation. Roflumilast, together with its active metabolite roflumilast N-oxide, is a potent PDE4 inhibitor (Figure). In both animal models and patients with COPD, roflumilast has been shown to suppress inflammatory mediator release, reduce airway inflammation, and reduce the neutrophil and eosinophil counts. These outcomes are very promising but did not always correlate with good clinical outcomes for all COPD patients. It would appear that the chronic bronchitis phenotypic group of COPD patients would tend to benefit the most.

Roflumilast is active orally and has been approved for the treatment of moderate to severe COPD. It is given orally, is highly bioavailable (f = 0.79), binds extensively to plasma proteins (98.9%), achieves a steady state in 4 days (daily dosing regime), has an elimination half-life of 7 to 25 hours, and is subject to negligible first-past hepatic metabolism. The pharmacokinetic profile is linear and predictable over the dose ranges of 250 to 1,000 µg.

The major metabolite is roflumilast N-oxide by the N-oxidation pathway. This is primarily by the cytochrome P450 isozymes CYP3A4 and CYP1A2. The half-life of roflumilast N-oxide is considerably longer than that of its parent, at approximately 27 hours. This suggests that the pharmacological ability of roflumilast to produce a long-lasting, competitive, 24-hour inhibition of PDE4 is in fact through its metabolite. Roflumilast N-oxide is finally deactivated and excreted via the renal pathway.

There are no specific contraindications except for specific allergy to roflumilast or its excipients. Care should be taken in patients with moderate to severe hepatic impairment (Child-Pugh B or C) in view of the cytochrome P450 pathways. Data suggest that roflumilast has little adverse interaction with erythromycin, ketoconazole, montelukast, digoxin, sildenafil, midazolam, and inhaled salbutamol, formoterol and budesonide. Oral magnesium hydroxide was also found not to affect the pharmacokinetics of roflumilast.

Inducers of the cytochrome P450, such as rifampicin, have been shown to significantly affect the efficacy of roflumilast. Strong inducers, such as carbamazepine, phenytoin and phenobarbital, could potentially limit the efficacy of roflumilast.

**The Evidence**

The early studies used forced expiratory volume in the first second of expiration (FEV1) and QOL as end points. Rabe et al and Calverley et al found roflumilast to be effective in moderate to severe
COPD (M2-107 trial) and severe COPD (M2-112 trial), respectively.\(^{27,28}\)

In the former study conducted over a treatment period of 24 weeks, significant improvements in post-bronchodilator \(\text{FEV}_1\) were found in subjects taking roflumilast 250 or 500 \(\mu\)g as compared with placebo (difference, 74 mL for 250 \(\mu\)g, and 97 mL for 500 \(\mu\)g; \(P < 0.0001\)). QOL using the St George's Respiratory Questionnaire total score was also found to be improved as compared with placebo (-1.6 for 250 \(\mu\)g, and -1.7 for 500 \(\mu\)g).

The latter trial focused on subjects with severe COPD and studied the effect of roflumilast 500 \(\mu\)g daily in these patients for a year. Concomitant ICS were permitted (60% of subjects). The results found improvements in post-bronchodilator \(\text{FEV}_1\) (39 mL; \(P = 0.001\)) and a non-significant reduction of moderate to severe exacerbations. Subsequent post hoc analysis of M2-112 and its replicate M2-111 demonstrated a significantly reduced exacerbation rate (14.3%; \(P = 0.026\)), with the following subgroup of patients benefitting the most: patients with chronic bronchitis (26.2%, \(P = 0.001\)), or with high cough (20.9%, \(P = 0.006\)) or sputum scores (17.8%, \(P = 0.03\)) prior to randomization, or patients receiving concomitant ICS or SAMAs (18.8%, \(P = 0.014\)). The finding that roflumilast preferentially reduced exacerbations in COPD patients who had characteristics of chronic bronchitis, with or without ICS, led the investigators to craft the design of the subsequent phase III studies to examine the effect of roflumilast on acute exacerbations of COPD.\(^{13}\)

Two 12-month studies, M2-124 and M2-125, were pivotal in establishing the therapeutic benefits of roflumilast in severe COPD cases. They were of identical design and compared roflumilast 500 \(\mu\)g daily with placebo, and were different only in their study population ethnic composition. The subjects were not allowed ICS, and only half used long-acting bronchodilators. There was improvement in pre-bronchodilator \(\text{FEV}_1\) of 48 mL (\(P < 0.0001\)) as well as post-bronchodilator \(\text{FEV}_1\) of 55 mL (\(P < 0.0001\)). There was also a relative risk reduction of 17% in rate of exacerbations (\(P = 0.0003\)), which was greatest in moderate exacerbations.

The pooled analyses of M2-124 and M2-125 by Calverley \textit{et al} revealed that the mean rate of moderate and severe exacerbations were significantly lower in patients receiving roflumilast as compared with placebo, be it with concomitant inhaled LABA (20.7%, \(P = 0.01\)), SAMA (13.1%, \(P = 0.0458\)), or previous ICS (19.3%, \(P = 0.0038\)).\(^{29}\)

Two further 6-month studies provided the evidence for roflumilast use as an add-on to long-acting bronchodilator therapy. M2-127 studied the concomitant use with salmeterol and M2-128 with tiotropium. The tiotropium subjects recruited were more symptomatic, and in both studies the subjects were randomized to roflumilast 500 \(\mu\)g or placebo added on to inhaled salmeterol or tiotropium. The salmeterol group showed improved pre- and post-bronchodilator \(\text{FEV}_1\) of 49 mL and 60 mL (both \(P < 0.0001\)), respectively whereas the tiotropium group similarly showed improvement for both pre- and post-bronchodilator \(\text{FEV}_1\) of 80 mL and 81 mL (both \(P < 0.0001\)), respectively.\(^{30}\)

Safety

The most common adverse effects encountered with roflumilast are gastrointestinal, with diarrhoea (9%) being the most common, followed by nausea (5%) and decreased appetite (3%). Weight loss (12%) was also commonly reported. The rates of cardiovascular events were similar in both the treatment and placebo groups in pooled safety studies, and there were 6% of roflumilast subjects exhibiting psychiatric disorders compared with 3% in those receiving placebo. There remain concerns about the incidence of completed suicides in the COPD safety pool, although none have been identified as being related to roflumilast.

Conclusion

COPD is a multiorgan and multisystem disease. It not only involves the airways and lung parenchyma but also has effects far removed from its origins in the respiratory system. The inflammatory process that accompanies COPD often progresses even when smoking has ceased, and therapies in the past were unable to address this.

Historically, the drugs used to manage COPD have primarily been bronchodilators and, in cases of recurrent exacerbations, ICS. Prior to the arrival of roflumilast, these therapies did not adequately address the issue of inflammatory processes in COPD. The mainstay of the benefits from roflumilast use in COPD is through its unique anti-inflammatory effect.
COPD. The mainstay of the benefits from roflumilast use in COPD is through its unique anti-inflammatory effect. Even though it does not have a direct bronchodilator effect, studies have shown that FEV1 improves following regular administration of roflumilast.

Many questions remain unanswered. Long-term survival studies are needed to address whether or not the benefits of roflumilast are only confined to the severe-stage chronic bronchitis phenotype cohort, or whether it extends to other phenotypes and severity stage and under what conditions.

Would roflumilast be the panacea for COPD, by suppressing inflammation and reducing mortality as well as the rate of decline of FEV1, ie, lung function? Only time will tell.

References
A diet that is low in FODMAPs (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) has been shown to be effective in reducing gastrointestinal symptoms in patients with functional gut disorders.

Functional gastrointestinal symptoms are common and their management is often a difficult clinical problem. There is a link between food intake and symptom induction and it has been shown that restricting the intake of rapidly fermentable, short-chain carbohydrates (FODMAPs – fermentable oligosaccharides, disaccharides, monosaccharides and polyols) reduces these symptoms. Functional gastrointestinal symptoms are common and their management is often a difficult clinical problem. There is a link between food intake and symptom induction and it has been shown that restricting the intake of rapidly fermentable, short-chain carbohydrates (FODMAPs – fermentable oligosaccharides, disaccharides, monosaccharides and polyols) reduces these symptoms.1,2 FODMAPs are widespread in the diet and their ingestion results in delivery of readily fermentable substrate and more water to the distal small intestine and proximal colon, where this osmotic load and the gas produced are likely to induce luminal distension and functional gut symptoms.3,4

Dietary management strategies for functional bowel disorders have changed markedly since the recent introduction of the low FODMAP diet.

**Functional Bowel Disorder**

The term ‘functional gastrointestinal disorder’ (FGID) refers to gastrointestinal symptoms in the absence of a clear pathologically evident cause. Because FGID can originate from anywhere in the gastrointestinal tract, a symptom-based classification comprising eight categories, the Rome III classification, was developed by a consensus body. Categories include chronic symptoms derived from the proximal gut (functional heartburn and functional dyspepsia) and from the small and large intestine (irritable bowel syndrome, functional bloating, functional constipation and functional diarrhoea).

Although this system is useful to ensure homogeneity in classifying patients for trials (particularly those that are multicentred), in clinical practice there is a large degree of overlap between categories, and it is not uncommon for patients to move from one category to another over time. The classification therefore has yet to be a good guide for therapeutic decision-making.

This review will use the term ‘functional bowel disorder’ (FBD) to cover symptoms originating from the intestine. The term includes the categories of irritable bowel syndrome, functional bloating, functional constipation and functional diarrhoea.

**Why Should We Be Interested in FBD?**

Reasons for being concerned about FBD include those listed below.

- **FBD is very common,** with a prevalence of 5% to 12% in Western countries.7,8
- **The various disorders are chronic conditions of unknown cause and cannot be ‘cured’**. Approaches therefore need to focus on strategies to manage symptoms.
- **Patients with FBD commonly seek attention from medical and other health professionals.** FBD accounts for up to 10% of consultations for general practitioners and 50% of referrals to gastroenterologists.9
- **FBD can lead to substantial reduction in quality of life.** The impact on quality of life is comparable with that of depression and of chronic renal failure and is associated with increased use of healthcare resources.7,8,10
- **Treatment has had limited success.** The therapeutic approach is ‘palliative’ and, until recently, therapeutic interventions have been frustratingly unreliable and targeted at treating only one symptom. For example, a patient who has IBS with constipation as the predominant bowel function can be treated with laxatives, but this often has little effect on the bloating and abdominal discomfort that are
commonly found in conjunction. Furthermore, benefit of therapeutic interventions is usually marginal, with some studies reflecting no efficacy over placebo.11

**Understanding the Pathogenesis of FBD**

Although the aetiologies of the various conditions included in FBD are not known, there is increasing understanding of the pathophysiological basis for the genesis of symptoms. A central underlying problem appears to reside in the enteric nervous system, which is estimated to have as many neurones and synapses as the brain and is arranged with immense complexity that includes complex reflex pathways and memory. The enteric nervous system has been called the ‘gut brain’.

The two major characteristics of the enteric nervous system that are seen in patients with FBD are discussed below.

**Visceral hypersensitivity.**

Patients with FBD have a low sensory threshold. This is best demonstrated by barostat studies where distension of the gut (of the rectum by a balloon, or the stomach by liquid) leads to the sensation of distension or pain.12 The sensory threshold of patients with FBD is often much lower than would usually be encountered. This might be due to sensitization of the stretch receptors of the gut, which provide a major sensory input, or from altered signalling from colonic mucosa to the enteric nervous system.12,13

Immune stimulation in the gut in response to dietary proteins (allergic or hypersensitivity mechanisms) may also stimulate the enteric nervous system via, for example, serotonin or histamine release.14,15

- **Changed motility response to sensory stimulation.** This has been best demonstrated by gas distension studies where some patients with FBD do not develop the normal propulsive response (hence expelling the gas) and the gas remains within the lumen.16

The enteric nervous system is connected to the central nervous system, suggesting the brain also plays a substantial role in the genesis of symptoms via the ‘gut-brain axis’. There is little doubt that the brain can influence motility patterns and visceral sensitivity, as shown by the commonly observed occurrence of diarrhoea and/or abdominal pain in times of stress, such as sitting for an examination.

There is also a large body of data indicating the brain’s involvement in the genesis of FBD symptoms. Information sent to the brain via the enteric nervous system will cause regional patterns of stimulation that are different in patients with FBD from those in healthy controls, leading to a different interpretation of the sensory input. Thus, in patients with FBD, a similar sensory input from the enteric nervous system may be interpreted as, for example, abdominal pain rather than mild discomfort.17 Thus, the brain is an important modifying factor in symptom genesis and in symptom interpretation.

**Current Therapeutic Strategies for FBD**

Ideally, the best way of dealing with FBD is to ‘retune’ the enteric nervous system or the central nervous system, just as the best approach to food allergy or hypersensitivity is to stop the immune reaction to the inciting protein. The ability to do this is poor. Hence, other more palliative approaches to dealing with the symptoms are needed. Approaches to controlling FBD symptoms include the following:

- minimizing stimulation of the enteric nervous system: potential targets for therapy include stimuli that may be present in food (having effects either directly or secondarily) and possibly also in the gut microbiota
- treating specific symptoms: pharmacological or other approaches to deal with specific symptoms, such as analgesics for pain, laxatives and prokinetics for constipation, and hypomotility agents for diarrhoea
- managing the gut–brain axis: pharmacological and psychological therapies, such as anxiolytics, antidepressants, cognitive behaviour therapy and hypnotherapy, to modulate symptom perception and the distress it causes.

**Dietary Change as a Therapeutic Tool in FBD**

Until recently, dietary management of FBD has included reduction of fat (on the basis that fat influences motility); avoidance of caffeine (presumably related to its bioactive nature); alteration of dietary fibre intake (to improve the quality of colonic contents); and elimination of suspected dietary triggers such as milk and wheat, with a purely trial-and-error approach.9,18,19

Many other dietary regimens, including low salicylate, gluten-free and very low carbohydrate diets, have been reported in the medical literature or are discussed on the internet. Although many of these diets may produce some improvement in symptoms, the evidence for efficacy is anecdotal only and there is no rational way of matching an appropriate dietary modification to individual patients. Another problem is that protocols using strict elimination diets followed by fixed rechallenges
are labour-intensive and require seriously devoted patients to carry them out. Such protocols also give no opportunity to assess dosing of dietary triggers in the induction of symptoms.

Dietary management strategies for FBD have changed markedly since the recent introduction of the low FODMAP diet. This dietary approach is based on known and validated pathophysiological principles and has a high level of evidence for efficacy.\(^2,4,20\) Moreover, this treatment appears effective across many centres and is supported by detailed food composition analysis.\(^21,22\)

**FODMAPs**

The acronym FODMAPs refers to fermentable short-chain carbohydrates that are poorly absorbed and may then have effects on the gastrointestinal tract – fermentable oligosaccharides, disaccharides, monosaccharides and polyols.\(^1\) The specific carbohydrates are:

- **oligosaccharides:** fructans (including fructo-oligosaccharides [FOS] and insulin) and galacto-oligosaccharides (GOS)
- **disaccharide:** lactose
- **monosaccharide:** fructose (in excess of glucose, see later under ‘Small intestinal absorption of FODMAPs’)
- **polyols:** including sorbitol and mannitol.

The effects of the various FODMAPs are additive and these carbohydrates should be viewed together as a group rather than individually.

The concept of reducing dietary FODMAPs to control gastrointestinal symptoms in patients with FBD relates to their physiological effect. FODMAPs are poorly absorbed in the small intestine and have the same physiological effects in the distal small bowel and proximal colon, namely luminal distension with solids, liquids and gas. FODMAPs contribute particularly to luminal distension by liquids and gases: liquids because of the large osmotic load they cause due to their small molecular size, and gases because of their rapid fermentation by intestinal bacteria (rapid due to their short chain length).\(^4\) They have a smaller contribution to the solids content, through their fibre content and the microbial mass expansion associated with their fermentation.

The increased water content of the colon exerts a natural laxative effect, and the fermentation of the unabsorbed FODMAPs by intestinal bacteria leads to the production of short-chain fatty acids as well as gas.\(^3,4\) In small amounts, some FODMAPs (fructans and GOS) may exert beneficial prebiotic effects by promoting differential expansion of bacterial populations, which will suppress potential colonic pathogens.\(^23\)

Conversely, the increased water load and gas production caused by FODMAPs can lead to laxation and distension of the bowel that results in symptoms of bloating, pain and secondary motility disturbances.\(^4\) Such effects are exaggerated in patients with FBD because of the presence of visceral hypersensitivity and abnormal motility responses. This explains why FODMAPs exacerbate gastrointestinal symptoms in patients with FBD, with studies confirming this hypothesis.\(^3,4\) Furthermore, studies have shown that reducing the intake of dietary FODMAPs in this population group has been successful in reducing gastrointestinal symptoms.\(^2,20\) The features unique to FODMAPs that explain this impact are listed in Table 1.

### Small Intestinal Absorption of FODMAPs

The various FODMAPs are digested and adsorbed in the small intestine to differing extents. There are three patterns of digestion and absorption, as described below.

- **Totally malabsorbed:** the fructans and GOS. As the human body does not possess enzymes to hydrolyse these oligosaccharides, they cannot be absorbed and their fate is to be fermented by bacteria in the distal small intestine and, particularly, the colon.\(^1,24\)
- **Partly malabsorbed:** the polyols. Absorption of polyols is considered to be by passive diffusion, which is inefficient (because of the presence of the attached alcohol group). Thus, there will usually be some malabsorption of polyols;
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Indeed, on average, about 70% of sorbitol (the most commonly found dietary polyol) will be malabsorbed.\textsuperscript{25}  
- **Partly malabsorbed in only some people:** fructose and lactose. In the presence of equimolar glucose, fructose is rapidly absorbed by the proximal small intestine due to glucose-mediated activation of a high capacity transporter. However, fructose in excess of glucose (‘free fructose’) is transported by a slow and low capacity transporter that acts all along the small intestine.\textsuperscript{24}  This transporter varies in its capacity across individuals and can be readily overloaded by too much free fructose or by too rapid a transit along the small intestine.\textsuperscript{24}  Lactose, on the other hand, is a disaccharide (galactose plus glucose) and requires splitting into its component molecules (by lactase in the small intestinal brush border) to be absorbed. The activity of lactase varies across individuals according to ethnicity and other factors. Thus, only some people malabsorb fructose and/or lactose.

### The Low FODMAP Diet

#### Determining FODMAP Absorptive Capacity

As the aim of the low FODMAP diet is to restrict the intake of short-chain carbohydrates that are poorly absorbed and delivered to the colon, it would be helpful to know whether fructose and/or lactose is completely absorbed in an individual because this may permit a less restrictive diet. Fructose and lactose absorption may be explored through dietary trials, but experience has shown the inaccuracy of this method. It is preferable to determine an individual’s absorptive capacity by performing breath hydrogen tests.

Breath hydrogen tests are based on the principles that the only source of hydrogen in the breath is from bacterial fermentation of carbohydrates in the intestine and that a rise in breath hydrogen following the ingestion of a specific carbohydrate implies malabsorption of that carbohydrate. A relatively large dose of lactose (50 g) or fructose (35 g) is generally given to determine whether complete absorption is achieved. Results showing absorption of the load given indicate that restriction of that particular short-chain carbohydrate is not necessary. Interpretation of the test can be improved by also performing a test with lactulose (15 g), which is not absorbed in anyone, as the control.

Breath methane can also be measured, but results are not as easily interpreted as breath hydrogen responses and the test should only be used if there is a poor hydrogen response (often reflected in the lactulose control breath test).

#### Interpreting Breath Hydrogen Tests

There has been a tendency to misinterpret or overinterpret the results of breath testing. Important points to note include those listed below:

- Carbohydrate malabsorption is present in all populations, not just those with FBD. It is physiologically normal to have fructose or lactose malabsorption, both of which occur with similar frequency in healthy individuals and patients with FBD.\textsuperscript{26}  Therefore, breath testing does not indicate visceral hypersensitivity and is not a diagnostic test for FBD. Breath testing is therefore indicated only in symptomatic patients who would consider adopting dietary modification to treat their symptoms.
- Breath testing does not provide information as to whether the low FODMAP diet should be used; rather, it gives information on the design of the diet, tailoring it to the individual.

After all, fructans and GOS, and to a lesser extent polyols, are malabsorbed by all people. Their restriction forms the core of the diet for symptomatic patients.

- The presence of malabsorption does not give an indication of the proportion of ingested sugar malabsorbed, so cannot be used to predict therapeutic reductions in food sources.
- It is difficult to interpret symptoms that are generated during (or after) breath testing because the predictive value of symptoms relates to usual intake of the sugar from dietary sources. Also, dietary FODMAPs are seldom consumed alone and different FODMAPs have additive effects on the bowel.

#### Instituting the Low FODMAP Diet

The low FODMAP diet is a dietitian-taught diet. As with all conditions requiring dietary restriction, nutritional adequacy and, therefore, degree and length of time of restriction are important in tailoring the low FODMAP diet to the individual patient.

A dietitian with a good knowledge in implementing the low FODMAP diet will assess the patient and adapt the diet to accommodate the greatest possible food variety while achieving good symptom control, to improve the patient’s quality of life. This will often involve replacing foods rich in FODMAPs (high FODMAP foods) with appropriate alternatives that are poor in FODMAPs (low FODMAP foods). Detailed lists of foods are available in the article *J Gastroenterol Hepatol* 2010; 25: 252–258 and in the literature available on the Monash University Eastern Health Clinical School’s website [www.med.monash.edu.au/ehcs/research/index.html].\textsuperscript{23}  The most common high FODMAP
foods and suitable low FODMAP alternatives are shown in Table 2.25,26

The best procedure in finding this balance of food restriction and symptom control is to over-restrict all potential FODMAPs (while considering breath test results, if completed) until the best symptom control is achieved and maintained. This usually takes 6 to 12 weeks, depending on the patient’s dietary compliance and symptoms.

Once symptom relief is achieved, controlled doses of foods are reintroduced to assess the patient’s absorptive capacity for the partly absorbed FODMAP (if breath testing has not been performed) as well as the amount of malabsorbed FODMAPs that may still be tolerated. Improvement of FBD symptoms is relatively rapid (some improvement is usually seen within days), but clinical improvement has been noted to occur over a few weeks, particularly in patients with constipation-predominant IBS who may require more time to rid the effects of luminal distension.

On review, the dietitian will aim to widen the patient’s knowledge of the FODMAP-content of foods, so that the patient may best predict the role of FODMAPs in inducing symptoms. Dietary restriction may then be in the control of the patient, and be flexible enough to suit the patient’s lifestyle and preferred food choices. If there is no improvement in symptoms from the low FODMAP diet and adherence to the regimen is confirmed, another symptom management strategy must be considered.

The flowchart on page 302 summarizes the diagnosis and management of patients with FBD.

**Modified Approaches to the Low FODMAP Diet**

Educating patients about the concept of the low FODMAP diet to reduce FBD symptoms can be quite involved. As such, the dietitian may use simplified versions or perhaps an adapted ‘reduced’ FODMAP diet for patients with limited education or understanding or for those with English as a second language. Elderly patients, children or patients at risk of malnutrition may also require a less restrictive approach to ensure adequate intake from a greater variety of food sources. Furthermore, a patient with a diet history that is very high in FODMAPs may require only a reduction in the amount of FODMAPs in the diet, rather than a diet that is low in FODMAPs. Conversely, patients with extreme visceral hypersensitivity may require a very low FODMAP diet with strict ongoing adherence.

Costs associated with implementing the strict low FODMAP diet are ideally short-term. Consultation with the dietitian usually only requires two consultations. Extra food costs mainly relate to specialty breads and pastas. Most low FODMAP alternatives are commonly found in the supermarket with no additional costs. Nonetheless, socioeconomic status and food availability should also be taken into account on assessment.

**Success of the Low FODMAP Diet**

In clinical practice, the low FODMAP diet is very successful in assisting the management of FBD. The diet is now widely practiced across Australia and New Zealand, in the United Kingdom and to a lesser extent in North America. Three out of four patients report significant reduction of symptoms and improvement in quality of life.2,20

Although patients with extreme visceral hypersensitivity may not achieve complete symptom resolution, improvement is usually enough to motivate continued

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**Table 2. Top eight sources of FODMAPs and their alternatives**

<table>
<thead>
<tr>
<th>High FODMAP food</th>
<th>FODMAP present</th>
<th>Low FODMAP alternatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onions (all varieties) and garlic</td>
<td>Fructans</td>
<td>Chives, green section of spring onions, garlic-infused oils, ginger, chili, fresh herbs</td>
</tr>
<tr>
<td>Wheat- and rye-based breads, pastas and cereals</td>
<td>Fructans</td>
<td>Rice, gluten-free breads and pastas, oats, cornflakes</td>
</tr>
<tr>
<td>Legumes (eg, lentils, chickpeas, baked beans, kidney beans)</td>
<td>Fructans and GOS</td>
<td>Tofu, eggs, meat, poultry, fish</td>
</tr>
<tr>
<td>Honey</td>
<td>Fructose</td>
<td>Golden syrup, maple syrup, sugar, jam (with no added fructose)</td>
</tr>
<tr>
<td>Apples and pears</td>
<td>Fructose and sorbitol</td>
<td>Bananas, grapes, citrus fruits, strawberries</td>
</tr>
<tr>
<td>Stone fruit</td>
<td>Sorbitol</td>
<td>Bananas, grapes, citrus fruits, strawberries</td>
</tr>
<tr>
<td>Mushrooms, cauliflower</td>
<td>Mannitol</td>
<td>Broccoli, green beans, capsicum, carrot, potato, pumpkin, spinach</td>
</tr>
<tr>
<td>Milk, yoghurt, ice cream</td>
<td>Lactose</td>
<td>Lactose-free milks, yoghurts and cheese, rice milk</td>
</tr>
</tbody>
</table>

GOS = galacto-oligosaccharides.
compliance. Combination therapy with pharmacological agents or psychological therapies may be advantageous in this select patient group.

**Long-term Strategies of the Low FODMAP Diet**

The most important aspect in restricting FODMAPs in patients with FBD is that there is a dose-dependent relation to symptom induction. Often small amounts of FODMAPs are well tolerated. Therefore, after symptom control is achieved, liberalization of the diet to the individual threshold of the patient is encouraged to gain the health benefits of FODMAP-containing foods and to continue good food variety while still managing symptoms.

Furthermore, the extent of dietary restriction should accommodate the individual patient’s satisfaction of symptom control, food knowledge, understanding of his or her condition and ability to interpret information.

**Other Uses for FODMAP Manipulations**

In addition to reducing gastrointestinal symptoms in patients with FBD, reducing FODMAP ingestion also appears effective in other illness situations. It is effective in controlling functional gut symptoms in patients with quiescent inflammatory bowel disease and in reducing the frequency of bowel actions in patients with an ileal pouch. It may be also be useful in decreasing effluent volume in patients with high output ileostomies, and the selecting of low FODMAP enteral solutions might be effective in preventing diarrhoea in patients receiving enteral nutrition.

Conversely, increasing FODMAP intake may possibly improve general gastrointestinal health. FODMAPs may exert a prebiotic effect, with the putative health benefits of this. Because FODMAPs assist in laxation (as outlined above), they may play an important role in bowel function in patients with visceral sensitivity or other physiological abnormalities associated with FBD. The fermentation of FODMAPs in the large bowel yields short-chain fatty acids that appear to be anticarcinogenic. For these reasons, a low FODMAP diet should not be considered a ‘diet for good health’, but rather a therapeutic diet for those

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**Diagnosis and management of patients with functional bowel disorders**

- **Patient presents with functional gut symptoms**
  - **Assess alarm features**
  - **Perform coeliac testing and other appropriate investigations**
  - **Diagnosis of functional bowel disorder**
  - **Is breath testing available?**
    - **Yes**
      - **Breath hydrogen (and methane) testing with fructose and lactose to assess absorptive capacity**
      - **Core diet (restriction of fructans, galacto-oligosaccharides, polyols)**
      - **If fructose malabsorption present, restriction of fructose**
      - **Liberalization of dietary FODMAPs to patient’s symptom threshold, lifestyle and preferred food choices**
    - **No**
      - **Complete FODMAP restriction (fructans, galacto-oligosaccharides, polyols, fructose, lactose)**
      - **Liberalization of dietary FODMAPs to patient’s symptom threshold, lifestyle and preferred food choices**

  - **Other diagnoses**
  - **Appropriate treatment**

* Alarm features include significant weight loss, family history of inflammatory bowel disease, coeliac disease or colorectal cancer, gastrointestinal blood loss, nocturnal symptoms, fever, steatorrhoea, severe pain, anaemia or iron deficiency, elevated inflammatory markers (C-reactive protein, erythrocyte sedimentation rate), significant change in symptoms and new-onset symptoms at age over 40 years.
individuals troubled by functional gut and possibly other symptoms.

Other Strategies for Treating FBD Symptoms

The low FODMAP diet is the first dietary approach proven to be successful in treating FBD symptoms. Unfortunately, well-designed clinical trials investigating other dietary approaches have not yet been completed. These other approaches are discussed below.

Food Chemical Sensitivities

Salicylates, amines and glutamate are food chemicals hypothesized to induce gastrointestinal symptoms in some patients with food chemical sensitivities. Patients will often present with non-gastrointestinal symptoms as well, including skin, respiratory and ‘systemic’ symptoms (e.g. ‘fuzzy head’, extreme fatigue and headaches).

As foods included in the low FODMAP diet are often still high in food chemicals, patients who are food chemical-sensitive can usually be identified. Currently, the protocol recommended for assessing food chemical sensitivities requires a very restrictive diet and must be carried out in conjunction with a dietitian.

Non-coeliac Gluten Intolerance

Gluten restriction to aid FBD symptoms in patients thought to be ‘non-coeliac gluten intolerant’ is frequently promoted by naturopaths and other alternative health practitioners. Evidence for its basis is presently being investigated; while its existence is likely, how commonly it occurs and who should be offered a gluten-free diet, is unknown.

Before recommending a gluten-free (or reduced gluten) diet, it is crucial that coeliac disease is properly excluded. As a minimum, coeliac serology should be performed while the patient is on a gluten-containing diet. Ideally, all patients in whom coeliac disease is suspected should have a small bowel biopsy before adopting a gluten-free diet. HLA-D gene status can exclude coeliac disease if neither HLA-DQ2 nor HLA-DQ8 are present, but the presence of either or both does not make the diagnosis and so genetic testing is only useful for excluding the condition.

Probiotics

There is a body of research on the role of probiotics in controlling symptoms in patients with FBD. Unfortunately, studies have not generally shown much benefit, although there have been some notable exceptions. It is clear, however, that results from one probiotic cannot be extrapolated to another. The recommending of probiotics generally has no negative implications, but their use should be ceased if symptoms remain unchanged.

Supportive Resources

Essential in the successful implementation of the low FODMAP diet is the provision of supporting written information, food lists, recipes and other advice such as suitable websites to access accurate information. Refer to www.med.monash.edu.au/ehcs, www.shepherdworks.com.au or www.dietsolutions.net.au for useful resources including information booklets, cookbooks, supportive journal articles, and dietitians specializing in FBD.

The importance of good education resources, quantity of free-time and level of education was evident in a study of patients with functional gut symptoms and quiescent inflammatory bowel disease. It was found that the best predictors of improved response included the use of low FODMAP cookbooks, working less than or equal to 35 hours per week and having a post-secondary school qualification.

Conclusion

FBDs are common conditions and until recently therapies have been largely unsuccessful. There is increasing evidence that the implementation of the low FODMAP diet offers a new and effective strategy to symptom management. Through dietetic guidance, an appropriate balance between maintainable dietary restriction and symptom management may be achieved in most patients.

Declaration of Interests

Ms Halmos and Dr Muir: None. Dr Shepherd is the author of five low FODMAP cookbooks and a low FODMAP shopping guide. Dr Shepherd and Professor Gibson are co-owners of the FODMAP trademark.

A complete list of references can be obtained upon request from the editor.


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CME Article:
Functional Bowel Disorders and FODMAPs

Please indicate on your answer sheet whether the following statements are True or False.

1. The Rome III classification, developed to help classify functional gastrointestinal disorder patients for trials, consists of five categories.

2. Visceral hypersensitivity and changes in motility response to sensory stimulation are two major characteristics of the enteric nervous system seen in patients with functional bowel disorder (FBD).

3. The brain can influence motility patterns and visceral sensitivity in times of stress.

4. Many dietary regimens used in the past have been shown without doubt to be effective in the treatment of FBD.

5. FODMAPs refer to fermentable oligosaccharides, disaccharides, monosaccharides and polyols.

6. FODMAPs cause an increase in water content in the colon which exerts a constipative effect.

7. The various FODMAPs are digested and adsorbed in the small intestine to differing extents.

8. An individual’s FODMAP absorptive capacity can be determined by performing breath hydrogen tests.

9. The low FODMAP diet is yet to be proven as an effective approach for treating FBD symptoms.

10. Salicylates, amines and glutamate are thought to induce gastrointestinal symptoms in some patients with food chemical sensitivities.
Low Back Pain Management: Approaches to Treatment

Gerard A Malanga, MD; Kevin R Dunn, MD

Management of low back pain includes a variety of approaches. These approaches include remaining active, use of lumbar traction and bracing, and treatment with acetaminophen, NSAIDs, muscle relaxants, opioid analgesics and oral corticosteroids.

Management of low back pain (LBP) involves a multifaceted approach with the goals of relieving the patient’s pain and restoring normal function. With a detailed evaluation, clinicians may establish an appropriate diagnosis and formulate a targeted treatment plan. Approaches to treatment include lifestyle modification, medications, physical therapy and various modalities, psychological counseling and, where appropriate, interventional procedures.

In this article, we provide an update on approaches to LBP management and explore the treatment options.

Lifestyle Modification

Education

After a thorough history, physical examination, and review of diagnostic testing, the clinician should involve the patient in the discussion of the treatment plan. This is the appropriate time to review the pertinent anatomy, biomechanics, and underlying pain generators of the spine.

Discussion of the treatment plan should include a description and rationale for additional diagnostic testing, if necessary, and medications, therapeutic exercises, or interventional procedures (Figure). The patient should be encouraged to become an active participant in his or her treatment. The clinician can engage the patient in the discussion with a review of proper posture, spine biomechanics in activities of daily living, and simple methods to minimize symptoms.

Bed Rest

Historically, bed rest was the treatment for patients with LBP. Although some benefits may be gained from reducing intradiskal pressure while the patient is prone, bed rest has many deleterious effects on bone, connective tissue, muscle, and cardiovascular fitness. The proactive approach emphasizes activity modification rather than strictly bed rest.

Remaining active is more effective than bed rest for patients who have acute or subacute LBP.1,2 The patient should be instructed to avoid activities that increase intradiskal pressure, such as sitting, bending, and lifting.

Traction

Lumbar traction has long been a preferred method for managing lumbar disk problems. About 1.5 times a patient’s body weight is required to develop distraction of the vertebral bodies. In a recent literature review, there was no evidence to support lumbar traction as a treatment.3 In fact, there was the suggestion that sustained traction might cause more harm than good. However, a randomized controlled trial conducted by Fritz and associates4 showed that there may be a subgroup of patients who may benefit from traction in the short term. This subgroup is characterized by the presence of leg symptoms, signs of nerve root compression, and either peripheralization with extension movements or a positive crossed straight-leg raising test result.

Lumbar Bracing

Braces have been used prophylactically to prevent injury to the lumbosacral spine, and they purportedly help manage existing pathology. The use of lumbar bracing has not demonstrated efficacy as a means to prevent LBP in the workplace.5

Lumbar supports are not more effective than other marginal therapies in reducing LBP, and there is minimal
Evidence to support their use. Lumbar bracing may help prevent reinjury by serving as a kinesthetic reminder for using proper biomechanics when lifting or bending, although this has not been demonstrated in the literature.

**Exercise**

There is no good scientific evidence to support therapeutic exercise in acute LBP. In subacute back pain, however, an intensive interdisciplinary rehabilitation programme that includes physician consultation with psychological, physical therapy, and social/vocational intervention has been shown to be moderately effective. In patients with chronic LBP, programmes that incorporate tailoring to individual needs, supervision, stretching, and strengthening are associated with the best outcomes.

The overall goals of exercise programmes for LBP are to reduce pain, restore normal motion, and develop muscular strength of the trunk and spine sufficient to diminish stress to the intervertebral disk and static stabilizers of the spine. In addition, therapy should be directed to the patient who demonstrates reasonable understanding of his pain and good technique in performing the exercises on his own and to implementation of an appropriate home exercise programme.

**Manipulation**

There is conflicting evidence about spinal manipulation and manual mobilization in the management of LBP, although recent clinical guidelines suggest that spinal manipulation in the hands of trained professionals provides a small to moderate short-term benefit in relieving pain. Moderate evidence...
suggests that the effect of manipulation in combination with strengthening exercise is similar to the effect of prescription NSAIDs with exercise in both the short and long terms.\(^1\)

Spinal manipulation has not been found to be more effective than other treatments, such as analgesics, exercise, and physical therapy. However, there appears to be a subgroup of patients with LBP for whom spinal manipulation results in significant reductions in pain and disability.\(^12^-^14\) Manipulation should be performed in conjunction with and to facilitate an active physical therapy programme.

**Medications**

Patients with LBP have been treated with medications in a number of classes, including acetaminophen, NSAIDs, muscle relaxants, opioid analgesics, and oral corticosteroids. Each agent has unique trade-offs between risk and anticipated benefits. Therefore, before prescribing a medication, the clinician should be aware of its contraindications, common adverse effects, and mechanism of action.

**Acetaminophen**

This para-aminophen derivative has analgesic and antipyretic effects equal to those of aspirin, but it has weak anti-inflammatory effects. Acetaminophen is relatively inexpensive and is available without a prescription. It is effective for mild to moderate pain but lacks other desirable effects on inflammation and muscle spasm. In acute LBP, studies have shown no difference between acetaminophen and no treatment,\(^15\) and no clear difference was seen in pain relief between acetaminophen and NSAIDs.\(^16^-^17\)

Acetaminophen generally is not a first-line medication for LBP unless there are contraindications to other medications. Prolonged use is contraindicated because of the potential for liver toxicity.

**NSAIDs**

These agents are a reasonable first-line treatment for acute LBP because of their combined analgesic and anti-inflammatory effects. Non-selective NSAIDs have been shown to be more effective for pain relief than acetaminophen.\(^17\) The dose needed to produce anti-inflammatory effects differs substantially from that for analgesic effects. These medications often are taken intermittently, and a significant level is not sustained to take advantage of the anti-inflammatory properties. Patients should be advised to take the medications at regular intervals to maximize both the analgesic and the anti-inflammatory effects.

Not one NSAID has been shown to be more effective than the others in terms of pain relief for patients with LBP. In a systematic review, the selective cyclooxygenase-2 inhibitors showed fewer adverse effects than the traditional NSAIDs.\(^18\) The major adverse reactions to NSAIDs include gastrointestinal bleeding and renovascular damage. NSAIDs also have been shown to slow bone and tissue healing.\(^19\) Prolonged use should be avoided to minimize the associated risks. The lowest effective dose is recommended for the shortest duration that is necessary.\(^20\)

**Antidepressants**

There is good evidence to support the analgesic effect of tricyclic antidepressants in the treatment of patients with LBP. In a systematic review, tricyclic antidepressants were more effective than placebo in controlling pain.\(^21\) Other antidepressants in the selective serotonin reuptake inhibitor class and trazodone have been shown to be no more effective than placebo.\(^22^-^23\)

Antidepressants typically take up to 4 weeks to achieve effect, but whether the same time is required to achieve pain relief is unknown.\(^23\) Of note, depression is a common problem in patients with chronic LBP, and it should be addressed appropriately.\(^24\)

**Muscle Relaxants**

These often are prescribed in the management of acute LBP to relieve pain, improve range of motion, and interrupt the pain-spasm-pain cycle. They have been shown to be more effective when they are used in conjunction with NSAIDs.\(^25\)

Tizanidine has been shown to be effective in the management of acute LBP.\(^26\) Other studies have not determined superiority for any particular muscle relaxant in terms of benefit or adverse effects. The most frequently reported effect of muscle relaxants is sedation; they usually are prescribed at bedtime to take advantage of this property.

**Opioid Analgesics**

The use of opioid analgesics in the management of LBP should be limited to pain that is unresponsive to other treatments or when other medications are contraindicated. A careful risk-benefit analysis should be considered before starting these medications because of the potential risk of aberrant drug-related behaviours with long-term use in patients who have a history of or predilection to addiction or abuse. There is no evidence to support the use of one opioid versus another.\(^27\) Prolonged or repeated use of opioids is not necessary for most patients who have acute LBP.

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Tramadol
This centrally acting analgesic has a combined mechanism of binding to μ receptors and a mixed serotonin/norepinephrine reuptake inhibitor. Although no studies have compared tramadol with acetaminophen, NSAIDs, or opioid analgesic monotherapy, there is evidence to suggest that tramadol is effective for short-term pain relief and improved function.28

Antiseizure Medications
Gabapentin, an antiepileptic medication widely used in the management of neuropathic pain, has been shown to provide short-term benefit in patients with radicular pain.29,30 The most frequently noted adverse effects include drowsiness, loss of energy, and dizziness. There is insufficient evidence for or against other antiepileptic medications in the management of LBP with or without radiculopathy.20

Oral Corticosteroids
The use of oral corticosteroids in the management of LBP is unsupported in the literature, especially when there are radicular symptoms, because these agents have not been shown to be more effective than placebo.20,31-34 In a double-blind placebo-controlled trial, Holve and Barkan35 demonstrated that patients treated with a tapering course of prednisone have a more rapid return to baseline in pain, mental well-being, and disability scores and require fewer subsequent epidural injections. There was no difference in physical examination findings, the use of NSAIDs or other pain medications, or return to work. Better studies clearly are needed to determine the role and effectiveness of oral corticosteroids in LBP, particularly for lumbar radiculopathy.

Modalities
Modalities offer an adjunct to evidence-based treatment in patients with LBP. However, the evidence to support their use is generally poor, despite their widespread use.

Transcutaneous Electrical Nerve Stimulation (TENS)
TENS, the use of electrical impulses over surface electrodes to provide symptomatic relief by modifying pain perception, has not been shown to be effective for chronic LBP. In recently published American Academy of Neurology guidelines, TENS is not recommended for chronic LBP because it has not been shown to be more effective than placebo.36

Electrical Stimulation
High-voltage pulsed galvanic stimulation has been used to reduce muscle spasm and oedema in patients with acute LBP. The use of electrical stimulation typically is limited to the initial stages of treatment to allow patients to progress to more active treatments in restoring normal range of motion and strength. There is insufficient scientific evidence for or against its use in patients who have LBP.37

Ultrasonography
This deep-heating modality has been shown to improve the distensibility of connective tissue and facilitate stretching.38 Ultrasonography is contraindicated in acute inflammatory conditions because it may exacerbate the inflammatory response. In addition, this modality is contraindicated over a previous laminectomy site.

There is insufficient evidence for or against the use of ultrasonography in LBP.37 It may be best used to improve segmental limitations in range of motion by facilitating soft tissue mobilization and stretching with a skilled physical therapist.25

Superficial Heat
This modality produces effects to a depth of 1 to 2 cm and has been shown to reduce muscle spasm and pain. Heat packs often are used in combination with electrical stimulation therapy. Heat wrap therapy has been shown to be more effective than placebo in short-term pain relief and functional status.39 These effects typically last for less than 1 week and are not more effective than exercise.

Therapeutic Injections
Trigger Point Injections
Myofascial trigger points are thought to be hyperirritable foci within muscles and fasciae that are associated with taut muscle bands. Trigger points are identified on palpation, which produces a focal twitch response and referred pain distal to the site of muscle irritability. Palpation examinations have poor inter-rater reliability.50 In an assessment of intra-rater reliability, local twitch response and referred pain varied from one session to the next; taut bands, tender points, and ‘jump sign’ remained consistent.41
Trigger points are managed initially with stretching; restoration of normal posture and biomechanics; and modalities, such as superficial heat or cryotherapy. Muscle relaxants also may be useful.

Trigger point injections may be considered when more conservative measures have not succeeded. However, there is no evidence that injections of normal saline with corticosteroids are more effective than normal saline alone. The benefit may result from needling alone or from placebo or nonspecific effects.

In one study, there was no difference among dry needling, injection with lidocaine, lidocaine with corticosteroid, and vasocoolant spray with acupressure. As a result, the type of injections, appropriate dosage, and interval are not known.

Trigger point injections remain an option for myofascial-related LBP resistant to conservative treatments. They should be limited and used in conjunction with an appropriate functional rehabilitation programme.

**Epidural Corticosteroid Injections**

These injections are a frequently performed interventional procedure aimed at reducing pain and inflammation resulting from disk herniation and subsequent nerve root irritation. The effectiveness of these injections is increased if they are used in the first weeks after the onset of pain and followed with an active exercise programme. Even though they are used widely, good scientific evidence for their use in the management of LBP is limited. In a multicenter randomized controlled trial, epidural corticosteroid injections offered transient benefit in symptoms at 3 weeks in patients with sciatica but no sustained benefits in terms of pain, function, or the need for surgery.

Epidural injections should be used when clinical evidence based on the history and physical examination correlates well with radiographic evidence. To minimize the risks, they should be performed with fluoroscopic guidance and contrast enhancement. There is no indication for performing injections in 'series'. Typically, one or two injections are sufficient to improve the radicular pain symptoms and facilitate a successful course of rehabilitation.

**Facet Injections**

Although lumbar facet joints are a potential source of LBP, there is a poor correlation between history and physical examination findings and true facet-mediated LBP. In addition, diagnostic imaging is unreliable for identifying underlying facet joint pathology. In spite of various attempts reported in the literature, an identifying clinical feature of facet-mediated pain has yet to be found. Thus, the only means of diagnosis is through facet joint blocks.

Facet joint injections with corticosteroids have not been shown to be more effective than placebo in controlling pain. Therefore, lumbar medial branch blocks or radiofrequency neurotomies remain a potential treatment, given an appropriate patient response to diagnostic blockade.

**Sacroiliac Joint Injections**

The sacroiliac joint is a potential pain generator in the lumbar spine, with an overlapping referral pain pattern around the posterosuperior iliac spine. Sacroiliac joint–mediated pain should be considered in patients for whom a comprehensive rehabilitation programme and a trial of NSAIDs, ice/heat, and mobilization or manipulation have not succeeded. Injection should be considered for both diagnostic and therapeutic purposes; if the results are positive, it should
be followed with an active physical therapy programme.

**Prolotherapy**

This therapy involves injection of solution to promote healing of loose tissue, ligaments, tendons, and joint capsules. Prolotherapy remains poorly studied and validated in spite of a long history of use to manage various conditions thought to be the result of ligamentous instability.

In the management of LBP, prolotherapy has been shown to be effective in combination with spinal manipulation therapy.\(^{47,48}\) It has yet to be studied as a single treatment without co-interventions.

**Acupuncture**

This modality has been used to manage various conditions for more than 2,000 years. Evidence for the use of acupuncture in the management of acute LBP is sparse,\(^ {49}\) but it has been shown to be effective in the management of chronic LBP.\(^ {50,51}\) The literature on acupuncture is not of high quality.\(^ {49}\)

**Psychological Counselling**

Cognitive-behavioural therapy is an effective component in the treatment of patients who have chronic pain.\(^ {52}\) However, it needs to be combined with other therapeutic components, such as physical therapy, to deal with physical deconditioning issues. Currently, there are no studies that directly address what combination of components might provide the best therapeutic outcomes for what type of chronic pain syndrome.\(^ {52}\)

**Spinal Cord Stimulation**

With this modality, an implantable device is used primarily to manage failed back surgery syndrome, complex regional pain syndrome, and chronic back pain. As the number of low back surgeries increases, so do the number and the use of spinal cord stimulation therapies.\(^ {53}\)

In a recent systematic review, Frey and associates\(^ {53}\) found strong evidence for the clinical use of spinal cord stimulation in failed back surgery syndrome in terms of pain relief and cost-effectiveness. Spinal cord stimulation does involve risk, which is estimated to exist in up to 43% of patients. The most common complications include electrode or lead problems, infection, generator problems, extension cable problems, and cerebrospinal fluid leakage.\(^ {53}\)

**Conclusions**

LBP is a frequently encountered complaint associated with great costs that continue to increase. Most patients improve with time if they remain active. Physicians need to have a clear understanding of the pertinent anatomy and physiology of the spine and correlate this with their findings in the history and on physical examination to develop a good differential diagnosis and a proper treatment plan. The literature may help guide the decision-making process, but much of the evidence is not well validated. The best evidence is for a short course of NSAIDs, active exercise and, as soon as possible, a return to normal activities.

Physical therapy, injections, and other approaches to treatment may help in properly selected patients.

**References**


About the Authors
Dr Malanga is director of the PM&R Sports Medicine Fellowship and Dr Dunn is a PM&R sports medicine fellow at Atlantic Health System in Summit, New Jersey. Dr Malanga also is director of pain management at Overlook Hospital, also in Summit.
CME Questions

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CME Article:
Low Back Pain Management: Approaches to Treatment

Please indicate on your answer sheet whether the following statements are True or False.

1. Bed rest used to be the treatment of choice for low back pain (LBP).
2. Lumbar bracing is effective in preventing LBP.
3. The goals of exercise programmes for LBP patients are to decrease pain, restore normal motion, and develop muscular strength of the trunk and spine.
4. Spinal manipulation has been demonstrated to be more effective than other treatments such as analgesics, exercise and physical therapy in the management of LBP.
5. The analgesic and antipyretic effects of acetaminophen are superior to those of aspirin.
6. Gastrointestinal bleeding, renovascular damage, and slow bone and tissue healing are some of the major adverse reactions to NSAIDs.
7. Studies have shown that tricyclic antidepressants are less effective than placebo in controlling LBP.
8. Tizanidine has not been demonstrated to be effective in the management of acute LBP.
9. Electrical stimulation reduces muscle spasm and oedema and restores normal range of motion and strength in patients with acute LBP.
10. One or two epidural corticosteroid injections are usually not sufficient to improve radicular pain symptoms.