Anatomy

The large intestine, which is about 1.5m long and 6.5cm in diameter, extends from the ileum to the anus.

Structurally, the four major regions of the large intestine are the cecum, colon, rectum and anal canal.

The rectum, the last 20cm of the gastro-intestinal tract, lies anteriorly to the sacrum and coccyx. The terminal 2-3cm of the rectum is called **the anal canal**. The rectum is totally sheathed in longitudinal muscle fibres, and is continuous with the anal canal.

The colorectum is lined with columnar epithelium as far as the dentate line in the middle of the anal canal, where sensitive squamous epithelium in continuity with that of the perineum takes over.

Mass peristaltic movements push faecal material from the sigmoid colon into the rectum. The resulting distention of the rectal wall stimulates stretch receptors, which initiates a defecation reflex that empties the rectum.

The defecation reflex occurs in response to distention of the rectal wall, receptors send sensory nerve impulses to the descending colon, sigmoid colon, rectum and anus. The resulting contraction of the longitudinal rectal muscles shortens the rectum, thereby increasing the pressure within it.

This pressure, plus parasympathetic stimulation, opens the internal anal sphincter.

The amount of bowel movements that a person has over a given period of time depends on various factors such as diet, health and stress. The normal range of bowel activity varies from two or three bowel movements per day to three or four bowel movements per week.

Epidemiology and Aetiology

Colorectal cancer is the second most common cancer in both men and women in Australia (Cancer Council Australia 2009). Eighty per cent of cases are sporadic with no known hereditary genetic associations.

In Australia, there are more than 12,500 new cases diagnosed each year. The risk of being diagnosed by age 85 is 1 in 10 for men and 1 in 15 for women. More than 4372 people die of colorectal cancer each year.

Individuals with certain known single-gene disorders are at an increased risk of developing rectal cancer. Single gene disorders related to known symptoms account for about 10-15% of colorectal cancers.

Hereditary non-polyposis colorectal cancer (HNPCC) results from defects in MMR genes and represents the most common form of hereditary colorectal cancer. Less than 5% of all colorectal cancer cases are HNPCC.

People with HNPCC often develop large bowel cancer before the age of 50. They commonly have one or more adenomas in the bowel. The majority of genetically defined cases involve hMSH2 on chromosome 2p, and hMLH1 on chromosome 3p.In affected families, 15-60% of family members are found to have mutations in hMSH2 or hMLH1; the mutation prevalence depends on features of the family history.

Other risk factors include: personal history of colorectal adenomas, first degree family history of colorectal cancer or colorectal adenomas, inflammatory bowel disease, obesity and smoking.

Histology and Pathology

The wall of the large intestine contains the typical four layers found in the rest of the GI tract: mucosa, sub-mucosa, muscularis and serosa.

The epithelium of the mucosa is simple columnnar epithelium that contains mostly absorptive and goblet cells.

The absorptive cells function primarily in water absorption; the goblet cells secrete mucus that lubricates the passage of the colonic contents.

Solitary lymphatic nodules are also found in the lamina propria of the mucosa and may extend through the muscularis mucosae.

The management of localised rectal cancer is increasingly multidisciplinary and patient focused, involving the patient and family, the surgeon, medical and radiation oncologists, radiologist, pathologist, and others.

Decision making is strongly influenced by patient preference and co-morbidities, as well as tumour staging and other prognostic factors. Many of the latter are determined primarily by the pathologist. The amount and complexity of information required from the pathologist has increased apace with the development of increasingly sophisticated surgical and adjuvant or neo-adjuvant treatments.

Accurate, detailed and comprehensive pathology reporting has become essential, and the role of the pathologist in the multidisciplinary team is being appreciated increasingly.

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Histology and Pathology (cont)

Pathological reporting of rectal cancer provides important prognostic information about the risk of both systemic relapse and local pelvic recurrence. Ideally, the report should provide the clinician with all the known pathological variables that have been shown to influence prognosis. These include:

-Tumour type
-Maximum depth of penetration of rectal wall
-Tumour diameter
-Tumour differentiation
-Distance to nearest margin
-Number of nodes examined
-Vascular invasion
-Stage
-Circumferential margin involvement
-Macroscopic description of tumour situ
-Position of positive nodes
-Peri-neural invasion

For the surgeon, the pathology report of a rectal cancer specimen has added significance. If circumferential margins are carefully examined and reported they provide useful feedback on the quality of surgery and an indication of the risk of local recurrence in a given patient.

Accurate pathology reporting allows appropriate pathological staging, and provides an assessment of the effect of neo-adjuvant therapy and a guide to the need for post-operative adjuvant therapy if pre-operative treatment has not been administered.

Uniformity of staging allows direct comparison of patient outcomes between centres.

Natural History, Diagnosis and Staging

Signs and symptoms of colorectal cancer include diarrhea, constipation, cramping, abdominal pain, and rectal bleeding, either visible or occult.

Natural History, Diagnosis and Staging (cont)

The colonic and rectal mucosa are only one cell thick and have a glandular architecture of epithelial cell inter-spread with goblet cells that synthesize mucus.

The pathologic stage of rectal cancer relates to the degree the tumour extends through the mucosa and colon wall, which in turn relates to prognosis and treatment selection.

Over the past decades several classification systems have been in use internationally to stage rectal tumours.

The **TNM staging system** is now recognised as the standard for colorectal cancer staging internationally in all disciplines.

The TNM system has three main advantages over the other systems.

Firstly, it is **data-driven** and has a process in place for **continuous improvement** based on ongoing expert review of existing data.

Secondly, it has a **comprehensive set of definitions** and rules of application that ensure **uniform use**.

Third, it is **multidisciplinary** in design and is pertinent to all modern techniques of stage evaluation.

As newer anatomic and molecular markers are uncovered and their value in rectal cancer staging, predictability to treatment response and treatment selection is defined, the role of such markers in the TNM system may need consideration.

Accurate staging of rectal cancer provides crucial information about the location and size of the primary tumour in the rectum and if present the size, number and location of any metastases.

Natural History, Diagnosis and Staging (cont)

Accurate initial staging can influence therapy by determining the type of surgical intervention and the choice of neo-adjuvant therapy to maximise the likelihood of clear margins.

In primary rectal cancer, pelvic imaging (CT, MRI, PET) helps to determine the depth of tumour invasion, the distance from the anal sphincter, the potential for negative surgical margins and the involvement of loco-regional lymph nodes or adjacent organs.

Additionally clinical evaluation and staging procedure may include:

1. **Digital rectal examination** and/or recto--vaginal examination and rigid proctoscopy to determine if sphincter saving surgery is possible.

2. **Complete colonoscopy** to eliminate cancers elsewhere in the bowel.

3. **Endo-rectal ultrasound (EUS)** to assess the depth of tumour growth in the rectal wall. EUS is reported to have accuracies for T staging varying between 69% and 97%, and remains the most accurate imaging modality for assessing tumour in-growth into the rectal wall.

The natural history of rectal cancer demonstrates major lymphatic spread in a cephalad direction contained within the peri-rectal fascia and along the mesorectum, that is commonly dissected by standard TME (total mesorectal excision) surgery.

Outside the mesorectum is a space containing vessels, nerves and lymphatics; that is usually not dissected. The external iliac nodes may only become at risk with anterior tumour extension and adjacent organ involvement. Lesions that extend to the anal canal or lower third of the vagina can spread to the inguinal nodes.

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Natural History, Diagnosis and Staging (cont)

Rectal cancer is an ideal model for cancer screening due to its relatively well defined natural history and when diagnosed in the early stages effective treatment can be offered.

Management Strategies

Surgery is the primary treatment for rectal cancer.

Early stage tumours are also candidates for removal of the tumour through a flexible endoscope or other minimally invasive surgery approaches.

Combined radiation therapy and chemotherapy improve local control for patients with tumour extending beyond the rectal wall or lymph node involvement. These combined treatments may also be indicated for patients whose cancers relapse at the primary site or in nearby lymph nodes after initial treatment.

Pre-operative staging is used to determine the indication for neoadjuvant therapy as well as the indication for local excision versus radical cancer resection. Local excision is likely to be curative for patients with a primary tumour that is limited to the sub-mucosa (T1N0M0), without high-risk features and in the absence of metastatic disease.

In appropriate patients, minimally invasive procedures, such as local excision or laparoscopic resection allow for improved patient comfort, shorter hospital stays and earlier return to pre-operative activity levels.

Management Strategies (cont)

Once the tumour invades the muscularis propria (T2), radical rectal resection in acceptable operative patients is recommended. In patients with transmural or node positive disease (T3, T4 and/ or N1) with no distant metastases, preoperative chemoradiation followed by radical resection according to the principles of total mesorectal excision has become widely acceptable.

During the planning and conduct of a radical operation for a locally advanced rectal cancer, a number of significant issues are considered. These include:

-total mesorectal excision (TME)
-autonomic nerve preservation (ANP)
-circumferential resection margin (CRM)
-distal resection margin
-sphincter preservation
-options for restoration of bowel continuity
-laparoscopic approaches
-postoperative quality of life

Although preoperative short-term radiotherapy for rectal cancer results in increased local control, there is more long-term bowel dysfunction in irradiated patients than in patients who undergo total mesorectal excision (TME) alone. Rectal cancer patients should be informed on late morbidity of both radiotherapy and TME. Future strategies should be aimed at selecting patients for radiotherapy who are at high risk for local failure.

Management Strategies: Radiation Therapy

During the past decades a range of radiation therapy treatment modalities have been utilised for rectal cancer patients. These options include:

1. post-operative chemo-radiation with different 5-fluorouracil (5-FU) based schedules

2. pre-operative radiotherapy short course (5 fractions of 5Gy in 5 days)

Management Strategies: Radiation Therapy (cont)

3. long course radiation therapy with or without chemotherapy

4. intra-operative radiation therapy (IORT)

Local control and acute and late effects on normal tissue are dependent on the volume, total dose, dose per fraction and overall treatment time. To achieve a high probability of sterilisation of microscopic disease, a dose of the order of 50Gy in 25 fractions given over 5 weeks is required.

In trials of short course pre-operative radiotherapy 5 fractions of 5Gy corresponds approximately to a dose of 42Gy in 21 fractions of 2Gy over 29 days.

n increasing body of data suggests the superiority of pre-operative radiotherapy combined with chemotherapy in terms of local control, disease-free survival and reduction of bowel toxicities. As mentioned above there are two types of pre-operative radiotherapy:

fractionated radiotherapy and **short course.**

Short-course pre-operative radiotherapy is delivered one week before surgery in 5 daily fractions of 5 Gy without any chemotherapy.

Preoperative fractioned radiotherapy is delivered in a period longer than 5 weeks (daily doses of 1.8–2 Gy for total doses of 45–50 Gy), usually with a 5-FU schedule, and is followed by surgery which is performed 4–6 weeks after in order to restore the acute damage and as well as to reduce tumour volume.

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Management Strategies: Radiation Therapy (cont)

Probably the most important argument in favour of pre-operative radiation therapy is tumour regression, which may improve the likelihood of a successful resection with free margins. The possibilities of preserving the sphincter are increased for regressing tumours arising in the distal rectum.

From this point of view, short-course radiation offers low tumour reduction probabilities due to the surgery timing. The choice of treatment is fractionated radiotherapy because it offers a high probability of sphincter preservation.

After pre-operative chemo- and radiotherapy, a pathologic complete response rate of 10–25% has been reported as well as a tumour down staging rate of 40–80% with both improved local control and survival.

Radiation Therapy PLANNING

The advantage of preoperative radiation therapy planning relies on the presence of tumour tissue, which can be easily located and radiologically defined for target-volume definition. The GTV and CTV can be delineated as soft tissue anatomy on CT images, often accompanied by other imaging modalities (Positron Emission Tomography (PET), and MRI). Unfortunately, the standard CT-based GTV delineation remains associated with considerable inaccuracy and extension of rectal carcinoma into the rectal wall or peri-rectal tissue structures usually is not visible.

Therefore, target-volume definition is frequently achieved by bypassing the location inaccuracy of target structures, and the small pelvis is outlined directly and generously to include all target structures.

Management Strategies: Radiation Therapy (cont)

The planning target volume (PTV) used in many clinical centres for rectal radiation therapy is therefore large and concave, due to the inclusion of the primary tumour or its surgical bed, the local lymphatics, and the pre-sacral area.

The upper limit of the field can be just above the top of the sacrum, and the inferior margin may extend 4-5cm below the inferior limit of the tumour. Laterally, the pelvic side walls and internal iliac nodes may also be included.

Small bowel toxicity due to the close proximity and large PTV is common.

At simulation or CT the patient is positioned prone. Depending upon the centre protocol and the radiation oncologist's preference, the patient may be placed on the " belly board". The theory behind the belly board is that the patient's "belly" falls into the hole, as does the small bowel. This is using gravity to move the small bowel away from the radiation fields, so reducing dose to that critical structure, and ultimately minimising toxicity. If the patient has a full bladder this can also help push small bowel out of the treatment fields.

The planning of rectal cancer involves taking the information acquired at simulation/CT and optimising the dose distribution for the CT for that patient.

Management Strategies: Radiation Therapy (cont)

Many departments will treat rectal cancer patients with a threefield technique, consisting of a posterior and two opposed lateral fields. Since the rectum is a posterior structure, for early stage disease (that is, the disease is not adhered to nearby structures such as bladder, prostate or vagina) and anterior field would only increase the toxicity of the treatment.

For long course pre-operative radiation therapy the prescribed doses is usually 45 Gy in 25 fractions to the tumour bed and regional lymph nodes, treating all fields once a day, five times a week. A reduced field size may then be delivered up to 50.4 Gy, and sometimes 54 Gy, for those patients with gross or microscopic residual disease and is treated on consecutive treatment days.

A reduced field size to the tumour bed coming off the lymph nodes is used to reduce small bowel toxicity.

The prescribed doses equate to 1.8 Gy per fraction. (This is lower than the 2 Gy per day used for many other treatment sites.) The smaller fraction size is essential due to the large size of the fields, and the inclusion of some bowel in the fields should reduce some of the toxicity.

If the patient is also having chemotherapy, the bowel may be even more sensitive. Remember that the belly board and full bladder also help reduce small bowel volume within the fields. If treatment is planned with a full bladder, the patient should be treated with a full bladder daily.

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Management Strategies: Chemotherapy

Recurrence for rectal cancer tends to occur in the liver, lung and bone.

For this reason adjuvant chemotherapy has a good rationale.

The aim of adjuvant chemotherapy is to eradicate micro-metastases

Regardless of whether chemotherapy is delivered pre-operatively or post-operatively it has been shown to have no effect on overall survival, however is seen to increased local control.

It is recognised that rectal cancer needs a multidisciplinary approach, radiotherapy and chemotherapy being necessary complements of surgery to obtain the best chance of cure in stage II and III disease. The problems encountered in everyday practice in administering combination adjuvant therapy in the operated colon and the success in treating locally advanced rectal lesions with neo-adjuvant radio-chemotherapy has favoured attempts in treating operable tumours with a pre-operative multidisciplinary approach.

Chemotherapy schedules for rectal cancer usually have a 5- florouracil (5-FU) base, combined with leucovorin, capecitabine, oxaliplatin or irinotecan. The pre-operative toxicity of these drug combinations has been found to relatively low. In the post-operative setting, the toxicity of chemotherapy depends on the individual patient and the local situation after surgery.

Management Strategies: Chemotherapy (cont)

5-FU is an inhibitor of thymidylate synthase and its anti-proliferative effect is primarily the inhibition of DNA synthesis. The mode of action of 5-FU together with its ability to render cells more sensitive to radiation, demonstrated both in vitro and in vivo, make this drug highly appropriate for combined chemo-radiotherapy.

The challenge of the future will be the selection of patients on the basis of biological prognostic factors and the choice of the best chemotherapy regimen according to predictive molecular markers.

The other direction taken in research in the neo-adjuvant setting is to **assess new biological therapies able to selectively target pathways that are critical for tumour growth and development, like angiogenesis** (the development of new blood vessels)

Side Effect Management

The use of chemo-irradiation has been shown to diminish the risk of local recurrence.

There is strong evidence though that both pre-operative and post operative radiation therapy for rectal patients results in adverse effects to bowel function.

During combined modality treatments, acute side effects such as diarrhea and increased bowel frequency, acute proctitis, and dysuria are common.

These conditions are usually transient and resolve within a few weeks following the completion of radiation. Management involves the use of antispasmodic and/or anti-cholinergic medications.

The symptoms appear to be a function of the dose volume and fraction size, rather than the total dose.

Late onset complications from chemo-radiation for rectal patients include:

Side Effect Management (cont)

-small bowel enteritis
-small bowel obstruction
-fibrosis resulting in urogenital dysfunction
-vascular toxicity
-bladder and urethral sphincter dysfunction
-urinary dysfunction
-sexual dysfunction
-psychological issues

Late onset complications occur less frequently than acute side effects but are more serious. The initial symptoms commonly occur 6–18 months following completion of radiation therapy.

Some surgical techniques may also contribute to many of these late onset complications.

The primary goals of post therapy follow up for rectal cancer patients are: improve survival, manage treatment toxicities and adverse effects, assess the efficacy of the initial therapy, detect new malignancies, detect potential curable recurrence, provide supportive care to the patient and carers, and assist in the maintenance or improvement of quality of life.

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