1. Screening for Colorectal Cancer

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Colorectal Cancer: Who is at risk?

- People aged 50 years and over
  - Adenomatous colonic polyps are found in about 25 per cent of people by the age of 50; the prevalence continues to increase with increasing age
- Family history of polyps and bowel cancer
- Personal history of polyps and bowel cancer
- Inflammatory bowel disease
- Environmental risks
- Others

Screening vs. Surveillance

Screening: Investigation of patients who have no symptoms or signs of disease

- Average Risk Patients: Faecal Occult Blood Test (FOBT) vs. Colonoscopy
- High Risk Patients: Focus on colonoscopy screening

National Bowel Cancer Screening Program

- Faecal Immunochemical Test (FIT) vs. gFOBT
- Immunoassay specific for faecal human haemoglobin – no need to avoid red meat etc.
- Negative for upper GI bleeding – globin is digested in GI transit (e.g. ok to test on aspirin)
- Equally accurate for R vs. L colon bleeding (i.e. globin is digested)

Surveillance: Refers to follow-up testing in patients who have a history of:

Colon Polyps

- Once identified by screening, patients should be entered in a colonoscopy surveillance program
- Modifiers:
  - Patient factors (patient's opinion/anxieties, listen to improve compliance)
  - Number and morphology of polyps
  - Extent of family history of CRC
  - Quality of preparation and procedure
  - Anti-platelet agents (Warfarin, NOAC)

Colorectal Cancer

- Patients should have full visualization of the colon at the time of diagnosis or soon after surgery

Inflammatory Bowel Disease (IBD)

Chromoendoscopy

Clinical Applications

- Esophagus
  - Esophageal carcinoma
  - Barret's esophagus
- Stomach
  - Intestinal metaplasia
  - Polyps
  - Early gastric cancer
- Duodenum
  - Celiac disease
- Colon
  - Polyps and early colon cancer
  - Ulcerative colitis
  - Cancer surveillance in IBD

Magnification Chromoendoscopy and Narrow Band Imaging

- Improves detection of small, flat and depressed neoplastic lesions and also results in the detection and removal of clinically insignificant non-adenomatous polyps
- Differentiation between non-neoplastic and neoplastic tissue is frequently possible
- Subject to operator-dependence
- Training required for recognition of different mucosal patterns and flat or depressed lesions
- A standard terminology has not been validated or universally adopted

Colonoscopy

Complications

- Pre-procedure: issues with fasting, preparation fluids and changes to medications
- Bloating and pain: negligible if CO2 insufflation and with use of water immersion/exchange
- Anaesthetic risk: including aspiration
- Bleeding requiring admission: 8/1000
- Perforation: 0.6 – 2/100
- Death (from any cause): 1/10000

Why Is Colonoscopy Not Perfect?

- Poor bowel preparation
- Inexperienced endoscopists
- Rapid extubation
- Failure to recognize small or flat neoplastic lesions

Colonoscopy for Colon Lesions Should Include:

- Evaluation of macroscopic appearance
- Evaluation of mucosal pattern

Colorectal Cancer

- Screening programs are based on the adenoma-adenocarcinoma sequence
- Colon cancers are believed to arise from elevated lesions that are visible with endoscopy
- Some lesions in the colon are flat or depressed and may be missed during routine colonoscopy

Non-Protruding Colonic Lesions

- Flat adenomas may represent up to 25% of colon adenomas
- Flat adenomas are:
  - More likely to have high-grade dysplasia and cancer despite their smaller size
  - Harder to detect with conventional endoscopy
- Narrow Band Imaging (NBI) or chromoendoscopy is necessary for detection of flat lesions

Aberrant Crypt Foci (ACF)

- ACF may be the earliest identifiable neoplastic lesions in the colon
- ACF may be identified by magnification chromoendoscopy in otherwise normal appearing mucosa
- These lesions are oval or semicircular and slightly raised above the surrounding mucosa
- The hyperplastic foci have a stellate or slit-like pit pattern
- The neoplastic foci have a tubular pattern

Hereditary Non-Polyposis Colorectal Cancer

Clinical Features

- Early but variable age at CRC diagnosis (age ~ 45 years)
- Multiple primary cancers
- Proximal colon distribution of CRC
- Poorly differentiated, mucinous with lymphocytic infiltrate
- Extracolonic cancers – endometrium, ovary, stomach, urinary tract, small intestine, bile ducts, sebaceous skin tumours

Identification – Revised Amsterdam Criteria by The International Collaborative Group on HNPCC

- There should be at least three relatives with HNPCC-associated cancer (colorectal cancer, cancer of the endometrium, small bowel, ureter, or renal pelvis)
- One should be a first degree relative of the other two
- At least two successive generations should be affected
- At least 1 should be diagnosed before age 50
- Familial adenomatous polyposis should be excluded in the colorectal cancer case(s) if any
- Tumours should be verified by pathological examination

Screening

- Mismatch repair genes correct nucleotide base pairing and other errors
- HNPCC – germline mutations so that cells accumulate DNA errors throughout their genome
- Accumulation of abnormalities of short sequences of DNA called microsatellites
- Microsatellite instability (MSI) with disturbance of growth regulatory genes

Familial Adenomatosis Polyposis

- AD – germline mutations in the APC gene
- 1 in 10000 to 30000 births
- Multiple adenomas with ~100% risk of CRC
- Extracolonic tumours – upper GI lesions, desmoid tumours, osteomas etc.

Hyperplastic Polyposis Syndrome (HPS)

- At least 5 hyperplastic polyps proximal to the sigmoid colon with at least 2 being 10 mm diameter or,
- Any number of hyperplastic polyps occurring proximal to the sigmoid colon in an individual with 1° relative with HPS, or
- 30 or more hyperplastic polyps distributed through the colon
- No germline mutation identified yet

Hyperplastic Polyps/Serrated Adenoma

- 18% of 'Hyperplastic polyps' are SSA
- Larger, proximal distribution, flat
- Genetically stable until loss of MLHI gene with rapid progression to malignancy
- SSA are the precursor for the 15% of sporadic CRC that are MSI-H but account for 'interval' CRC
- Interval cancers are 3X more likely to be MSI-H and be proximally sited in the colon

Colon Cancer and Ulcerative Colitis

- Colon cancer complicating chronic ulcerative colitis is believed to develop through a chronic inflammation-dysplasia-carcinoma sequence
- Dysplasia and colitis associated-cancer can occur in macroscopically normal mucosa
- The standard of care is to obtain random biopsies at 10-cm intervals throughout the colon during routine surveillance
- Recent data suggest that narrow band imaging (NBI) and Chromoendoscopy improves detection of dysplasia and early colon cancer

Terminology

Endoscopic Image Enhancement

- Image processing to improve the features of a given image

Image Analysis

- Analysis of a stored image and extraction of characteristics in numerical parameters for subsequent reconstruction

Resolution

- Ability to distinguish between two points that are close together
- High resolution imaging improves ability to discriminate mucosal surface details
- Resolution increases with the number of pixels in the CCD

Magnification Endoscopy

- Ability to enlarge the image from 1.5x to 170x optical power using a moveable lens controlled by the endoscopist

Chromoendoscopy

- Use of stains to delineate mucosal surface

Enhanced Magnification Endoscopy

- Use of acetic acid to improve mucosal visualization

2. Latest Advances in Surgical Management Of Colorectal Cancer

Mr Tilan Beneragama MBBS, FRACS (General Surgeon)

What's Different About Rectal Cancer?

Neoadjuvant Chemoradiotherapy

- Long course
  - Combined chemoradiotherapy over 5-6 weeks
  - Surgery then delayed for 6 weeks
- Short course
  - Radiotherapy only over 5 days
  - Surgery performed 2-4 days later

Who Gets Neoadjuvant Chemoradiotherapy?

- Cancers less than 12cm from the anal verge
  - T3 (through the rectal muscle wall)
  - N1 evidence of lymph node involvement
- Cancers of the lower third where by restorative resection is planned to downstage the primary
- Risk factors for local recurrence:
  - Size of local depth of invasion
  - Involvement of CRM
  - Short distance to anal verge
  - Lymph node involvement

Local Treatment Options

- Local excision

Option of No Surgical Treatment

- Complete reliance on the chemo-radiotherapy alone

Local Excision

- Without neoadjuvant chemoradiotherapy
  - High rates of local recurrence
  - T3 cancers: 100% local recurrence
  - T2: 50% local recurrence
  - T1: 5-20% LR
- There is role for local excisions of carefully selected T1 rectal cancers
- The role of local excisions after neoadjuvant chemotherapy
  - Still under investigations

Intersphincteric Dissections

- Patients will all require long course neoadjuvant chemoradiotherapy
- Involves standard abdominal approach
- Per anal approach
  - Transection at the dentate line
  - Hand-sewn pull through anastomosis
- Slightly worse functional outcomes but high overall patient satisfaction compared with APR

Outcomes

- The functional outcome is assessed by:
  - Number of stools: mean 5 per 24 hours
  - The urgency for defecation: 20%
  - Nocturnal defecation: 25%
  - Use of hygiene pads: 20%
  - Use of antidiarrheal medications: 30%
  - Constipation due to stenosis
  - **Patient's satisfaction with the outcome reaches <u>90%</u>**
- The oncological outcome is assessed by:
  - Local recurrence: 8%
  - Distant metastases: 15%
  - 3-year survival: 83%
  - 5-year survival: 83%
  - Disease-free survival at 3 years: 82%
  - Disease-free survival at 5 years: 76%
  - While in lower anterior resection, it has been estimated: **3-year survival of 89%, 5-year survival of 81%, disease-free survival at 3 years of 71% and at 5 years of 64%**

Transanal Minimally Invasive Rectal Dissections

- Laparoscopic instruments places transanally
- Theoretically allow easier access to the lower mesorectal plane
- Few case series
- Discussion in meetings
- No established role (yet)

Abdomino-Perineal Excision of the Rectum

- Required when tumour extends to or is below the dentate line
- Extra-levator abdomino-perineal excision rectum
  - Huge defect which may need flap or mesh reconstruction
  - Otherwise a perineal hernia will develop
- If patient does not wish to have APR, there may be a role for:
  - Local excision of smaller superficial cancers
  - Watch and wait approach

Radical Peritonectomy + Heated Intraperitoneal Chemotherapy

- Treatment of peritoneal carcinomatosis for colon cancer
- Currently uncertain
- Supported by enthusiasts
- Primary surgical management of patients presenting with colon cancers with peritoneal metastasis
- Second look laparotomy/laparoscopy in high risk patients after completion of chemotherapy
- Uncertain how this radical protocol compares with modern chemotherapy
- Available at Peter MacCallum Cancer Centre

Laparoscopic vs. Open Surgery (Colon Cancer)

- Advantage with laparoscopic approach in terms of morbidity

Laparoscopic vs. Open Surgery (Rectal Cancer)

- Advantage in the literature is less definite
- The presence of permanent or temporary stoma negate the advantages of laparoscopic surgery

Laparoscopic vs. Robotic Surgery

- Several technical advantages reported by surgeons who have access to the robot
- No RCTs comparing laparoscopic vs. robotic surgery
- Robotic surgery is far more expensive
- Advantage is the potential to spare nerves
- Nerves are only an issue in rectal cancer surgery

Conclusions

- Lots of new developments in the surgical management of colon and rectal cancer, however they have not penetrated into mainstream practice
- Importance of accurate preoperative assessment
- Discussion and review of investigations in an MDT setting

3. Role of Radiation In Multidisciplinary Management of Colorectal Cancer

Dr Marcus Foo MBBS, BMedSci, FRANZCR (Radiation Oncologist)

Rectal Cancer Radiotherapy

- Current neoadjuvant management approaches
  - Short course in Scandinavia/Europe/UK
  - Long course in US/Australia
- More effective 'tailoring' of neoadjuvant therapy
- RT (+- Stereotactic RT) For Metastatic Disease

What's involved?

- CT simulation ('measurement' session): 40-45 minutes
- 1 week later: start treatment
- Painless 'high energy x-ray treatment': 7-8mins/day (20-30mins/day in dept.)

Acute Toxicities

- Generally well tolerated
- Mild-moderate lethargy
- Diarrhea (proctitis): Gastrostop/Lomotil etc.
- Occasionally cystitis (usu. mild)
- Sometime perianal/natal cleft skin reaction
- Nausea uncommon
- 5-FU/Capecitabine toxicities
  - Temporary, worse at the end (for 7-10 days), then resolves over a few weeks

Low Tumours

- Distal tumours: APR's and higher rate of positive CRM
- Long course preoperative CRT could provide sufficient down-staging, and possible avoid APR/permanent end colostomy

Older Patients

- ?Local Excision
- Unacceptable failure rates regional/nodal and distant
- Poorer survival in T2 or higher

Can We Avoid Surgery Altogether?

- Watch/wait approach
- Long course pelvic chemo-radiotherapy (CRT)
  - 10-15% pCR
  - ?10-30% cCR
- Some sustained cCR for >12 months, with no surgery
- ~5-20% LR: all successfully salvaged
- 0-7% distant metastases
- 2-5 year OS 93-100%

Identifying CR

- Difficult
- Endoscopy
- ?biopsy
- MRI
- PET

Distant Recurrences

- LR recurrence rates reduced
- DR rates still >20-40%
- Interest in trying to incorporate systemic therapy in the mix early
- Optimal timing and sequencing of neoadjuvant therapies
- Preoperative chemotherapy and short course RT
- Preoperative chemotherapy: risk-adapted selective pelciv CRT
- 'Sandwich' CRT protocol

Metastatic Disease

- Pattern of failure
  - Peritoneal/Lung/Liver metastases
  - Bone/Brain metastases
- Palliation
  - Primary pelvic disease
- SBRT for aggressive Rx
  - Lung mets.
  - Liver mets.
  - Brain mets.
- Radiotherapy: well established role in palliating symptomatic disease
  - Pelvic disease: rectal bleeding, pain (pre/sacral invasion) etc.
  - Bone metastases

Oligo-Metastatic Disease

- 'Oligometastases'
- Intermediary state between disseminated cancer and 'localised'

Lung/Liver metastases

- Systemic chemotherapy
- Surgery: thoracic/liver/hepatobiliary
- Other 'local' therapies:
  - RFA
  - Microwave ablation
  - ?Stereotactic body radiotherapy (SBRT)

4. Recent Advances in Systemic Therapy of Colorectal Cancer

Dr Ben Markman MBBS (Hons), FRACP (Medical Oncologist)

Adjuvant Chemotherapy: Colon Cancer

- Stage III: Yes
- Stage I: No
- Stage II: Maybe
- Consider patient's age and fitness
- Benefit of ~10-15%
- FOLFOX is standard
- Single agent vs. doublet
- No evidence for the use of biologicals
- Survival benefit relatively small: 3.6%
- No advantage to combination therapy over monotherapy

High Risk Features

- Low number of lymph nodes examined (<12)
- Poorly/undifferentiated histology
- T4 disease
- Obstruction/perforation
- Lymphovascular invasion

Less Likely to Benefit

- Age >70 years
- MMR deficient

Mismatch Repair (MMR)

- MMR is critical for maintenance of genomic stability
  - One of the several mechanisms for DNA repair
- In MMR deficiency, replication errors accumulate, resulting in a mutator phenotype, promoting cancer progression
- Mainly affects small repeat segments (microsatellites) causing microsatellite instability (MSI)
- Predicts for resistance to chemotherapy
- Associated with better prognosis

Chemotherapy: Rectal Cancer

Chemoradiotherapy

- For locally advanced disease
  - T3/4, node positive
- Combined chemoRT better than RT alone
  - Improved OS
- Pre-op chemoRT better than post-op
  - No difference in distant failures or OS
  - Fewer APRs, reduced toxicity, fewer local failures
- Use single agent 5FU/capecitabine
- No role for biologicals

Adjuvant Chemotherapy

- Role less clear
- Many results are an extrapolation from colon cancer studies
- Often given for locally advanced disease
  - Fluoropyrimidine monotherapy
  - FOLFOX/XELOX
- Various attempts to intensify chemotherapy to reduce distant failures
  - During chemoRT
  - Pre/post/peri chemoRT (prior to surgery)
- No role for biologicals

Chemotherapy

Doublet

- Cytotoxic doublet in most patients
- Combines with biologicals
- First and second line Rx
  - FOLFOX/XELOX/FOLFIRI

Monotherapy

- Fluoropyrimidine monotherapy +/- bevacizumab
  - For those not needing or not fit for aggressive Rx
- Irinotecan +/- cetuximab in later lines of Rx

Triplet

- FOLFOXIRI
  - Uncertain which patients
    - ❖ BRAF mutant patients +/- bevacizumab
    - ❖ Borderline resectable metastases +/- bevacizumab (especially in KRAS mutant patients)

Anti-Angiogenics

- Well tolerated
  - HT, proteinuria
  - Arterial thrombosis, intestinal perforation, wound healing
- More impact on PFS than OS
- First line mCRC
  - Combination chemo plus bevacizumab
  - Fluoropyrimidine monotherapy plus bevacizumab
- Second line mCRC
  - Bevacizumab naïve
  - Beyond progression in 1L bevacizumab
    - ❖ Bevacizumab, aflibercept, ramucirumab

Biologicals

- No role in the adjuvant setting
- Both VEGF and EGFR inhibitors improve outcomes in mCRC
- Indicated in 1L Rx for most, unless contraindications
- Extended RAS testing as a predictor of resistance to anti-EGFR antibodies
- No unequivocal evidence for superiority of one biological over another in 1L Rx
  - Choice influenced by Rx strategy, safety, QoL, reimbursement, patient choice

BRAF mutations in CRC

- Approx 5% of mCRC
- Poor prognosis
- Debatable efficacy of EGFR inhibitors
- BRAF inhibitor monotherapy ineffective
- Strategies
  - Chemo intensification: FOLFOXIRI
  - Combination biological therapy
    - ❖ BRAF and EGFR inhibitors
    - ❖ BRAF, EGFR and MEK inhibitors

Conclusions

- No predictive biomarker for chemotherapy
- Monotherapy for less fit / elderly patients
- Doublets or triplets for a higher response rate
- FOLFOX / XELOX and FOLFIRI similar efficacy
- Only all-RAS wild type (50%) benefit from EGFR inhibition
- No biomarker to select for anti-angiogenics
- Treatment duration variable
- Sequence of drugs less important than exposure to all drugs, including biologics