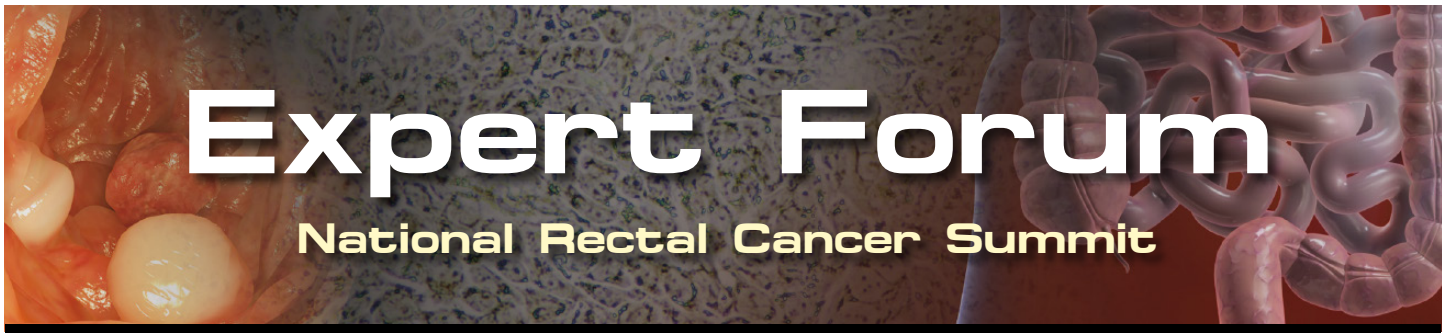

Expert Forum

National Rectal Cancer Summit

Making Education Easy August 2013

In this review:

Abbreviations used in this review

CRC = colorectal cancer
CRM = circumferential resection margin
CT = computed tomography
CTC = computed tomography colonography
EMR = endoscopic mucosal resection
EMVI = extramural vascular invasion
EUS = endoanal ultrasound
FDG PET = 18-fluoro-deoxyglucose positron emission tomography
FIT = faecal immunochemical test for haemoglobin
GI = gastrointestinal
IORT = intraoperative radiotherapy
IOUS = intraoperative ultrasound
LVI = lymphovascular invasion
MDM = multidisciplinary meeting
MDT = multidisciplinary team
MOH = Ministry of Health
MRI = magnetic resonance imaging
MSI = microsatellite instability
OS = overall survival
PET = positron emission tomography
QOL = quality of life
RCT = randomised controlled trial
TAE = transanal excision
TEM = transanal endoscopic microsurgery
TME = total mesorectal excision
TNM = tumour-nodes-metastasis

About Research Review

Research Review is an independent medical publishing organisation producing electronic publications in a wide variety of specialist areas.

Research Review publications are intended for New Zealand medical professionals.

About Expert Forums

Expert Forum publications are designed to encapsulate the essence of a local meeting of health professionals who have a keen interest in a condition or disease state. These meetings are typically a day in duration, and will include presentations of local research and discussion of guidelines and management strategies.

Even for local events it is not always possible for everyone with a similar therapeutic interest to attend. Expert Forum publications capture what was said and allows it to be made available to a wider audience through the Research Review membership or through physical distribution.

Welcome to this review of the inaugural National Rectal Cancer Summit held in August 2013 in Wellington, New Zealand.

This meeting, convened by Dr Christopher Jackson, was launched to bring together experts from New Zealand and Australia from all disciplines relevant to rectal cancer to share their knowledge about this disease and its management. Presentations made at the summit have been summarised for your information.

SESSION 1: EARLY RECTAL CANCER

Chaired by Professor Frank Frizelle and Associate Professor Cristin Print

Short-course versus long-course preoperative radiotherapy for rectal cancer

Presenter: Associate Professor Sam Ngan

Ultra short-course preoperative radiotherapy using a single 5 Gy dose does not increase tumour control over surgery alone.[1,2] Randomised trials from Sweden and The Netherlands have investigated short-course preoperative radiotherapy (5 x 5 Gy).[3-5] The Swedish Rectal Cancer Trial demonstrated that short-course preoperative radiotherapy reduced the risk of local recurrence by half. In this study, improved overall survival was also evident.[3] The Dutch Rectal Cancer Trial demonstrated that short-course preoperative radiotherapy maintains its benefit when combined with the best surgical practice - TME.[4-5] Short-course has become the standard of care in many countries.

Long-course preoperative chemoradiotherapy of 50.4 Gy in 5 weeks and 3 days with concurrent chemotherapy has been widely practised in the last 15 years. In the German rectal cancer trial, its superiority in terms of local control was demonstrated when compared with postoperative chemoradiotherapy.[6] Long-course preoperative chemoradiotherapy has been adopted as the standard of care in many countries.

Both short-course preoperative radiotherapy and long-course preoperative chemoradiotherapy have been practiced in parallel for many years. Two randomised trials have been performed comparing these two approaches. A Polish trial compared short-course vs long-course preoperative radiotherapy with abdominoperineal resection rates as the major end-point: no significant difference in abdominoperineal rates was found.[7] A Trans-Tasman Radiation Oncology Group trial (TROG 01.04) compared short-course preoperative radiotherapy with long-course preoperative chemoradiotherapy, with local recurrence rates as the major end point.[8] It demonstrated a small difference in local recurrence rate at three years, 3.1%, favouring long-course ($p = 0.24$). The 95% confidence interval includes differences of 8% or more in favour of long-course, so the trial has not excluded there being a clinically important difference in 3-year local recurrence rates. The data are consistent with either no difference or an important clinical difference in favour of long-course. There was also a large observed difference for distal tumour favouring long-course (6 of 48 short-course versus 1 of 31 long-course patients recurred locally), but it was not statistically significant.

On-going research in this area includes a Dutch study (RAPIDO), designed to assess the efficacy of initial local short-course radiotherapy followed by systemic adjuvant full-dose up-front chemotherapy in six cycles prior to surgery, and a Trans-Tasman Radiation Oncology Group phase II study by Associate Professor Ngan looking at intensive full-dose chemotherapy and long-course chemoradiotherapy before surgery (PROArCT).[9,10]

MRI to predict mesorectal margin in rectal cancer

Presenter: Dr Kirsten Gormly

Accurate staging of rectal cancer has a significant impact on treatment.[11,12] Poor prognosis tumours have reduced recurrence rates with the use of neoadjuvant treatment.[13-15] MRI is able to identify poor prognostic factors prior to surgery, particularly T3 tumours >5 mm, node positivity, EMVI and involved mesorectal fascia.[16-19] The European Society of Gastrointestinal and Abdominal Radiology (ESGAR) guidelines acknowledge that endoscopic ultrasound is the recommended modality for staging T1 tumours, but recommend MRI for more advanced tumours to assess the whole mesorectum.[20]

MRI staging of rectal cancer was first reported in the1980s.[21,22] By the end of the 1990s, high-resolution MRI (1.5T) had expanded in Europe, with numerous publications reporting the accuracy of this technique, which was able to stratify patients into low, intermediate and high risk, facilitating the more confident choice of patients for neoadjuvant treatments and a decrease in R1 and R2 resection rates.[11,23-26] Staging MRI is now accepted

practice for all patients diagnosed with rectal cancer and re-scanning is often recommended after long-course chemoradiotherapy.[20]

In assessing the rectal cancer MRI, start with the T2 sagittal image to identify low, mid and upper cancers. The centre of the tumour is then imaged with a high resolution T2 sequence in the axial oblique plane, being true axial to the rectal wall. This enables accurate measurement of the distance of T3 extension of tumour beyond the low signal muscularis propria. High resolution sequences need to include all mesorectal lymph nodes. The mesorectal fascia is usually seen as a low signal line surrounding the mesorectal fat and represents the circumferential resection margin of TME. With upper tumours, the peritoneal reflection must be identified. For low tumours, their relationship to the anal canal and sphincters must be ascertained by identifying the upper border of the puborectalis sling. Tumour types include polypoidal, villous and mucinous, the latter of which can have high signal and be difficult to see against fat. The most common tumours are the annular and semi-annular tumours, which may be ulcerating. When assessing these tumours it is useful to first identify the advancing raised rolled edges and then find the central invasive margin. This will often exhibit desmoplasia due to an inflammatory response at the site of muscularis invasion, but does not necessarily mean there is T3 invasion. T3 invasion is a nodular projection of tumour signal beyond the muscularis with a pitfall being separation of the longitudinal fibres of the muscularis propria.

Tumours are pathologically staged according to the following criteria: T1- tumour invades submucosa; T2 - tumour invades muscularis propria; T3a - <1 mm histological perforation beyond muscularis; T3b - 1-5 mm histological perforation beyond muscularis; T3c - >5-15 mm histological perforation beyond muscularis; T3d - >15 mm histological perforation beyond muscularis; T4a - perforation of visceral peritoneum; T4b - invasion of adjacent organs or structures.[27] On MRI, depth of extramural spread has shown excellent correlation with histopathological results.[28] However, a difficulty for radiologists is distinguishing between T2 and early T3 (<5 mm) tumours.[25] Dr Gormly stressed that the numerical depth of penetration must always be reported.

EMVI is a poor prognostic feature in rectal cancer and should be looked for and reported.[19] Tumour signal is seen within expanded vessels exiting the tumour and is measured as T3 extension. Any T3 extension, which is elongated along a vessel or turns a corner, is considered to be EMVI.

Nodal disease is staged according to the number of involved lymph nodes: N1- 3; N2 ≥ 4.[29] The use of morphological criteria (border contour and signal intensity) instead of size criteria has been found to significantly improve nodal staging of rectal cancer by MRI.[30,31] Despite this it is still a challenging area and the scans need to be of high enough quality to properly assess the nodes. Dr Gormly stressed the importance of imaging all of the superior mesorectum, as the majority of mesorectal nodes visible on MRI will be found at the level of the tumour or within 5 cm above its superior margin.[32,33]

The CRM is the mesorectal fascia, involvement of which is highly prognostic of local recurrence.[34] Pathologically, the mesorectal fascia is considered to be 'involved' when the tumour lies within 1 mm of this structure.[17,35] A positive margin may be due to direct tumour extension, EMVI, involved lymph nodes or tumour nodules.

Dr Gormly explained the importance of the MDT in managing rectal cancer patients and reported on the findings of an audit by Burton et al., who found that MDT discussion of MRI findings and implementation of a preoperative treatment strategy resulted in significantly reduced positive CRMs.[36] The value of MRI for restaging post-chemoradiation was also discussed as was its potential to alter initial surgical plans; the ESGAR recommends undertaking restaging MRI post treatment.[20]

The MRI report should include the following: location and morphology (site of invasion, relationship to puborectalis sling/peritoneal reflection); T-stage (depth of penetration and involvement of anterior peritoneum); the N stage; EMVI (negative or positive); the CRM (clear or involved, by tumour, node or venous deposit) and the presence of pelvic sidewall lymph nodes.

Take-home messages:

- MRI provides accurate preoperative staging
- MRI identifies intermediate and high-risk patients who will benefit from neoadjuvant therapy.

Polyp cancers: Who needs further resection?

Presenter: Associate Professor Ian Bissett

A malignant polyp contains dysplastic epithelium that has invaded through the muscularis mucosa. These polyps have two forms, pedunculated and sessile. Colonoscopy features that may indicate whether the polyp is malignant or not include size, the presence of ulceration, a hard consistency on biopsy, morphological appearance, pit pattern, spreading edge and whether or not it lifts.[37]

Case report:

Associate Professor Bissett presented one of his cases, a 46-year-old woman with a history of diarrhoea who underwent a colonoscopy and was found to have a mid-rectal, sessile polyp measuring <1 cm. The polyp was removed and found to be a tubular adenoma with high-grade dysplasia and focal microscopic adenocarcinoma. There was no evidence of poorly differentiated tumour, no LVI and no loss of expression of mismatch repair gene proteins. However, the closest resection margin was only 0.2 mm.

With such a small resection margin, comes the dilemma of balancing the risks of residual disease and operative morbidity. Associate Professor Bissett and colleagues performed a systematic review investigating outcomes for patients with malignant polyps of the colon or rectum and found 30 suitable papers including a total of 3334 patients. Analysis of the studies revealed the following: 4.2% of patients had recurrence after endoscopic assessment only; 2.6% of patients died of cancer after endoscopy assessment only; 15% had residual disease at surgery; 3% had recurrence after surgery; 3.5% died of cancer after surgery. Significant risk factors identified for recurrence and residual disease were: venous invasion; lymphatic invasion; positive resection margin; poorly differentiated disease; incomplete resection; level of invasion; sessile morphology and cancer volume >50%.

In 2005, Hassan and colleagues undertook a pooled analysis of data from 31 studies involving 1900 patients with colorectal malignant polyps and found that those with a positive margin had a 26% risk of residual disease and a 7% risk of lymph node involvement, while those with a negative margin had corresponding rates of 1.6% and 9%.[38] Associate Professor Bissett pointed out that patients with a positive margin and no other risk factor, such as his patient presented above, may best be served by full thickness resection with TEM. Hassan and colleagues also found that those with poorly differentiated carcinoma had higher rates of residual disease (17.8%), lymph node involvement (23.2%), haematogenous spread (9.6%) and cancer mortality (14.6%). Those with LVI have a much higher risk of lymph node involvement (35.3%) than those without LVI (7.2%) and should undergo lymph node removal. These researchers found that residual disease is almost non-existent in patients with no risk factors.

The Auckland Pathology Reporting Study

Associate Professor Bissett presented the Auckland Pathology Reporting Study, which looked at reporting of malignant polyps. Only 19/121 (16%) malignant polyps identified at Auckland Hospital between 1999 and 2011 had synoptic reports. While all synoptic reports were considered adequate, 46% of non-synoptic reports were found to provide inadequate information for decision-making.

The management of malignant colorectal polyps in New Zealand – presented by Dr Jesse Fischer

Dr Fischer outlined the NZ MAPS study, a multicentre (six DHBs) retrospective study looking at data between 1999-2009 from 365 patients (mean age 69.7 years; 80% European) with malignant polyps. Initially, 78.9% of the patients underwent colonoscopic polypectomy and 14.5% underwent colorectal resection; approximately half of the patients who had undergone initial colonoscopic polypectomy went on to colorectal resection as their definitive treatment. Among 170 patients analysed, the OS rate at 7.5 years was ≈ 72% (63% with definitive colonoscopic polypectomy and 78% with colorectal resection). Death by any cause (n = 182) was higher in those with polypectomy only vs those who had undergone resection (34.8% vs 21.3%). The risks of local recurrence and metastases were lower in those undergoing polypectomy (1.4% and 1.4% vs 3.2% and 16.0%, respectively), but this may be due to the fact that those undergoing surgery have poorer prognosis polyps. Additional data will be analysed to determine risk factors for local recurrence, metastatic disease and death.

Endoscopic mucosal resection

Presenter: Dr Steven Ding

While polypectomy is an effective treatment for pedunculated and smaller sessile polyps, and has been shown to reduce the incidence of CRC and mortality, this technique is not effective for sessile lesions >10-15 mm or for flat lesions (a subset of sessile polyps). If this technique is used on such lesions, it may result in incomplete resection, perforation or other complications.[39] Flat lesions are increasingly being diagnosed, with a prevalence of up to 34%, and are more likely to be malignant.[40-44]

Endoscopic mucosal resection (EMR), a minimally invasive endoscopic technique developed from polypectomy, allows for the resection of flat and sessile lesions. It is not suitable for cancerous lesions. With this technique, the lesion is lifted via submucosal injection and a cushion created, reducing the risk of injury to the underlying muscle. A snare is then used to remove the polyp en bloc (up to 20 mm diameter) or piecemeal. The procedure is undertaken under conscious sedation as a day case. Careful lesion and patient selection is imperative; EMR is contraindicated in malignant lesions and depressed lesions or those that do not lift with injection.

The efficacy of EMR was examined in single centre retrospective studies showing technical success rates of 90-100%, complication rates of 0-9% and recurrence rates of <30%.[45,46] In an Australian multicentre study involving 479 patients (514 lesions; mean size 35.6 mm), complete single session lesion excision was achieved in 89.2% of cases in a mean time of 25 minutes.[47] In that series, recurrent or residual adenoma occurred in 20.4% of patients and previous failed polyp intervention was found to be the strongest independent predictor of a suboptimal outcome (OR 3.75; 95% CI 1.77-7.94); other factors predictive of a poor outcome were ileocaecal valve involvement and difficult polyp position. Perforation occurred in 1.3% of patients and pain in 3.8%.

Take-home messages:

- EMR is an advance on polypectomy for large flat and sessile lesions
- EMR is an effective and safe treatment of mucosal disease – i.e. benign lesions, not cancers
- EMR is limited by skills and experience, time and resource constraints, complications and risk of recurrence.

TEM and local excision of rectal cancer

Presenter: Mr Ralph Van Dalen

The aims of excision of rectal cancer are: 1) remove the primary and avoid local recurrence; 2) remove local lymph nodes and determine spread and the need for adjuvant radiotherapy; 3) minimise complications; 4) obtain the best function possible. The two options for excision are radical excision (TME) or local excision via a colonoscopic or a transanal approach. TME is considered the gold standard for excision of rectal cancer, but this procedure carries significant risk. With local excision, the lymph nodes are not removed and there may be incomplete or piecemeal excision of lesions; however, the complication rates are much lower than with TME. Further, stomas are avoided and the sphincter is preserved, allowing for avoidance of bowel/urogenital dysfunction.

Lymph node involvement is best determined by MRI, EUS, or histology and although no modality is conclusive in and of itself, combining these modalities gives best results.[48] With regard to histology, studies have found the following three factors to be predictive of lymph node involvement in CRC; depth of tumour invasion, grade of tumour and LVI.[49-51] In the future it may be possible to determine lymph node status by distinct gene expression signatures from primary rectal adenomas according to a study by Kalady et al.[52]

The TEM procedure uses endoscopes, which provide excellent visualisation, and allows for the removal of tumours up to 20 cm using instruments configured for rectal surgery. The procedure results in retrieval of complete specimens with clear margins and carries low complication rates.[48] In comparison with transanal excision (TAE), TEM results in lower positive margins rates and lower rates of local recurrence.[53-57] Comparing TEM with TME, the local recurrence rates are similar for T1 tumours; however, for T2 tumours the rates are higher for TEM. [58]

Incidental cancers found at TEM do not appear to compromise outcome if TME is undertaken promptly after the TEM procedure.[59] Studies are currently investigating the use of local excision plus chemoradiation for T2 rectal adenocarcinomas.[60,61]

Waikato's experience with TEM

At Waikato hospital, two surgeons performed a total of 210 TEM procedures between 1998 and 2012. Lesions ranged in size from 1.5 to 10 cm. 1% of procedures were converted to TME. Most lesions were located in the mid and upper rectum. 56% of tumours were low-grade adenomas, 16% were high grade and 18% were carcinomas. Among the 36 patients with rectal cancer, 18% had TEM as a palliative procedure, 6% opted for no further surgery, 40% opted for TME and 36% had T1 tumours. Rates of local recurrence were 6% in those with low-grade dysplasia, 0% in those with high-grade dysplasia and 3% in those with T1 tumours.

Take-home messages:

- Local excision by TEM results in low complication rates, good functional outcomes and complete excision of tumours
- Radical excision of rectal tumours has significantly higher complication rates than local excision
- TEM should be the procedure of choice for local excision of rectal lesions.

Gut bacteria and colorectal cancer

Presenter: Dr Jacqui Keenan

CRC is the second most common cancer in NZ and >90% of cases are considered sporadic. The Western diet in particular is considered to be a significant risk factor for development of this type of cancer. Dr Keenan believes the cancer risks associated with this diet are likely to be mediated via the larger number of bacteria residing in the colon. Such bacteria are acquired at birth and form a colony that is unique to each individual. In a healthy gut, microbial homeostasis is present, but occasionally microbial dysbiosis occurs where there is an overabundance of bad bacteria. Dysbiosis is a risk factor for cancer, type 2 diabetes mellitus, inflammatory bowel disease and cardiovascular disease.

Recently developed molecular techniques allow for the analysis of stool samples to determine the relative abundance of the major families of bacteria. Sobhani et al identified a composition change in the microbiota of colon cancer patients, raising the question as to whether dysbiosis is a cause or consequence of this type of cancer.[62] Tjalsma et al suggest that the presence of microbial dysbiosis increases the risk of adenoma developing into carcinoma and present the concept of driver bacteria which may cause damage to the gut epithelium.[63]

The most well known driver bacterium is *Helicobacter pylori*, which the World Health Organisation has classified as a carcinogen associated with gastric cancer. While *H. pylori* is the only bacterium in the stomach, a number of bacterial species are present in the colon and some appear to have possible carcinogenic potential.[64] One such bacterium, *Bacteroides fragilis*, is present in ≈80% of individuals, but a minority will have strains of this bacteria that produce enterotoxin. A study from Turkey found an increased prevalence of enterotoxigenic *B. fragilis* in CRC patients.[65] Dr Keenan and colleagues have undertaken a similar study, the results of which are soon to be analysed.

Dr Keenan pointed out that individuals are colonised by bacteria through maternal transmission and it is not surprising that if they are colonised with a toxin-producing strain they may over time be susceptible to DNA damage potentially leading to cancer.

Strong evidence that diet shapes the relative abundance of the gut microbiota comes from a study in mice in which switching from a low-fat polysaccharide-rich diet to a high-fat, high-sugar 'Western' diet altered the relative abundance of microbiota in a single day.[66] Possible evidence for preventing cancer with diet comes from areas of Africa where the diet is rich in polysaccharides and the incidence of cancer is low. Evidence for preventing cancer with antibiotics comes from data showing that over the last 100 years the incidences of *H. pylori* colonisation and gastric cancer have decreased in parallel.

SESSION 2: LOCALLY ADVANCED RECTAL CANCER

Chaired by Associate Professor Ian Bissett and Dr Adrian Balasingam

Surgery for recurrent rectal cancer and advanced primary rectal cancer: how far should we go?

Presenter: Professor Michael Solomon

Pelvic exenteration for locally advanced primary or recurrent rectal cancer was first described in 1948, but remains a surgical challenge with high mortality and significant morbidity. Despite promising evidence of a marked improvement in survival with pelvic exenteration, it remains a contentious procedure. Professor Solomon described his experience with this procedure which he has undertaken in more than 340 patients over the last 20 years. In 2008, Professor Solomon and colleagues published findings from their Australasian series of 160 patients who had undergone radical or extended radical resection for locally recurrent rectal cancer. Their study revealed negative resection margins in 61% of patients and an OS of 43 months, with a 37% 5-year survival rate (in patients with an R0, 5-year survival was 54%).[67] Professor Solomon commented that one should aim for an R0 clearance and that where recurrence abuts an organ, the organ should be removed.

A 2001 Japanese study in 60 patients has shown that recurrence site in the pelvis is associated with survival. Those with localised central compartment recurrence had a 38% 5-year survival rate, while rates in those with sacral or side wall recurrence were 10% and 0%.[68] However, Professor Solomon reported a series of 100 sacrectomies that found a 5-year survival rate (40%) that did not differ from that observed where there was no sacral involvement. There was no difference in R0 rates, survival, complications, length of hospital stay or mortality between high (S2 or above) and low (S3 or below) sacrectomies. For lateral recurrence, an en bloc lateral pelvic wall dissection and vascular resection with pelvic exenteration increased the R0 rate from 21% to 54%, with an OS of 69% after a mean follow-up of 19 months.[69] For anterior compartment involvement, Professor Solomon compared the techniques of total soft tissue exenteration (n = 54) and total soft tissue exenteration plus pubic bone removal (n = 6), which resulted in R0 rates of 63% vs 100%.

In summary, using radical exenteration for patients with recurrent rectal cancer, R0 rates have increased from 49% to 71% in the central compartment, from 21% to 54% in the lateral compartment, from 63% to 100% in the anterior compartment and from 30% to 74% in the posterior compartment.

In Professor Solomon's series of T4 advanced rectal cancers, 65 cases had extended radical resection (rectum plus partial excision of attached major pelvic organs) while 72 received exenteration, the overall R0 was 85% and the 5-year OS was 63%; the R0 5-year OS was 75%.

While there is still some disagreement among international experts, Professor Solomon believes that with improved R0 and mortality and morbidity rates, and good patient QOL, exenteration is a viable option.

Reirradiation for pelvic recurrence

Presenter: Associate Professor Sam Ngan

A systematic review and meta-analysis of 22 RCTs involving a total of 8507 patients has shown that adjuvant radiotherapy at doses ≥30 Gy significantly reduces the risk of local recurrence and death from rectal cancer.[70] For patients who do experience a pelvic recurrence, their management is a difficult challenge. Reirradiation for this group of patients is controversial. A study involving 32 patients with recurrent rectal cancers following previous pelvic ultra high-dose radiation (median dose 45 Gy) looked at outcomes following reirradiation (median dose 34.2 Gy); 15 patients were irradiated for palliative relief of symptoms, while 17 patients also underwent radical resection.[71] The study concluded that in selected patients, radical surgical resection after cumulative ultra high doses of radiation is safe and that such irradiation for palliative care can be effective without unusual risks of complications.

In the late 1990s, Associate Professor Ngan and colleagues initiated reirradiation for suitable patients for whom no other effective treatment options remained. A report on 20 of their patients who underwent reirradiation (39.6 Gy in 1.8 Gy/fraction) a median of 19.5 months after previous radiotherapy (17 of whom also received concurrent 5FU [fluorouracil]) found no grade 3 or 4 toxicity and no requirement for treatment break.[72] Median survival was ≈12 months, rectal bleeding stopped in 100% of patients, pain improved in 36%, 57% experienced a reduction in analgesic use and the median duration of pain palliation was 8 months. Two patients underwent subsequent surgical resection and both were disease free at 20+ months.

Associate Professor Ngan discussed reirradiation and extended resection with IORT. The intent with this treatment is curative and raises different issues as this group of patients may survive longer and experience long-term radiation effects. These patients must be carefully selected and include those in whom a wide surgical margin is not achievable (lateral pelvic side wall involvement or presacral recurrence at level of S1-2).

Associate Professor Ngan and colleagues assessed the efficacy and toxicity of once-daily reirradiation in 56 patients treated between 1997 and 2008, and found that while acute toxicity was higher than identified in their previous study, it was still at an acceptable level.[73] Symptomatic response at 3 months was 88%, median OS was 19 months (15 months in the palliative group [n = 43] and 39 months in those who underwent radical surgery).

Take-home messages:

- Reirradiation remains a controversial strategy for local recurrence after previous pelvic radiotherapy
- Reirradiation can be delivered safely in experienced centres
- Reirradiation is effective in symptomatic control
- Extended surgery can be performed after reirradiation
- Long-term morbidity seems to be acceptable.

Gene sequencing studies of rectal tumours from the international TCGA consortium and New Zealand work

Presenter: Associate Professor Cristin Print

Technological advances in the form of microarray analysis and DNA sequencing have revolutionised our understanding of CRC, and genomic and clinical data from patients and their tumours have enabled a deeper understanding of the biology of this disease.

Microarray analysis measures the expression of genes by measuring the abundance of all RNAs in the cell (the transcriptome) and has enabled the identification of the combinations of genes that need to be turned on or off at high levels for rectal cancers to grow and survive. DNA sequencing can measure DNA mutations, amplifications, deletions and methylation, and has added to information from microarrays to transform our understanding of rectal cancer. Sequencing can include the whole genome, the part of the genome that encodes proteins (the exome) or a targeted panel of genes. An example of the clinical utility of genomic analysis is *KRAS* mutation testing for susceptibility to cetuximab therapy in metastatic CRC.

The Cancer Genome Atlas (TCGA) colon and rectal cancer project analysed a larger number of tumours across multiple tumour types and provides a valuable dataset available to researchers worldwide through the TGCA portal (http://www.cbioportal.org/public-portal/).

Associate Professor Print described methods of analysing the vast array of data generated by genome sequencing of colorectal tumours, emphasising the wide variety of mutations present in symptomatically similar tumours. In some tumours, only a single mutation occurs, whilst in others multiple mutations occur and affect multiple molecular pathways. He also noted recent work indicating intra-tumour heterogeneity, where there is a wide range of mutations in different molecular pathways in different parts of the same tumour.[74]

Associate Professor Print concluded that genomic technologies will play an increasing role as a supplement to traditional pathology, imaging and clinical acumen.

Christchurch experience of exenterative surgery

Presenter: Professor Frank Frizelle

Over the previous 20 years, 1017 complex radical pelvic resections have been undertaken in Christchurch. The pathway for management of recurrent rectal cancers is as follows: diagnosis; patient assessment for suitability for surgery; determination of disease extent; assessing if metastatic disease is resectable; analysis of the anatomy of the cancer; chemoradiotherapy; surgery. The surgery itself requires a team of surgeons from multiple disciplines. The surgery is individualised with an extremely large amount of planning involved. Many patients require double stomas. Removal of part of the bladder is acceptable as long as clear margins are achieved.[75] En bloc prostatectomy without bladder removal is now being undertaken. The sacrum may be removed below S3, but one may go as high as partial S1. If the lower anterior vagina is removed, the urethra and bladder will also be removed. Lateral pelvic sidewall dissection is difficult and Professor Frizelle commented that vascular surgeons are involved in this part of the surgery. A different team undertakes reconstruction.

Professor Frizelle discussed his personal series of 151 patients with recurrent rectal cancer aged 24 to 88 years. Changing patterns were seen over this period, with less time between first and second operation, an increased incidence of lower disease recurrence, a higher number of patients undergoing lateral sidewall dissection and fewer palliative operations. He explained that these surgeries are associated with numerous complications (the most frequent of which are urinary conduits, postoperative myocardial infarction and wound problems), but in his series there have been no deaths within 30 days of surgery. Among the 150 resections, 96 were R0 and the 5-year survival was 52% (excluding palliative cases); the survival rate was similar to that of other Christchurch surgeons performing resection for colorectal liver and lung metastases.[76] Analysis of how Professor Frizelle's patients failed their treatments revealed that 21 were deemed palliative on the day of the operation, 57 developed systemic recurrence, nine had local recurrence and 11 had local and systemic recurrence.

Professor Frizelle reported on a paper showing that perioperative chemotherapy with FOLFOX4 (oxaliplatin/leucovorin/5FU) for resectable liver metastases from CRC was more effective than surgery alone (7.3% absolute increase in rate of progression-free survival at 3 years).[77] He suggested that such therapy might be useful in patients undergoing radical pelvic resection. Currently, data is being collected from the UK, Australia and NZ on 625 patients in order to determine patterns of treatment failure and to investigate a potential role for postoperative chemotherapy.

Take-home messages:

- Exenterative surgery can be done at a cost
- A team approach is necessary
- Results are reasonable
- The surgery takes time.

Molecular testing and biomarkers in colorectal cancer

Presenter: Dr Martin Whitehead

Molecular testing in CRC is predominantly involved in testing for mismatch repair gene deficiency, which leads to microsatellite instability (MSI); microsatellites or simple sequence repeats are nucleotide repeats specific to an individual. Mismatch repair gene deficiency is present in 15-20% of CRCs and most are acquired as sporadic mutations. However, around 2% are germline mutations (Lynch syndrome or hereditary nonpolyposis CRC [HNPCC]). The nucleotide repeats in MSI are variable in tumour DNA when compared with non-tumour DNA from the same individual and, therefore, both tumour and normal tissue from an individual must be tested with PCR to analyse specific mono- and di-nucleotide markers; if >30% of these markers are present then MSI is considered high (MSI-high). Mismatch repair gene expression can also be assessed by immunohistochemistry, which identifies proteins as markers of gene expression and can act as a surrogate form of molecular testing. Specifically, four genes (MLH1, MSH2, MSH6 and PMS2) account for 90-95% of MSI-high tumours. Most sporadic mutations are related to loss of MLH1, which is due to hypermethylation associated with the *BRAF* mutation and in cases of loss of expression MLH1, reflex *BRAF*-V600E mutation testing should be undertaken; this only applies to CRC.

Currently, most testing is undertaken to look for Lynch syndrome (HNPCC) and guidelines suggest testing be undertaken in individuals <50 years of age, in synchronous or metachronous tumours, in tumours with histology suggestive of MSH-high expression and in those with a family history of HNPCC. However, testing is highly variable between institutions. Dr Whitehead pointed out that there is consistent evidence that MSI-high tumours are prognostic, carrying a reduced incidence of lymph node and systemic metastases; there is also some evidence suggesting that they are a predictive marker for response to therapy.

Another marker in CRC is the *KRAS* mutation, which is involved in the growth factor receptor/protein kinase pathway and occurs in ≈30-40% of such cancers. The *KRAS* mutation is mutually exclusive with the *BRAF* mutation, but has been shown to be predictive of resistance to anti-EGFR therapy. There is some evidence that the *KRAS* mutation is associated with a worse prognosis in CRC. The *BRAF* mutation is also involved in the growth factor receptor/protein kinase pathway downstream from *KRAS* and has been implicated in many cancers. BRAF is a prognostic marker in conjunction with MSI status: MSI-high with BRAF wild-type = best outcome; MSI-stable with mutated *BRAF* = worst outcome. There is also some evidence that *BRAF* is a predictor of resistance to anti-EGFR therapy. A number of other biomarkers in CRC have been identified, but so far none have translated into clinical use. Evidence suggests that a number of genes are involved in the development of individual cancers and next generation sequencing will allow for genome-wide analysis.

Dr Whitehead commented that pre-analytical handling and fixation is an important issue and needs to be addressed if we are to progress in this field of analysis.

SESSION 3: METASTATIC RECTAL CANCER

Chaired by Dr Maria Pearse and Dr Chris Jackson

Optimal imaging strategies in resectable metastatic disease

Presenter: Dr Adrian Balasingam

The role of imaging in resectable disease is to provide information on the TNM stage, the local stage, the nodal status, the distribution of metastatic disease and to assist in the planning of potentially curative therapies. Around 22% of initial CRC presentations are stage IV (metastatic) and two-thirds may be resectable.[78,79] Furthermore, 40% of cases will relapse with metastatic disease and up to 70% of all CRC patients will develop liver metastases (30% will have liver only disease).[79-81] It has been shown that in selected CRC patients, metastatic resections (liver and lung) may improve survival.[82]

With regard to performance, at a lesion level, there is no difference in sensitivity between CT, MRI and FDG PET.[83] However, at a patient level, MRI and PET have similar sensitivity, but CT is significantly lower. For liver lesions <10 mm, MRI sensitivity is better than CT or PET-CT and PET-CT is not recommended for the staging of primary CRC.

CT is the mainstay of screening for metastatic disease, is widely available, is relatively cheap and assesses large areas. This modality is used for presurgical planning for liver and lung resections and is useful for liver volume assessment to guide surgery.

MRI is an excellent modality for characterisation of all liver lesions and is the most sensitive and specific technique to assess liver for metastatic CRC (especially lesions <10 mm).[83] A multitude of different MRI sequences are available

including diffusion weighted imaging, post-contrast T1 imaging and hepatobiliary phase imaging. Hepatobiliary contrast agents (eg Gad-BOPTA and Gad-EOB-DTPA) improve sensitivity for the detection of colorectal liver metastases.

Dr Balasingam presented two CRC cases where CT was unremarkable, but MRI showed liver lesions. He pointed out, however, that not all liver lesions seen on CT are malignant and one must be careful with the diagnosis. He believes that MRI should be undertaken for any suspicious liver lesion in order to determine its status.

PET-CT shows tissue metabolism and function as well as structure and can pinpoint the exact location of lesions. This is achieved by the use of 18F-FDG, a radiopharmaceutical that marks the uptake of glucose in tissues. Cancer cells, being highly metabolic tissues use large amounts of glucose and show high uptake of FDG. In NZ, PET-CT is approved in CRC for the preoperative assessment of potentially resectable liver and lung metastases and for the evaluation of residual structural abnormality on diagnostic imaging following definitive treatment for CRC.

Limitations of PET-CT are that many normal structures may be FDG avid and small metastases (<5-10 mm) may not be visible (particularly in the liver).

IOUS is an imaging modality that is useful during surgical procedures (both open and laparoscopic) and involves putting an ultrasound probe directly on an organ (for example the liver). This technique provides very accurate real-time information to the surgeon and may guide intervention.

Take-home messages:

- CT is the mainstay of imaging for metastatic disease
- MRI is the best modality for imaging the liver
- PET-CT is useful for excluding extra-hepatic disease
- IOUS is useful for liver resection
- Multimodality imaging for metastases is critical in the decision-making process for using potentially curative therapies.

Selecting optimal systemic therapy for synchronous metastatic rectal cancer

Presenter: Associate Professor Eva Segelov

The challenge of managing CRC patients with synchronous metastatic disease is to balance the aggressiveness and timing of appropriate local therapy with the ability to deliver systemic treatment. The MDT is crucial in effective management of these patients.

Case report:

Associate Professor Segelov outlined the case of a 68-year-old man highlighting some of the issues around treatment. He presented in Dec 2007 with near obstructing rectal cancer with multiple liver metastases. He responded well to chemoradiation (capecitabine + oxaliplatin [XELOX]). In April 2008, he underwent planned staged hemihepatectomy and three further months of XELOX. In Aug 2008 the residual liver lesion was removed followed by closure of his ileostomy. He remained well until July 2009 at which time his carcinoembryonic antigen level was elevated and a 3 mm lung lesion was found on CT. FOLFIRI + bevacizumab was started and he was well in September 2009. In December that year he underwent liver resection. In 2010 he presented with further liver metastases and started on capecitabine to which he responded; however, he subsequently progressed and was restarted on oxaliplatin. Testing confirmed *KRAS* exon 2 wild-type and in October 2011 he developed a brain metastasis and underwent resection of a large lesion with oedema; at that time he received whole brain radiotherapy. In December that year he started cetuximab. In June 2012 he was diagnosed with lymphangitis, which was subsequently considered to be more likely fibrosis related to his cetuximab therapy. In August 2012 he received single agent irinotecan. He rapidly deteriorated and died in November 2012.

In patients with synchronous disease it is important to define treatment aims: Is cure possible?; If it is a palliative situation, will local disease be problematic and when?; How significant a tumour burden is the metastatic disease?; What is the natural history of such patients? Furthermore, the local, systemic and general treatment options need to be ascertained.

The aim for treating synchronous metastatic rectal cancer is to treat local symptoms if present without allowing significant systemic progression. Options for treatment are: short-course radiotherapy then chemotherapy; synchronous long-course chemoradiotherapy then more chemotherapy (followed by resection if appropriate); or high response-rate chemotherapy alone. If all disease (rectal and metastatic) is resected, chemotherapy is usually given for 6 months all up (neoadjuvant and adjuvant).

Differences exist in the treatment of colon and rectal cancer with synchronous metastases. With colon cancer, there is less concern about local symptoms and local recurrence. These cancers are genomically different and have different prognostic and predictive biomarkers. In rectal cancer with synchronous metastases, treatment timing is of significant importance. Studies of chemotherapy plus radiotherapy for rectal cancer have shown both 5-FU and capecitabine to have proven benefit over RT alone; however, to date, the addition of oxaliplatin has not increased pathological complete response in clinical trials. Another option for incurable disease is to give chemotherapy alone and defer or omit radiation, relying on the systemic chemotherapy to control the local disease, which it often does very effectively. Doublets used in NZ as standard first-line therapy are FOLFOX/XELOX or FOLFIRI. In other countries, doublet plus bevacizumab is the standard first-line option. Strong data is emerging on the efficacy of triplet therapy (FOLFOXIRI) with an even higher response rate in highly selected patients with the addition to the triplet of bevacizumab.[84] New data on cetuximab from the new EPOC study suggests that the agent should not be used in *KRAS* wild-type CRC patients with operable liver metastases.[85] However, another study has shown conflicting results.[86] The National Comprehensive Cancer Network Guidelines for treating resectable rectal cancer show many treatment options.[87]

When treating synchronous rectal cancer for palliation, one must be mindful that some patients will live a relatively long time and therefore local treatment (surgery or radiotherapy) may be relevant for those with well-controlled systemic disease and a slow natural history. A recent study has also shown survival benefit in resecting primary tumours in selected patients.[88]

Management of synchronous primary and metastatic rectal cancer

Presenter: Professor John McCall

Patients presenting with synchronous primary rectal cancer and potentially resectable liver metastases are a particular challenge because optimal treatment for each disease site may require differing neoadjuvant and surgical approaches that are mutually exclusive.

A 2009 systematic review and meta-analysis revealed median 5-year survival rates following radical treatment of colorectal liver metastases of just under 40%; the median perioperative mortality rate was 1.7%.[81] It would appear that liver disease can be managed surgically with approximately the same mortality risk as rectal cancer primary surgery.

The goals of management for synchronous primary rectal cancer and metastatic disease are as follows: 1) No compromise on safety or radicality of the rectal resection; 2) No compromise on safety or radicality of the liver (or lung) resection; 3) Incorporate neoadjuvant and adjuvant treatments that optimise oncological outcome. Possible surgical strategies include: 1) Primary resection first, liver resection later; 2) Simultaneous primary and liver resection; 3) Liver resection first, primary resection later. Chemotherapy, either peri- or post-operative, should be given to all patients and preoperative radiotherapy to selected patients.

Data suggests that simultaneous resection of CRC and synchronous liver metastases is safe, although most of the data pertains to colon resections involving ≤3 liver segments.[89] Practical considerations when considering simultaneous resection include the following: oncological risk (prognostic factors), technical risk (anatomic features), medical risk (residual liver volume and comorbidities). The procedure needs to be technically feasible, safe and sensible with careful consideration of oncological factors.

Several small studies have evaluated a liver first approach in patients with CRC and synchronous liver metastases and a recent meta-analysis has shown a median OS of 40 months (range 19-50 months).[90,91] By international standards, survival

>30 months in such patients is considered reasonable. Professor McCall pointed out that 99% of the patients had systemic chemotherapy first and 93% safely had liver resection with a mortality rate of 1%.

A pooled analysis of two phase III trials comparing surgery + adjuvant postoperative chemotherapy (5-FU + leucovorin) versus surgery alone for resectable colorectal liver metastases has shown a small but significant increase in progression-free survival with chemotherapy (27.9 vs 18.8 months).[92] The EORTC study revealed that perioperative chemotherapy with FOLFOX4 for resectable liver metastases from CRC was more effective than surgery alone (7.3% absolute increase in rate of progression-free survival at 3 years) and this is now the standard of care.[77] Preliminary data on preoperative chemotherapy in these patients shows it to be a feasible option and phase III trials are currently underway.[93]

A recent study from the Netherlands demonstrated the efficacy and tolerability of preoperative short-course radiotherapy followed by six cycles of capecitabine and oxaliplatin + bevacizumab then radical surgical treatment of metastases in patients with primary stage IV rectal cancer.[94]

At the Southern District Health Board, a chemotherapy (six cycles of FU/oxaliplatin) first approach is employed for CRC patients whose liver is a priority for treatment. This may be followed by short-course radiotherapy (5 x 5 Gy) and subsequent liver resection with or without rectal resection (or rectal resection may be undertaken subsequently), followed by chemotherapy. For those with unresectable liver disease, conversion chemotherapy may be an option.[95-97]

Take-home messages:

- Complete staging must be undertaken (including baseline liver MRI and PET/CT)
- The MDT must meet to discuss the patient prior to initiating treatment
- Re-stage at appropriate intervals (avoid futile surgery)
- Incorporate neoadjuvant and adjuvant treatments that optimise oncological outcome
- Do not compromise on safety or radicality of surgery.

SESSION 4: RECTAL CANCER IN NEW ZEALAND

Chaired by Professor Michael Findlay and Associate Professor Ian Bissett

Current policy initiatives in rectal cancer in New Zealand

Presenter: Associate Professor Susan Parry

Associate Professor Parry spoke on the wide range of policy initiatives being undertaken by the MOH Bowel Cancer Team to improve the diagnosis and treatment of CRC throughout NZ. Concerns along the rectal cancer pathway include: delays in diagnosis; delays in receiving treatment; advanced stage at diagnosis; inequities (access and quality); maintaining patient focus.

Current initiatives addressing delays in diagnosis are focusing on diagnostic test wait time. Diagnostic test wait time indicators were introduced in July 2012 for colonoscopy, CT and MR angiography, with monthly reports by DHBs to the MOH. Associate Professor Parry explained that wraparound initiatives need to be in place to support these policy initiatives. She gave the example of the development of the national Referral Criteria for Direct Access Outpatient Colonoscopy, which all DHBs are expected to use. Furthermore, the MOH bowel cancer team is visiting DHBs to discuss data collection and provide support to deliver a sustainable increase in capacity. Eventually, inequity in delivery of colonoscopy between comparable DHBs should be able to be identified and addressed. Modelling has estimated the colonoscopy burden of introducing population screening for CRC in NZ to be 28,000 colonoscopies per year by 2031.[98]

The Bowel Screening Pilot Study, currently underway at Waitemata DHB, is one initiative addressing the issue of detecting disease at an earlier stage. Associate Professor Parry also discussed The National Bowel Cancer Working Group (NBCWG), which was formed to promote early diagnosis and equitable and quality treatment for all individuals with bowel cancer, and The New Zealand Familial Gastrointestinal Cancer Service (NZFGICS), established in 2008. Initiatives to address quality along the pathway include the National Endoscopy Quality Improvement Programme (NEQIP) and the Faster Cancer Treatment Programme.

Rectal cancer: New Zealand's place in the world. Inequities in outcomes

Presenter: Associate Professor Diana Sarfati

NZ death rates from CRC rank among the highest worldwide. In NZ, CRC is the second highest cause of cancer death. Approximately 3000 CRCs are diagnosed every year, of which about one-third are rectal cancers. In NZ in 2009 there were 300 deaths from rectal cancer. Between 1981 and 2004 the incidence of rectal cancer remained fairly stable in non-Māori, but increased significantly for Māori.[99] Cancer incidence data from the MOH show that the incidence of CRC is declining. Associate Professor Sarfati emphasised, however, that as NZ has an aging population, the decline in incidence might not necessarily correspond to a decline in CRC burden. An important area of focus is in the primary prevention of CRC through initiatives focusing on diet, physical activity, smoking and alcohol use.

Worldwide, survival rates for CRC have improved over time, with a reduction in the excess mortality rate of 27% every 10 years in NZ since the early 1990s.[100] Of significant concern, Māori have a 33% poorer survival from CRC than non-Māori. Analysis of cancer incidence and mortality by deprivation shows that Māori are more likely to develop cancer and die from cancer than non-Māori across all NZ deprivation deciles. A study by Associate Professor Sarfati revealed that Māori with colon cancer were less likely to receive adjuvant chemotherapy and experienced lower quality of care than non-Māori.[101] This inequality was also observed in lung cancer, where Māori were four times less likely to receive curative rather than palliative therapy for non-metastatic disease than non-Māori.[102]

Associate Professor Sarfati presented findings from a hospital note review of 194 Māori and 194 non-Māori patients with rectal cancer diagnosed between 2006 and 2008.[103] Among this cohort, Māori patients were younger and were more likely to have comorbidities, but there were no differences between the groups in the grade, size or stage of their tumours. Overall, 97% of patients underwent definitive surgery (two-thirds by a colorectal surgeon). Waiting times between diagnosis and first treatment (37 days) were similar between the two groups. Among those with stage IV disease, non-Māori were more likely to be referred to palliative care.

NZ CRC standards – process, outcomes and implementation

Presenter: Professor Frank Frizelle

Professor Frizelle presented details of the MOH's draft NZ CRC Standards of Provision for Patients with Bowel Cancer document (June 2013). The standards, put together by the bowel cancer standards working group (a sub-group of the NBCWG), follow the 2011 release of the MOH guidelines for the management of early CRC.

Professor Frizelle explained that a standard is a quality tool for assessment to be used over time to compare a point (aspect) of care; it is able to be measured, is relevant and important, and is based on strong evidence. The standards were developed with feedback from interest groups and public consultation. After prioritisation, a number of standards were agreed upon in the following areas: timely access to services (4 standards); communication and referral (3); investigations, staging and diagnosis (3), treatment (5); follow-up and surveillance (1); care coordination (1); multidisciplinary care (3); clinical performance monitoring and research (2); supportive care (1). The draft is to be finalised and the standards implemented with appropriate resourcing and testing.

Panel discussion: How do we do better? Treatment, research, policy and the future

Panel: Frank Frizelle; Susan Parry; Diana Sarfati

The panel was asked for their opinion on what the initiatives around equity, standards and policy will mean in terms of resources and manpower.

Professor Frizelle commented that standards should drive where resources go. Ideally, the standards will roll over into the private sector.

Associate Professor Sarfati pointed out that prevention of CRC would ultimately reduce healthcare workforce expenditure in this area and that high-level initiatives focusing on diet, exercise and smoking cessation would be relatively straightforward. She commented that screening for CRC has a large impact on workforce, but it is important to get this up and running. She stressed the importance of good data collection for treatment and outcome analysis.

Associate Professor Parry believes that if doctors and patients decide a particular standard is important then it must be resourced and monitored.

Concerns were raised from the audience that some patients may not be appropriately screened in a timely manner. Associate Professor Parry responded that the gold standard will eventually be that every patient who meets the referral criteria, even with non-urgent symptoms, should be offered a colonoscopy within 6 weeks.

The panel was asked about the capacity to undertake effective MDT management of patients.

Associate Professor Parry commented that MDMs are time-consuming and not appropriately resourced, and that this issue must be addressed.

Professor Frizelle explained that public feedback during the development of the MOH guidelines for the management of early CRC strongly indicated that all rectal cancers should be discussed by an MDT.

Associate Professor Sarfati added that MDT meetings should have a chairperson and that clear recommendations for patient management should be derived.

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