Review article

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Colorectal cancer: from epidemiology to current treatment

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INTRODUCTION

Colorectal cancer (CRC) was the second most frequent cancer in Europe in 2004, responsible for 13% (376,400) of all incident cancer cases. It is also the second most frequent cause of cancer mortality in Europe, with 11.9% (203,700) annual deaths (1). When localized, CRC is often a curable disease, but the overall prognosis is determined by the extent of local and particularly metastatic tumour spread. The disease outlook is relatively poor, because advanced disease is a significant cause of worldwide cancer-related mortality. Thus, estimated 5-year survival rates range from nearly 90% in stage I disease (Dukes' A) to less than 10% in patients with metastatic disease (Dukes' D) (1). Comprehensive cancer care in the 21st century is dependent on a multidisciplinary approach to patients with malignant disease. Large bowel cancer is no exception, as there is increasing clinical trial data supporting multimodal treatment for both localized and advanced tumours. This review will focus on the important aspects in CRC including the latest treatment strategies (chemotherapy, radiotherapy and the targeted therapies).

EPIDEMIOLOGY AND INCIDENCE

Colorectal cancer is an important public health problem; it is one of the leading causes of cancer mortality in the industrialized world. There are nearly one million new cases of CRC diagnosed worldwide each year and half a million deaths (2). When detected

early, CRC is highly treatable and curable. Globally, the incidence of CRC varies 10-fold, with the highest incidence rates in North America, Australia, and northern and western Europe; developing countries have lower rates, particularly Africa and Asia (3). These geographic differences appear to be attributable to differences in dietary and environmental exposures that are imposed upon a background of genetically determined susceptibility.

Age is a major risk factor for sporadic CRC. It is a rare diagnosis before the age of 40, the incidence begins to increase significantly between the ages of 40 and 50, and age-specific incidence rates increase in each succeeding decade thereafter (4). Recent reports show that, in the USA, it is the most frequent form of cancer among persons aged 75 years and older (5). Given that the majority of cancers occur in elderly people and with the ageing of the population in mind, this observation gives further impetus to investigating prevention and treatment strategies among this subgroup of the population (5). The lifetime incidence of CRC in patients at average risk is about 5 %, with 90 % of cases occurring after age 50 (6, 7). The incidence is higher in patients with specific inherited conditions that predispose them to the development of CRC.

AETIOLOGY

Most colon cancers arise from adenomatous polyps. About 5% of adenomatous polyps are estimated to become malignant and this process takes approximately 10 years (5). The most important etiological factor to date is genetic predisposition. Genetic alteration such as mutation of the APC (adenomatous polyposis coli) tumour suppressor gene, K-ras proto-oncogene and P53 has been demonstrated to lead to polyps and cancer formation in the large intestine (8-10). Understanding of the molecular pathogenesis of CRC (both sporadic and inherited) is evolving rapidly. These findings have led to the identification of several specific genetic disorders, all of which are inherited in an autosomal dominant fashion, that are associated with a very high risk of developing colon cancer. Sporadic CRC is estimated to account for 80% of all CRCs and hereditary forms account for the remaining 20% (11). The hereditary syndromes include familial adenomatous polyposis (FAP) which accounts

for 1% of all CRC (12) hereditary nonpolyposis colon cancer (HNPCC) which accounts for 5-10% of all CRC (13), and familial colon cancer (FCC) which accounts for the remaining 10-15%. FCC is most likely to be of multifactorial origin and remains largely unexplained at this time.

Epidemiologic studies suggest that several exogenous agents, for example red meat and tobacco smoking, may increase the risk of developing CRC. Others, such as NSAID's (non-steroidal anti-inflammatory drugs), vegetables and hormone replacement therapy, may reduce the risk (14). Knowledge of agents responsible for development of CRC is still limited. High energy intake, especially from saturated fat, seem to be a definite risk factor and high consumption of dietary fiber and vegetables seem to be protective, especially when combined with physical exercise (15-19). However there is still much controversy concerning this "fat–fiber" hypothesis. It suggests that the epithelium in the colon and rectum will be exposed to mutagens for longer times due to prolonged transit time in the gut caused by fat-rich and low-fiber diets combined with low physical activity (20).

ADENOMA-CARCINOMA SEQUENCE

Colorectal carcinomas arise through a series of well-characterised histopatho-logical changes as the result of specific genetic 'hits' at certain oncogenes and tumour suppressor genes. At least four sequential genetic changes need to occur to ensure CRC evolution: The luminal third of the colonic crypt begins to proliferate and this is thought to be due to a mutation in the APC gene found in chromosome number 5. Persistence of this proliferation leads to the formation of an adenoma, which is benign, but premalignant. This stage is reversible as can be observed by the administration of sulindac (NSAID) (21). Ras oncogenes, especially Ki-ras, are thought to be responsible for the change from adenoma to adenocarcinoma. During neoplastic mitosis, accurate replication of the genome is not guaranteed. Small pieces of DNA are lost and even entire chromosomes may be lost. Thus, these lesions have genetic instability. Sometimes, the asymmetric mitosis results in the loss of critical genetic loci that are responsible for the restraint of cellular proliferation. As the neoplastic mitotic divisions continue, genetic instability progressively increas-

es leading to cells with a greater growth advantage and ultimately, invasive abilities are obtained.

STAGING

Cancer can grow inward toward the lumen of the colon or rectum, and-or outward through the walls of these organs. Advanced disease can cause perforation of the bowel, leading to infection. Metastasis of the disease may occur to the lymph nodes, liver, lung, peritoneum, ovaries, and brain. Accurate staging of CRC (see table below) can help to predict overall prognosis and select appropriate treatment options. It is also critical to evaluate the overall results of treatment.

Table: Comparison of TNM and Dukes' classification of CRC (22)

		TNM	Dukes
Tumour penetration through bowel wall	Invasion of submucosa only	T1	A
	Into muscularis propria	T2	
	Into subserosa or perirectal fat	T3	B
	Direct invasion of other organs or structures	T4	D
Regional lymph node involvement	None	N0	
	Metastasis in 1-3 nodes	N1	C
	Metastasis in 4 or more nodes	N2	
Distant metastasis	No	M0	
	Yes	M1	D

DIAGNOSIS

The main symptoms of CRC are changes of bowel habit and bleeding. If the tumour is located in the rectum there may be fresh red blood on the stool surface, while haemorrhagic proximal lesions result in dark faeces. The changes in bowel habit may involve any type of change in frequency or consistency of the stool. Diarrhoea, constipation, increased passage of flatus and/or urgency may occur. Other symptoms are abdominal pain, anaemia and weight loss may suggest a more advanced tumour.

Investigative procedures usually start with per rectum examination, rectoscopy and checking for occult blood in faeces. Frequently a radiological investigation with air-contrast barium enema is performed combined with endoscopic investigation of

the rectum and colon. Biopsies for histopathological evaluation are mandatory for making a firm diagnosis. Ultrasound, CT and MRI are methods used to determine the extent of tumour growth locally and to investigate if there is metastatic spread to the lymph nodes, liver or other organs. In rectal cancer MRI can detect tumour penetration through the rectal wall, into the perirectal tissue, as well as the presence of local lymph node metastases in 75% of the patients (23).

MANAGEMENT OF COLORECTAL CANCER

Curative management of CRC relies primarily on surgical resection, possibly accompanied by adjuvant chemotherapy. In rectal cancer, radiation therapy is also used.

SURGERY

About 50% of patients with newly diagnosed colon cancer are cured with surgery alone, predominantly patients with stage I and II disease.

Primary Tumour: The primary therapy for adenocarcinoma of the colon and rectum is surgical removal of the bowel segment containing the tumour, the adjacent mesentery, and draining lymph nodes. The type of surgical resection depends on the tumour's anatomic location. Right or left hemicolectomy is the surgical treatment of choice in patients with right- or left-side colonic tumours, respectively. Tumours in the sigmoid colon may be treated by wide sigmoid resection.

Major recent advances have improved understanding of rectal anatomy and the biology of the extraluminal spread of rectal cancer. In addition, the end-to-end anastomotic stapling device has made it easier to perform lower rectal anastomosis. However, inadequate resection and injudicious use of these devices has resulted in an unacceptably high pelvic recurrence rate. Appropriate proximal, distal, and radial resection margins with nodal clearance encompassed within the mesorectal fascial envelope has resulted in pelvic recurrence rates of 10% or lower (24). The technique of total mesorectal excision has been championed by Heald and is now accepted throughout the Western world. Total mesorectal excision should be performed for cancers of the middle and distal third of the rectum. The technique involves resection of the rectum and en-

tire mesorectum down to the pelvic floor with preservation of the pelvic sympathetic and parasympathetic nerves to preserve bladder and sexual function. Although a 2 cm distal margin is preferred, a margin of 1 cm is acceptable, since most rectal cancers do not exceed 1 cm of distal submucosal extension (25). Cancer of the upper third of the rectum should be resected with generous subtotal mesorectal excision; the distal rectal resection margin should be 5 cm with accompanying subtotal mesorectal resection of at least 5 cm from the distal edge of the tumour. Tumours at or just above the sphincter mechanism are treated by abdominoperineal resection; total mesorectal excision is an essential part of this resection. In a multivariate analysis, the most consistent predictors of long-term survival were stage of the primary tumour, percentage of tumour involvement (26) (with fewer than three metastases and small tumours conferring a better prognosis), and disease-negative surgical margins.

Metastases: Surgical excision is the standard of care in patients with resectable liver and pulmonary metastases from CRC owing to the potential for long-term survival after complete resection in these cases and to the fact that without surgery, such disease remains incurable at present. Twenty-five percent of CRC patients present with liver metastases (synchronous); about 50% of CRC patients develop liver metastases after surgical resection of the primary tumour (metachronous) (27). In six series with more than 100 patients each, 5-year survival rates of from 25% to 39% and a median survival of longer than 2 years were reported after resection of liver metastases (26, 28-31).

CHEMOTHERAPY

Adjuvant chemotherapy
Nearly half of the patients undergoing apparently curative resection of bowel cancer are destined to relapse and eventually die with either locally recurrent or distant metastatic disease. This is due to the presence of residual micro-metastases (Sub-clinical) invisible at the time of surgery. The aim of adjuvant chemotherapy is to eradicate these micro-metastases and thereby prevent future relapse.

A large randomised trial was conducted comparing surgery alone and surgery plus 5-FU/levamisol in patients with Dukes' C CRC. It

demonstrated that the group receiving chemotherapy had a 33% lower risk of death and 41% less recurrence risk (The Intergroup Study (32)). Other randomised trials have also shown increased disease-free and overall survival after adjuvant treatment with 5-FU/FA, which confer an absolute survival benefit of 5-6% (33, 34). As a result of many randomised trials it is now accepted that patients with Dukes' C carcinoma of the colon should be offered 5-fluorouracil based adjuvant chemotherapy if they are fit to receive it (35). Other newer chemotherapy agents may be more effective in the adjuvant setting and proved to have a safer profile like the use of Capecitabine (Xeloda) as an alternative to the 5-FU, also the last year's findings marked a shift in the standard of care in adjuvant therapy in CRC and extended by utilising the combination therapy in form of 5-FU+LV+Oxaliplatin regimen (FOLFOX) and the benefits appear clearly in terms of Disease Free Survival (DFS) (36).

The role of chemotherapy in the adjuvant setting is delineated in Dukes' C CRC, with an absolute survival benefit of 6-9% at 5 years, but not as yet established in Dukes' B where the absolute survival benefit is only between 2-3%. The standard procedure nowadays in the USA and Europe is to use the FU/LV for six months period (34, 37). However this standard is limited to stage III patients, whereas the management of stage II patients remains a controversial issue owing to a limited benefit in survival as mentioned in the previous paragraph.

Combined Chemotherapy for Advanced and Metastatic CRC

The outlook for patients with advanced CRC has improved substantially with the introduction of the combination regimens (38, 39) with median survival times almost doubling over the past 10 years (40). The administration of 5-Fluorouracil (5-FU) and Irinotecan (Camptosar) or Oxaliplatin (Eloxatin) are now widely used for the treatment of advanced CRC. The drugs work by different mechanisms, and colon cancers do not generally manifest cross-resistance to the two agents when they are used serially. More recently, combination regimens with irinotecan, 5-FU, and Leucovorin (LV) have produced survival benefits superior to 5-FU and leucovorin. In Europe, irinotecan is most frequently combined with an infusion regimen of 5-FU, whereas in the United States bolus 5-FU has been favoured until recently (41).

European data, evaluating infusional 5-FU with irinotecan and Leucovorin (FOLFIRI) followed by the infusional 5-FU schedule with oxaliplatin (FOLFOX) at the time of disease progression versus the opposite sequence of the combinations, have shown an overall median survival exceeding 20 months regardless of the sequence, representing the best survival statistics for patients with advanced and metastatic CRC (42).

FOLFOX and FOLFIRI appear to be the most effective in terms of efficacy and tolerability. Larger randomised trials comparing these 2 regimens are ongoing. Tournigand and his colleagues evaluated the FOLFOX and FOLFIRI regimens to find the best sequence for treating patients with metastatic CRC. (40) The study showed that a sequence of first line FOLFOX followed by second line FOLFIRI resulted in a similar survival time to that produced by the reverse sequence. However, as at least 30% of patients did not receive second-line therapy, the authors highlighted the importance of choosing the most appropriate first-line therapy. Although both first line therapies achieved similar response rates (FOLFIRI 56% vs FOLFOX 54%), second line FOLFIRI achieved a significantly lower response rate than did FOLFOX (4% vs 15%). The toxicity profiles for the two regimens were also different. As expected from previous studies, grade ¾ mucositis, nausea/vomiting, and grade 2 alopecia were more common with FOLFIRI, whereas grade ¾ neutropenia and neurosensory toxicity were more common with FOLFOX. At the present time some data coming from different recent clinical trials, which incorporated the targeted therapy in their protocols ,suggests that a longer survival advantage of 24 months has been achieved.

RADIOTHERAPY

Radiotherapy as a definitive or adjuvant modality for colon cancer lying above peritoneal reflection has not gained popularity. Radiotherapy has two major limitations when applied to colon cancer: A poorly defined target, since the colon is mobile, and the fact that dose-limiting structures surround the colon (i.e., large amount of small bowel, kidney, and liver). An exception is occasionally given to carcinoma of the cecum with extension into the abdominal wall, where it is possible to define the area at risk, particularly if it is marked with clips.

Radiotherapy is used, however, for palliation in colon cancer. To date, no randomised study results are available to substantiate the use of adjuvant radiotherapy for colon cancer. Chemotherapy remains the most important adjuvant treatment for colon cancer.

The role of radiotherapy in rectal cancer is more justified anatomically. The rectum is a relatively fixed structure in the pelvis and it is situated below the organs of limited tolerance to radiotherapy. It is feasible to deliver reasonably high doses of radiotherapy without severe toxicity.

ADJUVANT RADIOTHERAPY

Preoperative radiotherapy

Preoperative radiotherapy for clinically resectable tumours: Preoperative radiotherapy in these circumstances may have theoretical advantages. It may be more effective in killing tumour cells, since better vascularized and oxygenated cells are more sensitive to radiotherapy. Radiotherapy has a better defined target when the tumour is in place. Preoperative radiotherapy usually utilizes short regimens and therefore is more convenient for patients and more cost effective (1 week of treatment, dose 5 x 5 Gy/week).

Preoperative radiotherapy for unresectable tumours: For most surgeons and oncologists, the term "unresectable" indicates that the tumour is fixed to adjacent pelvic structures. The goal of radiotherapy here is to shrink the tumour and to make it surgically resectable. A substantial dose of radiotherapy should be delivered for two reasons:

A. Radiotherapy should affect gross macroscopic disease (unlike postoperative adjuvant radiotherapy, which is dealing with microscopic disease only).

B. In the case of a failure to facilitate resectability, radiotherapy will be the principal treatment modality, which can at least delay the progression of the disease.

Postoperative radiotherapy
In 1990, the National Institute of Health Consensus Conference on Adjuvant Therapy of Large Bowel Cancer evaluated the effectiveness of adjuvant treatment for rectal cancer. Their conclusion was that "combined postoperative chemotherapy and radiotherapy improves local control and survival in Stage II and III patients and is recommended (43).

Pre and postoperative radiotherapy trials

There has been much debate about whether adjuvant radiotherapy should be administered pre- or postoperatively. The first randomised trial directly comparing preoperative and postoperative radiotherapy is the Swedish Uppsala trial. In this trial 471 patients with resectable rectal and rectosigmoid cancer were randomly allocated to receive either preoperative short-term high-dose irradiation (25.0 Gy in one week) for all patients or prolonged postoperative radiotherapy (60 Gy in seven to eight weeks) only for patients with a Dukes B or C lesion. After a minimum follow-up of five years, the local recurrence rate was significantly lower after preoperative than after postoperative radiotherapy (13 % vs. 22 %; p= 0.02) (44). The cancer Collaborative Group carried out a meta-analysis of 22 randomized controlled trials comparing the outcomes of surgery for rectal cancer combined with pre- or postoperative radiotherapy with those of surgery alone (6350 patients in 14 preoperative and 2157 patients in 8 postoperative trials) (45). The investigators concluded that overall survival was only slightly better in those patients receiving radiotherapy compared with those allocated to surgery alone, (mortality 62% vs. 63%, p=0.06). The rates of apparently curative surgery were not increased by radiotherapy (86% controls and 85% radiotherapy). However, the yearly risk of recurrence in the group receiving preoperative radiotherapy was 46% lower than that in the group receiving surgery alone (p=0.00001) and 37% lower in the group receiving postoperative radiotherapy (p=0.002). The meta-analysis also demonstrated that preoperative radiotherapy was more efficacious at lower biological doses than the postoperative radiotherapy studies (range 30-37 Gy vs. 35-43 Gy), which correlates with the findings of the Swedish Uppsala trial (44). Preoperative therapy over a week is also easier to administer than postoperative treatment over 5 or 6 weeks. Other advantages include increased tumour radiosensitivity, decreased tumour seeding at surgery and increased rate of sphincter sparing.

In a recent trial conducted by the Dutch CRC Group 1861 patients were randomized to receive either preoperative radiotherapy (5 Gy for 5 days) followed by total mesorectal excision or total mesorectal excision alone. A significant decrease was found in the

rates of local recurrence in the radiotherapy arm compared with that in controls (2.4% radiotherapy vs. 8.2% surgery). The rates of overall survival at 2 years were not significantly different (82% radiotherapy vs. 81.8% control) athough a longer follow-up period might demonstrate differences in survival (46).

Various schedules of radiotherapy and chemoradiotherapy have been studied, with encouraging results. (47) The lyon R0-04 Phase II study treated 40 patients with operable T3/4, N1/2, M0 rectal cancers with radiotherapy 50 Gy over 5 weeks together with two cycles of oxaliplatin and infused 5FU in weeks 1 and 5 (48). Objective clinical responses were seen in 75%, and complete histologic response was seen in 15%. Complete resection was performed in all patients. A randomised study (German trial) of pre-operative vs post-operative chemoradiation enrolled 421 patients with endorectal ultrasound-staged T3/4 or node positive rectal tumours. (49) There was no difference in overall survival at 5 yrs, however, there was a statistically significant reduction in cumulative local relapse in the preoperative treatment arm (6 vs 13%, P=0.0006). In addition, both short and long term toxic effects were reduced in patients randomised to pre-operative treatment. The Polish trial demonstrated that patients who were randomized to short-course radiotherapy with immediate surgery had a similar rate of sphincter preservation (61%) to those receiving long-course chemoradiotherapy and delayed surgery (59%) (50).

In CR07 trial: Pre-operative radiotherapy and selective post-operative chemo-radiotherapy have been studied in patients with rectal cancer The preliminary results from this trial was presented in June 2006 during the ASCO annual meeting indicate that routine short course pre-operative radiotherapy results in a significant reduction in local recurrence and improved disease free survival at 3 years when compared with a highly selective post operative approach.

Preoperative radiotherapy, as an additional treatment to surgery in resectable rectal cancer, is superior to postoperative treatment in terms of dose-effectiveness and toxicity. Whether more sphincters can be preserved if neoadjuvant radiotherapy with or without chemotherapy is used is still not proven.

Palliative radiotherapy

Palliation of symptoms from primary lesion: Local recurrence of rectal cancer can be accompanied by signs and symptoms that can greatly affect patients' quality of life. Intractable pain from recurrence in the presacral space and sacral nerve root entrapment often causes a great deal of distress. Continuous bleeding from a rectal tumour can require frequent blood transfusions. The decision to treat a local recurrence is based on several criteria and is guided by an evaluation of the patient's benefit in terms of improved quality of life. Factors to consider include:

• Previous radiotherapy and time between treatment and recurrence.
• Tolerance of normal tissues.
• Volume of tissue to irradiate.
• Performance status of the patient.

Palliation of symptoms caused by distant metastases: Frequent sites of treatment include bones, lungs, and brain. Usually a short course of radiotherapy is sufficient (from a single treatment to 2 weeks of treatment). Radiotherapy is not advised, however, in situations where the patient has partial or complete obstruction of the intestine related to tumour. Instead, surgical correction in the form of colostomy should be a priority and radiation can be added later.

THE TARGETED THERAPY

The outcome for patients with advanced CRC has improved significantly as a result of the advances in chemotherapeutic agents. However, chemotherapies are restricted by both their lack of specificity and their frequent association with potentially severe dose-limiting toxicities. Therefore, better-tolerated treatments that specifically target the processes fundamental to tumorigenesis and metastasis are urgently required. Recent advances in the understanding of molecular biology have led to the development of target-specific agents. Two targeted agents (recently approved by the FDA) are a human epidermal growth factor receptor (HER-1/EGFR)-targeted mAb, cetuximab (Erbitux®), and an anti-vascular endothelial growth factor (anti-VEGF) monoclonal antibody (mAb), bevacizumab (Avastin®), as first- and second-line metastatic CRC therapy, respectively. These two agents are already having a significant im-

pact on metastatic CRC (MCRC) treatment strategies.

Cetuximab is a human:murine, chimeric anti-EGFR IgG1 MoAb that is indicated for use in combination with irinotecan for the treatment of patients with MCRC who have EGFR-expressing tumours that are refractory to irinotecan-based therapy or as monotherapy in irinotecan-intolerant patients with MCRC who have EGFR-expressing tumours. Preclinical studies have shown that when combined with cisplatin, paclitaxel, doxorubicin, topotecan, gemcitabine, 5-FU, or radiation the anti-tumour activity of cetuximab is potentiated (51). Some 70% of colorectal cancers express EGFR. (52) Cetuximab approval in the EU and USA was based on a pivotal European randomized phase II sudy (the BOND study) (53) and on two supporting clinical studies conducted in the USA (54). Bond study randomised patients with EGFR positive colorectal cancer who were irinotecan refractory to combination of irinotecan plus cetuximab or cetuximab alone. (53) The overall response rate and median time to progression were significantly better in the combination arm. Overall survival was no different between treatment arms, although this could be due to patients crossing over from single agent to multiagent therapy, as was permitted in the protocol. The major cetuximab specific toxicity was a reversible acneiform rash, which is common to all anti-EGFR agents. Interestingly, patients who developed this characteristic rash were significantly more likely to respond to cetuximab.

Bevacizumab is a MAB targeting the VEGF that is now approved in the EU and the USA for use in the first line treatment of advanced CRC. A phase III trial of the anti-VEGF mabs, bevacizumab, has demonstrated the clinical utility of VEGF targeting in patients with colorectal cancer. (55) A randomised study of 815 patients with advanced colorectal cancer to Irinotecan plus 5-FU/FA (IFL) monotherapy alone or IFL plus bevacizumab. The IFL plus bevacizumab arm was superior for both response rate (45% vs 35%, P=0.0029) and median overall survival (20.3 vs 15.6 months, P=0.00003), with only relative minor additional toxicity. Mild to moderate hypertension was the most common toxicity identified, and was easily controlled. Also additional risk of bowel perforation has been noticed. This trial represents powerful evidence of

the importance of VEGF-mediated cellular signalling in the biology of colorectal cancer, and clearly indicates a significant development in the management of metastatic colorectal cancer.

For the last 40 years 5-FU has been the mainstay for metastatic CRC. In the past few years the introduction of more effective chemotheraoeutic agents and targeted agents with their promising activities and mild toxicity profiles has raised the overall median survival from 12 months to 2 years. The adjuvant chemotherapy with 5-FU/FA (leucovorin) should be routinely offered to medically fit patients with stage III colon cancer. Combination adjuvant treatment (eg. Oxaliplatin) may be considered in high risk patients but the role of adjuvant chemotherapy in stage II colon cancer is still controversial. Adjuvant therapy can be offered to high risk patients (patients with intestinal obstruction, perforation, T4 tumours, poorly differentiated tumours, extramural venous or lymphatic invasion, or perineural invasion and no other contraindication). In metastatic disease in terms of efficacy and tolerability FOLFOX, FOLFIRI, and IFL plus Bevacizumab are the most effective first line regimens. However, it has not been confirmed yet which of these regimens is the most effective for individual patients, although bevacizumab plus FOLFOX or FOLFIRI is likely to have the most clinical benefit. Surgery remains the primary curative treatment for rectal cancer and TME is still the standard surgical procedure.

Postoperative chemoradiation is accepted as standard adjuvant treatment for high risk stage II and III rectal cancer. In addition, short course preoperative radiotherapy is routinely used in some European countries (e.g. Nordic countries). Furthermore, preoperative chemoradiation is now increasingly used to downstage locally advanced tumours to achieve microscopically complete resection with clear circumferential resection margin. Patients with distant metastases to lung or liver should be considered for resection of their metastases (Metastatectomy).

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