16. Lymph node dissection in colorectal carcinoma

Adequate lymph node yield is extremely crucial for optimal staging. Patients with node positive disease are categorized as having T3 stage III disease, signifying a poor prognosis. Even a single positive node would warrant adjuvant chemotherapy in these patients. As per the current guidelines, a minimum of 12 lymph nodes should be examined to avoid tumour understaging (nodal yield less than 12 is considered inadequate and chemotherapy may be given to the patient under the presumption of understaging). Notably, lymph nodes, as small as 2 mm, may also be metastatic. Hence, every attempt should be made to recover as many nodes from each specimen as possible.

Method of lymph node dissection

Lymph nodes are not dissected from the specimen 'before' tumour sampling is completed to avoid disruption of the serosa and NPS. Lymph nodes present in the sections containing the tumour are included in situ without dissection. After tumour sampling is complete, each of the slices containing the tumour is dissected for lymph node retrieval. Then, the remaining proximal and distal parts of the colon are dissected for lymph nodes.

17. Examine the rest of the bowel segment for any abnormality such as synchronous carcinoma, features of inflammatory bowel disease, polyps, etc. Each of the synchronous carcinomas is sampled in a similar fashion. In a setting of familial adenomatous polyposis syndrome, samples from multiple polyps should be taken, especially large polyps. The total number of polyps hasto be recorded.
18. Sample mesorectum/pericolonic fat to confirm the presence or absence of extramural venous invasion. Presence of extramural venous emboli outside the bowel wall is an adverse prognostic feature in colorectal tumours.

Sections submitted

1. Four or five sections of the tumour
2. All lymph nodes dissected from the specimen and submitted according to the level of the tumour
3. Longitudinal mucosal resection margins
4. Adjacent mucosa
5. Sample from any other grossly abnormal area

Grossing of a colorectal polyp

Issues to be addressed in the pathology report of a colorectal polyp:

1. Type of polyp
2. Degree of dysplasia, if any
3. Completeness of excision

Ideally, the polyp is received intact, preferably with the base of excision marked by the surgeon. If a polyp has a stalk, then the base of the stalk should be inked and a 2-mm thick end should be sampled as the excision margin. In cases of broad-based, sessile polyps, the entire base should be inked. Serial parallel sections of the polyp should be obtained, each containing the inked base. Thus, the excision margin in a sessile polyp is sampled in a perpendicular manner. More than one section will be examined to assess the margin. It is important to reinforce the ink at the margin in both types of polyps because if an invasive

carcinoma is found in the polyp, the distance of carcinoma from the excision margin is to be measured in millimetres.

Microscopic reporting of colorectal resection specimens

Tumour type

World Health Organization classification of colorectal carcinoma should be followed:

1. Adenocarcinoma: Conventional adenocarcinoma consisting of a predominant glandular component. This is themost common tumour type of the colon.
2. Mucinous adenocarcinoma (area of extracellular mucin should be greater than 50%)
3. Signet-ring cell carcinoma (component of signet-ring cells should be more than 50%). It consists of discohesive, diffusely infiltrating tumour cells containing intracellular mucin. Areas of mucinous and signet-ring cell adenocarcinoma often co-exist. Both these tumour types are associated with poor prognosis.
4. Squamous cell carcinoma
5. Adenosquamous carcinoma
6. Medullary carcinoma:This is a distinctive histologic type showing a solid growth pattern. Presence of numerous tumour infiltrating lymphocytes is a conspicuous finding. This type of morphology is associated with hereditary non-polyposis colon carcinoma (HNPCC) syndrome.
7. Small cell carcinoma (high-grade neuroendocrine carcinoma)
8. Undifferentiated carcinoma
9. Other (specify)

Grading the tumour

Diagnosis of conventional colonic adenocarcinoma is further qualified with respect to the grade of the tumour. Colorectal adenocarcinomas are graded according to the predominant area of the tumour. Grading can be a 2- or 3-tier system. In the 3-tier system, tumours are graded as well, moderately,or poorly differentiated adenocarcinomas,whereas in the 2-tier system, well and moderately differentiated tumours are clubbed together as low-grade tumours. Poorly differentiated adenocarcinomas show complex, irregular arrangement of small, irregular glands or there can be an absence of tubular formation. Undifferentiated carcinomas are a different tumour type and should not be equated with poorly differentiated adenocarcinomas. By default, signet-ring cell carcinomas, small cell carcinomas, and undifferentiated carcinomas are considered high grade. Tumour budding at the advancing edge of the tumour should be documented. High tumour grade is an adverse prognostic factor.

Histological features indicative of microsatellite instability-high (MSI-H) status

1. Right-sided mucinous or signet-ring cell adenocarcinomas
2 Poorly differentiated or undifferentiated carcinomas
3. Increase in tumour-infiltrating lymphocytes.

Immunohistochemistry for mismatch repair (MMR) gene proteins should be performed if any of these histological features are seen, with a consideration of HNPCC.

Determination of TNM

1. Local invasion: the 'T' status

The maximum depth of local invasion into the bowel wall is recorded in order to determine the 'T' stage. The importance of appropriate grossing steps to address this parameter is mentioned in the above section. The tumour is defined as being of pT4 stage when there is invasion of the visceral serosa (pT4a) and tumour infiltration of an adjacent organ (pT4b).Involvement of the serosal (peritoneal) surface is defined as tumour breaching of the serosa with tumour cells either visible on the peritoneal surface or free in the peritoneal cavity.

Direct invasion of an adjacent organ through the serosa is always staged as pT4,whereas intramural extension into an adjacent part of the bowel (e.g. extension of a caecal tumour into the terminal ileum) does not affect the pT stage. Extramural extension of rectal cancer into theskeletal muscle of the external sphincter, levatorani, and/or puborectalis is classified as pT4b.

2. Lymph nodes: the 'N' status

All lymph nodes that have been retrieved from the specimen should be examinedhistologically as described above.

Extramural deposits of tumour that have no lymph node structure are regarded as lymph nodes.

3. Histologically confirmed distant metastases: the 'M' status

This biopsy specimen from a suspected metastatic site may be submitted separately by the surgeon. Otherwise, parameter 'M' is not a part of routine histopathology reporting of resected colorectal specimens.

Response to neoadjuvant therapy

Tumours showing complete or marked regression following neo-adjuvant therapy have a better prognosis than those without significant response. Several systems for assessing treatment response exist. The following 3-score system can be easily used:

Score 1: No residual tumour cells and/or mucus lakes only

Score 2: Minimal residual tumour, i.e. only occasional microscopic tumour foci are identified

Score 3: No marked regression

Resection margins

Margins

The longitudinal resection margins and/or doughnuts should be examined histologically for the presence or absence of tumour.

Non-peritonealised ('circumferential') resection margin: NPS or CRM

Involvement of the NPS in rectal cancer is predictive of local recurrenceand poor survival. It is an indication of neoadjuvant therapy. Evidence for its significance at other colonic sites such as the caecum and ascending colon isalso emerging. The circumferential margin is **regarded as involved if** the tumour is within or less than 1mm away. The 'tumour' may be directly infiltrating or could show vascular invasion or a lymph node deposit at the NPS.

Extramural venous invasion

This is recorded when the tumour is present within an extramural endothelium-lined space that is either surrounded by a rim of muscle or contains red blood cells. The prognostic significance of extramural venous invasion is well established. This feature has been demonstrated as an indicator of unfavourable outcome and increased risk of occurrence of hepatic metastasis.

Background abnormalities

The presence of any pathological abnormalities in the background bowel should be recorded.

1. Polyp(s): If multiple adenomas are detected, adequate sampling from the entire length of the affected segment(s) should be performed. The polyps are histologically classified primarily into adenomatous or non-adenomatous polyps. Adenomatous polyps are further qualified according to the grade of dysplasia. Recognition of high-grade dysplasia is important. Completeness of excision is assessed by the presence of normal colonic glands at the base of the polyp. Presence or absence of invasive carcinoma (malignancy in an adenoma is defined by presence of unequivocal invasion of the muscularis mucosa by malignant glandular epithelium) is recorded. If invasive adenocarcinoma is detected in an adenoma, revision surgery is undertaken if the invasive tumour is poorly differentiated,there is angioinvasion, or the tumour is located within 1 mm of the resection margin of the polyp.

Non-adenomatous polyps are classified microscopically. This category includes a spectrum of serrated polyps (inclusive of variants of hyperplastic polyps, sessile serrated adenomas, and traditional serrated adenomas), hamartomatous polyps, inflammatory polyps, lymphoid polyps, etc.

Perforation

Tumour perforation is an uncommon complication of CRC, but one that is associated with a poor outcome, including high in-hospital mortality and morbidity. Perforation of the uninvolved colon proximal to an obstructing tumour is also associated with high mortality because of generalized peritonitis and sepsis. Reported perforation rates range from 2.6% to 9%. Perforation is more likely to occur in older patients.

Mesorectal envelope

The quality of the surgical technique is a key factor in the success of surgical treatment for rectal cancer, both in the prevention of local recurrence and in long-term survival. Numerous studies have demonstrated that TME improves local recurrence rates and the corresponding survival by as much as 20%. This surgical technique entails precise sharp dissection within the areolar plane outside (lateral to) the visceral mesorectal fascia to remove the rectum. This plane encases the rectum, its mesentery, and all regional nodes and constitutes Waldeyer's fascia. TME of high quality reduces local recurrence rates from 20–30% to 8–10% or less and increases 5-year survival rates from 48% to 68%[51,56]. Adjuvant therapy together with TME of a high quality may further reduce local recurrence rates from 8% to 2.6%[56]. Pathologic evaluation of the resection specimen has been shown to be a sensitive means of assessing the quality of rectal surgery. It is superior to indirect measures of surgical quality assessment such as perioperative mortality, rates of complication, number of local recurrences, and 5-year survival. It has been shown that macroscopic pathologic assessment of the completeness of the mesorectum of the specimen, scored as complete, partially complete, or incomplete, accurately predicts both local recurrence and distant metastasis[56]. Microscopic parameters such as the status of the CRM, the distance between the tumour and nearest circumferential margin (i.e., 'surgical clearance'), and the distance between the tumour and the closest distal margin, are allimportant predictors of local recurrence and may be affected by the

Appendix D: Chemotherapy Dosing and Modifications

Standard Adjuvant Chemotherapy Regimens for Colorectal Cancer

FOLFOX (2-weekly regimen)

Day 1	Oxaliplatin 85mg/m^2,infusion over 2h
	Folinic acid 350mg, infusion over 2 h
	5-FU 400mg/m^2, bolus
	5-FU 1200mg/m^2, continuous infusion over 24 h
Day 2	5-FU 1200mg/m^2, continuous infusion over 24 h

CAPOX (3-weekly regimen)

Day 1	Oxaliplatin 130mg/m^2, intravenous infusion over 2h
Days 1–14	Capecitabine 1700 mg/m^2 , oral in 2 divided doses

Age >75 years: reduced starting dose; oxaliplatin 100mg/m^2 and capecitabine 1300mg $m^{-2}day^{-1}$ for 14 days followed by a 7-day rest period

Capecitabine (3-weekly regimen)

Capecitabine: 2000mg/$m^{-2}day^{-1}$ in 2 divided doses for 14 days followed by a 1-week break.

Age >75 years:dose reduced to 1500mg/$m^{-2}day^{-1}$.

Age >80 years:dose reduced to 1000mg/$m^{-2}day^{-1}$.

Requirements:

Absolute neutrophil count >1.0 ×10^9/L, Platelets >75 ×10^9/L, Stable renal function (CrCl>30mL/min if on FOLFOX, CrCl>50mL/min if on Cape/CAPOX), Bilirubin < 1.4 mmol/L

Advanced Cancer Regimens

FOLFOX + cetuximab* (2-weekly regimen)

Day 1	Cetuximab 500mg/m^2,intravenous infusion over 2 h(subsequent doses over 1 h)
	Oxaliplatin 85mg/m^2, intravenous infusion over 2 h
	Folinic acid 350mg, intravenous infusion over 2 h
	5-FU 400mg/m^2, intravenous bolus
	5-FU 1200mg/m^2, continuous intravenous infusion over 24 h
Day 2	5-FU 1200mg/m^2 continuous intravenous infusion over 24 h

If oxaliplatin is not tolerated or contraindicated: **FOLFIRI + /- cetuximab* (2-weekly regimen)**

Day 1	Cetuximab 500mg/m^2, intravenous infusion over 2 h (subsequent doses over 1 h)
	Irinotecan 180mg/m^2, intravenous infusion over 1h

Folinic acid 350mg, intravenous infusion over 2 h

5-FU 400mg/m^2,intravenous bolus

5-FU 1200mg/m^2, continuous intravenous infusion over 24 h

Day 2 5-FU 1200mg/m^2 continuous intravenous infusion over 24 h

CAPOX/bevacizumab (3-weekly) regimen

Day 1 Bevacizumab 7.5mg/m^2, intravenous infusion over 15 min

Day 1 Oxaliplatin 130mg/m^2, intravenous infusion over 2–6 h

Days 1–14 Capecitabine 1700mg/m^{-2}, oral in 2 divided doses (followed by a 1-week break)

(Age ≥75 years, use starting dose oxaliplatin 100mg/m^2on day 1 and capecitabine 1300mg $m^{-2}day^{-1}$)

FOLFOX/bevacizumab (2-weekly regimen)

Day 1 Bevacizumab 5mg/kg,intravenous infusion over 10 min

Oxaliplatin 85mg/m^2,intravenous infusion over 2 h

Folinic acid 350mg,intravenous infusion over 2 h

5-FU 400mg/m^2, bolus

5-FU 1200mg/m^2, continuous infusion over 24 h

Day 2 5-FU 1200mg/m^2 continuous infusion over 24 h

FOLFIRI (2-weekly regimen)

Day 1 Irinotecan 180mg/m^2,intravenous infusion over 1 h

Folinic acid 350mg,intravenous infusion over 2 h

5-FU 400mg/m^2,intravenous bolus

5-FU 1200mg/m^2, continuous intravenous infusion over 24 h

Day 2 5-FU 1200mg/m^2, continuous intravenous infusion over 24 h

CAPIRI (3-weekly regimen)

Day 1 Irinotecan 200mg/m^2,intravenous infusion over 60 min

Days 1–14 Capecitabine 1700mg $m^{-2}day^{-1}$,oral in 2 divided doses followed by a 1-week break.

FOLFIRI/bevacizumab (2-weekly regimen)

Day 1 Bevacizumab 5mg/kg,intravenous infusion over 10 min

Irinotecan 180mg/m^2,intravenous infusion over 1 h

Folinic acid 350mg,intravenous infusion over 2 h

5-FU 400mg/m^2, intravenous bolus

5-FU 1200mg/m^2, continuous intravenous infusion over 24 h

Day 2 5-FU 1200mg/m^2, continuous infusion over 24 h

Irinotecan (3-weekly regimen)

Day 1 Irinotecan 350mg/m^2 (maximum,700mg),intravenous infusion over 1 h

Age >70 years, dose reduces to 250mg/m^2

Irinotecan/cetuximab (2-weekly regimen)

Day 1 Cetuximab 500mg/m^2, intravenous infusion over 2 h (subsequent infusions over 1 h)

Day 1 Irinotecan 180mg/m^2, intravenous infusion over 1 h

Cetuximab monotherapy (2-weekly regimen)

Day 1 Cetuximab 500mg/m^2, intravenous infusion over 2 h (subsequent infusions over 1 h)

Dose Modifications for FOLFOX

Toxicity NCI CTC grade	Therapeutic measures for toxicity	Initial doses (mg/m^2 course^{-1})		
		5-FU bolus 400	5-FU infusion 1200 × 2	Oxaliplatin 85
		Dose modifications (mg m^{-2}course^{-1})		
Neutrophils <1.0 (grade 3/4) (metastatic) See note below	Delay until > 1.0. Consider omitting bolus 5-FU	320 (consider omission)	960	65
Neutrophils<1.0 (grade 3/4) (adjuvant) See note below	Delay until > 1.0. Consider G-CSF for grade 4 neutropenia/febrile neutropenia	400	1200	85
Platelets 50–75 (grade 2)	Delay until grade 1 (≥75)	400	1200	85
Platelets <50 (grade 3/4) (see note below)	Delay until grade 1 (≥75) Consider omitting bolus 5-FU	320 (consider omission)	960	65
Stomatitis or Diarrhoea (grade 3)	Sucralfate, codeine,or loperamide, as indicated	320	960	85
Stomatitis or Diarrhoea recurrent (grade 3) or single (grade 4)	Sucralfate, codeine, or loperamide, as indicated	320	960	70
PPE (grade 3)	Emollients	320	960	None
Neuropathy		None	None	See below

In the metastatic setting, if severe toxicities recur despite dose modification,a second reduction can be made if clinically indicated. This is assessed on an individual basis.

In all cases, treatment should be delayed until recovery of toxicity to grade 2 (except thrombocytopenia, where recovery should be to grade 1 ≥75). Omission of the bolus of 5-FU can be considered in cases of neutropenia and thrombocytopenia.

In the adjuvant setting, if a patient develops grade 4 neutropenia, delay chemotherapy until recovery to grade 2 (neutrophils ≥1.0) and proceed with chemotherapy without any dose reductions (DRs) for subsequent cycles with granulocyte colony-stimulating factor support on days 7–11 post chemotherapy or pegylated granulocyte colony-stimulating factor(pegfilgrastim 6mg) 24 h following chemotherapy.

In cases of febrile neutropenia/neutropenic sepsis in patients on adjuvant treatment, subsequent cycles may require DR and/or the patient should be treated with prophylactic granulocyte colony-stimulating factor.

Mucositis or 'hand-foot'syndrome

In case of grade 3–4 toxicity, a reduction in dosage by 25% of both the 5-FU bolus and the continuous 5-FU infusion should be carried out for subsequent treatments.

Gastrointestinal toxicities

EVENTS	REDUCTION OF DOSE IN THE FOLLOWING CYCLE
Diarrhoea (grade 3/4) isolated or Diarrhoea + fever and/or neutropenia (grade 3/4)	First episode: reduce the irinotecan dose to 150 mg/m^2 and omit the bolus 5-FU dose on day 1 Second episode: in addition, reduce the oxaliplatin dose to 65 mg/m^2 and reduce the dose of continuous 5-FU by 25% Third episode: treatment discontinuation
Resistant diarrhoea ≥48 h despite high doses of loperamide	No reduction in the dose of irinotecan,oxaliplatin, or 5-FU after recovery,except in cases of diarrhoea grade 3/4, or diarrhoea + fever and/or neutropenia grade 3/4

EVENTS	REDUCTION OF DOSE TO FOLLOWING CYCLE
Febrile Neutropenia Neutropenia (grade 4) for more than 7 days Infection with concomitant neutropenia (grade 3/4)	First episode: reduce the irinotecan dose to 150 mg/m^2 and omit the bolus 5-FU dose on day 1 Second episode: in addition to the reduction in the irinotecan dose and omission of the bolus 5-FU dose, reduce the dose of oxaliplatin to 65 mg/m^2 Third episode: treatment discontinuation
Thrombocytopenia (grade 3/4)	First episode: reduce the oxaliplatin dose to 65 mg/m^2 and the continuous 5-FU dose by 25% Second episode: in addition, reduce the irinotecan dose to 150 mg/m^2 and the continuous 5-FU dose by an additional 25% Third episode: treatment discontinuation

Advise the administration of G-CSF for recurrent grade 3/4 neutropenia after a first-DR or after febrile neutropenia.

Haematological toxicities according to blood counts on day 15

NFS TO DAY 15	DELAY IN CYCLE	DOSE REDUCTION		
		Irinotecan	Oxaliplatin	LV/5-FU
Neutrophils ≥ 1.5 10^9/L and platelets ≥ 75 10^9/L	No delay in cycle	No DR		
Neutrophils < 1.5 10^9/L	Delay treatment until neutrophils ≥ 1.5 (until day 22 or day 29, if necessary). In case of non-recovery by day 29, stop treatment*	First episode: DR to 150 mg/m^2 Second episode: maintain the dose at 150 mg/m^2 Third episode: treatment discontinuation	First episode: no DR Second episode: DR to 60 mg/m^2 Third episode: treatment discontinuation	First episode: omit bolus 5-FU dose on day 1
Platelets < 75 10^9/L	Delay treatment until recovery (platelets ≥ 75 10^9/L). In case of non-recovery by day 29, stop treatment	First episode: no DR Second episode: DRto 150 mg/m^2 Third episode: treatment discontinuation	First episode: DR to 60 mg/m^2 Second episode: maintenance of the reduced dose Third episode: treatment discontinuation	First episode: DR of the bolus dose and of continuous infusion by 25%

Dose Modifications for FOLFIRI

Baseline/on treatment biochemistry assessments:

Renal function

CrCl >30mL/min: normal dose

CrCl 30mL/min: dose reduction of irinotecan by 50% and of 5-FU by 25%

Hepatic function:

Bilirubin 2.6 mg/dL: normal dose

Bilirubin 2.7–5.1 mg/dL: either withhold treatment or DR of irinotecan by 50%

Bilirubin >5.1 mg/dL: withhold treatment. Note that there is an increased risk of neutropenic sepsis in cases of abnormal liver function.

If patients have Gilbert's syndrome, DR of irinotecan by 25% should be considered.

Toxicity NCI CTC grade	Therapeutic measures for toxicity	Initial doses (mg/m^2/course)		
		5-FU bolus 400	5-FU infusion 1200 × 2	Irinotecan 180mg
		Dose modifications (mg m^{-2}course^{-1})		
Neutrophils (≥1.5)	Proceed	400	1200	180
Neutrophils 1.0–1.5	Delay until recovery to 1.5	400	1200	180
Neutrophils <1.0 (grade 3/4)	Delay until recovery to 1.5	320	960	135
Neutrophils <0.5 (grade 4) for >7 days, or second occurrence of neutropenia (grade 3/4) despite DR	Delay until recovery to 1.5	240 (consider omitting bolus)	720	90
Platelets ≥100	Proceed	400	1200	180
Platelets 50–100	Delay until recovery to 100	400	1200	180
Platelets 25–50 (grade 3), or second occurrence of 50–75 (grade 2)	Delay until recovery to 100	320 mg (consider omitting bolus)	960	135
Recurrent thrombocytopenia (grade 3/4)	Delay until recovery to 100	Omit bolus	720	90
Stomatitis or Diarrhoea (grade 3)	Sucralfate, codeine, or loperamide, as indicated	320	960	135
Stomatitis or Recurrent diarrhoea (grade 3)or first occurrence (grade 4)	Sucralfate, codeine, or loperamide, as indicated	320 (consider omitting bolus)	960	90
PPE (grade 3)	Emollient	320	960	None
Febrile neutropenia (grade 3/4)		320	960	135
If severe toxicities recur despite dose modifications,a second reduction can be made if clinically indicated, and this is assessed on an individual basis. If toxicity returns despite 2 DRs,FOLFIRI should be discontinued. In all cases, treatment should be delayed until recovery to grade 2 (except thrombocytopenia, where recovery should be to ≥100).				

Dose Modifications for Cetuximab

Allergic/hypersensitivity reaction

CTC Grade	Treatment
Grade 1 • Transient rash, drug-related fever <38 °C	• Decrease the cetuximab infusion rate by 50% and monitor closely for any worsening • The total infusion time for cetuximab at the weekly dose should not exceed 240 min
Grade 2 • Urticaria, drug-related fever of 38 °C and/ orasymptomatic bronchospasm	• Stop cetuximab infusion • Administer bronchodilators, oxygen, etc., as medically indicated • Resume infusion at 50% of the previous rate once the allergic/hypersensitivity reaction has resolved or decreased to grade 1 in severity and monitor closely for any worsening
Grade 3/4 • Grade 3: symptomatic bronchospasm requiring parenteral medication, with or without urticaria; hypersensitivity-related oedema, angioedema • Grade 4: anaphylaxis	• Stop cetuximab infusion immediately and disconnect infusion tubing from the patient • Administer epinephrine, bronchodilators, antihistamines, glucocorticoids, IV fluids, vasopressor agents, oxygen, etc., as medically indicated • Treatment must be withdrawn and the patient must not receive any further cetuximab treatment

Dose Modifications for Bevacizumab

Dose reductions are not made for bevacizumab-related toxicities. Any patient who develops any one of the following toxicities attributable to bevacizumab should not receive further bevacizumab:

- gastrointestinal perforation
- arterial thromboembolic events
- grade 3/4 haemorrhagic events
- symptomatic grade 4 venous thromboembolic events
- grade 4 hypertension (hypertensive crisis)
- grade 4 proteinuria (nephrotic syndrome)
- cardiac toxicity, including left ventricular systolic or diastolic dysfunction of grade 2–4 severity or decreased of left ventricular ejection fraction by >20%, arrhythmias of grade 3/4 severity, and myocardial ischaemia/infarction.

Management of Bevacizumab-Induced Hypertension:

Patients should be monitored for the development or worsening of hypertension via frequent blood pressure measurement. Angiotensin-converting-enzyme inhibitors and calcium channel blockers tend to be the most effective agents, but diuretics, -blockers, and β-blockers can also be used.

Grade 1 Hypertension:

Asymptomatic, transient (<24 h) increase by >20 mmHg (diastolic) or to >150/100 mmHg if previously within normal limits

Intervention not indicated.

Grade 2 Hypertension:

Recurrent or persistent (>24 h) or symptomatic increase by 20 mmHg (diastolic) or to >150/100 mmHg if previously within normal limits

Anti-hypertensive monotherapy may be indicated.

Once controlled to <150/100 mmHg, patients may continue bevacizumab therapy.

Grade 3 hypertension:

Requiring more than one anti-hypertensive agent or more intensive therapy than previously administered

Bevacizumab should be withheld for persistent or symptomatic hypertension and should be permanently discontinued if hypertension is not controlled.

Grade 4 hypertension: Life-threatening consequence (e.g. hypertensive crisis)

Occurrence of grade 4 hypertension should lead to permanent discontinuation of bevacizumab

Dose Modifications for Capecitabine

Haematological toxicity:

This is likely due to oxaliplatin and not capecitabine, but omit capecitabine in the following situations: Neutrophils <1.0, Platelets <75, If febrile neutropenia is present or the neutrophil levelis <0.5 or platelet count is <50, omit capecitabine until the neutrophil level is ≥ 1.0 and the platelet count is ≥ 75. Re-start capecitabine at 75% dose.

Non-haematological toxicity:

Toxicity grading according to NCICTC	During a course of therapy	Dose adjustment for the next cycle (% of the starting dose)
Grade 1	Maintain dose level	Maintain dose level
Grade 2		
First appearance	Interrupt until resolved to grade 0–1	100%
Second appearance	Interrupt until resolved to grade 0–1	75%
Third appearance	Interrupt until resolved to grade 0–1	50%
Fourth appearance	Discontinue treatment permanently	
Grade 3		
First appearance	Interrupt until resolved to grade 0–1	75%
Second appearance	Interrupt until resolved to grade 0–1	50%
Third appearance	Discontinue treatment permanently	
Grade 4		
First appearance	Discontinue permanently or If the physician deems it to be in the patient's best interest to continue, interrupt until resolved to grade 0–1	50%

All patients should be prescribed treatment for symptoms, such as loperamide, sucralfate, and emollients for diarrhoea, stomatitis, and hand-foot syndrome, respectively.

Renal function: For creatinine clearance 30–50mL/min the dose of capecitabine should be reduced by 25%.

Liver function: Capecitabine can cause an increase in bilirubin and liver transaminases. This is usually mild and of no clinical significance. However, if the bilirubin level increases to >3× normal or aspartate aminotransferase/alanine aminotransferase levels increase to >2.5× normal,capecitabine should be withheld until the bilirubin level is <2.5× upper normal limit and alanine aminotransferase is <2.5× upper normal limit, at which point treatment, can recommence without DR. If patients (with liver metastasis) have abnormally elevated liver transaminase levels prior to commencing capecitabine, only changes in the bilirubin level should be taken into account.

Appendix E: Radiotherapy Planning

(A) Patient positioning

The patient may be positioned supine with the hands on the chest or prone with the hands above the head. A belly board may be used in the prone position.

(B) Immobilization

The patient is immobilized using a customized thermoplastic immobilization device in the intended treatment position.

(C) CT simulation with fiducials (preoperative radiation): Three-dimensional conformal therapy

CT simulation for treatment planning is performed in the treatment position with the immobilization device in situ. The planning CT is a contrast-enhanced CT scan with orallyand intravenously administered contrast. The following steps are followed:

1. The patient is asked to void his/her bladder. Oral contrast (1 L water with 30 mL oral contrast)is administered over 30–45 min, 90 min before CT simulation. No bladder voiding is allowed after the oral contrast has been administered.
2. The patient is placed on the couch of the CT scanner
3. A 3-mm copper marker is placed at the anal verge and secured with a thin tape
4. The immobilization device is applied
5. Three copper fiducial markers are placed in a single plane at the level of a fixed bony landmark (e.g. 2 at the iliac crests on either side and 1 on the anterior abdomen) using the CT lasers
6. A scout film is taken
7. Contrast is injected intravenously (2 mL/kg body weight; 100 mL maximum) either manually or using an injector syringe. When manually injected, the scan is taken immediately after the entire contrast is injected from the cranial to caudal direction. When using the injector syringe, the rate of contrast flow is 2.7–3.2 mL/s depending on the IV cannula, with a scan delay of 15 s followed by scanning in the cranial to caudal direction.
8. The scan thickness is usually 3 mm throughout the scan

(D) CT simulation with fiducials (postoperative radiation): Three-dimensional conformal therapy

CT simulation for treatment planning is performed with the patient in the treatment position and the immobilization device in situ. The planning CT is a contrast enhanced CT scan with orallyand intravenously administered contrast. The following steps are followed:

1. The patient is asked to void his/her bladder. Oral contrast (1 L water with 30 mL oral contrast)is administered over 30–45 min, 90 min before CT simulation. No bladder voiding is allowed after oral contrastadministration.
2. The patient is placed on the couch of the CT scanner
3. A copper wire is taped to the APR scar or a 3-mm copper marker is placed at the anal verge and secured with a thin tape

4. The immobilization device is applied.
5. Three copper fiducial markers are placed in a single plane at the level of a fixed bony landmark (e.g. 2 at the iliac crests on either side and 1 on the anterior abdomen) using the CT lasers.
6. A scout film is taken
7. Contrast is injected intravenously (2 mL/kg body weight; 100 mL maximum) either manually or using an injector syringe. When manually injected, the scan is taken immediately after the entire contrast is injected from the cranial to caudal direction. When using the injector syringe, the rate of contrast flow is 2.7–3.2 mL/s depending on the IV cannula, with a scan delay of 15 s followed by scanning in the cranial to caudal direction.
8. The scan thickness is usually 3 mm throughout the scan

(E) Transfer to the treatment planning system:

The scans are exported through Digital Imaging and Communications in Medicineafter image reconstruction and imported into the planning system.

(F) Contouring guidelines (preoperative radiation): Clinical target volume delineation (CTV) (level 5)[73].

Three nodal CTVs are defined:

1. CTVA: internal iliac, pre-sacral,and perirectal nodal stations
2. CTVB: external iliac nodal stations
3. CTVC: inguinal nodal stations

For rectal cancer, in most cases, CTVA would be the only volume to receive elective radiation. However,for certain presentations (e.g. extension into genitourinary structures and extension to the perianal skin) one could consider adding the external iliac (CTVB) and even the inguinal regions (CTVC).

Three anatomical sites of the pelvis are considered for contouring:

Lower pelvis: The caudad extent of this elective target volume should be a minimum of 2 cm caudad to the gross disease, covering the entire mesorectum to the pelvic floor. Unless there is radiographic evidence of extension into the ischiorectal fossa, extension of the CTVA does not need to extend more than 5 mm beyond the levator muscles. For very advanced anal or rectal cancers extending through the mesorectum or the levators add a 1–2 cm margin up to the bone wherever the cancer extends beyond the usual compartments.

Mid pelvis: The posterior and lateral margins of CTVA should extend to the lateral pelvic sidewall musculature or, where absent, the bone. Anteriorly, CTVA should extend for 1 cm into the posterior bladder to account for day-to-day variation in bladder position. Include at least the posterior portion of the internal obturator vessels (which lie between the external and internal iliac crests in the mid pelvis) with CTVA.

Upper pelvis: The recommended superior extent of the perirectal component of CTVA is at the rectosigmoid junction or 2 cm proximal to the superior extent of macroscopic disease in the rectum/perirectal nodes, whichever is more cephalad. The most cephalad extent of CTVA will be higher than the perirectal component in order to properly cover the internal iliac and pre-sacral regions. The most cephalad aspect of CTVA should be at the bifurcation of the common iliac vessels into the external and internal iliac vessels (approximate bony landmark: sacral promontory).