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edited by
Andrés Cervantes
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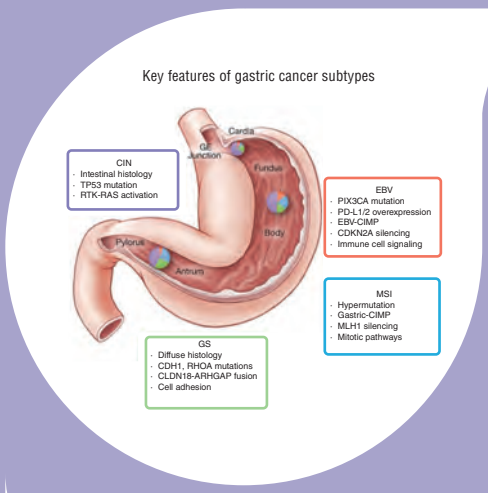
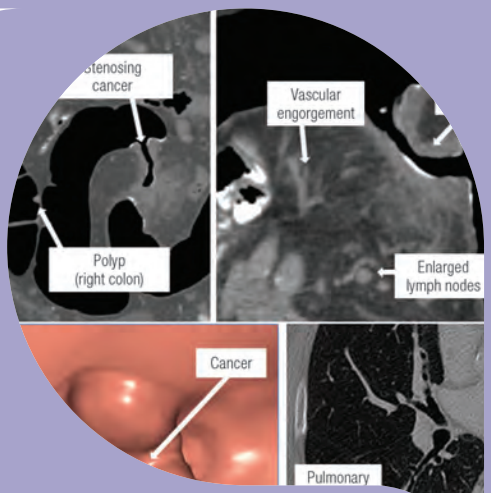
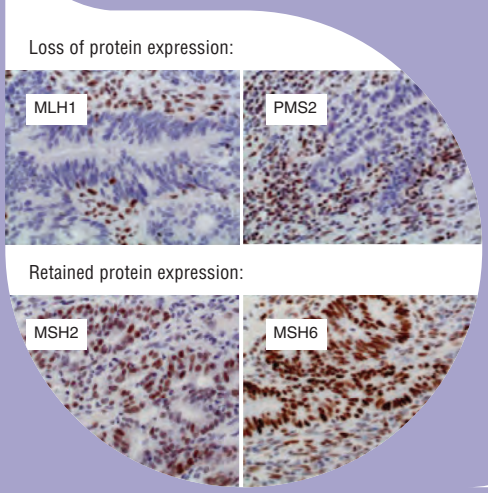
GASTROINTESTINAL TRACT TUMOURS

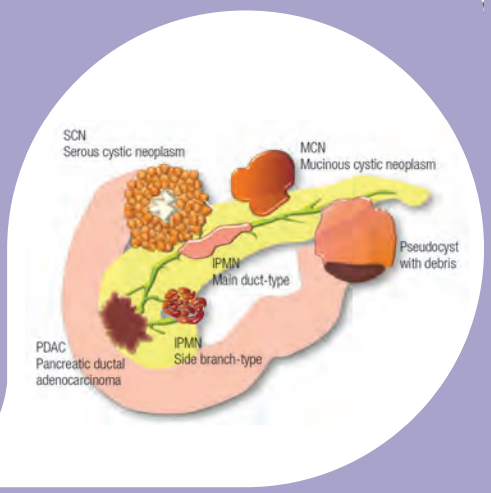
SECOND EDITION

ESSENTIALS *for* CLINICIANS









ESMO Press

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Gastrointestinal Tract Tumours Essentials for Clinicians

Second edition

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Essentials for Clinicians

Second edition

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Preface

Few professions are more challenging than medicine, and, particularly, oncology. The enormous advances in molecular genetics, biology, imaging and new drug development, as well as their integration into a multidisciplinary care strategy, make our profession a continuously changing field. In this evolving scenario, this second edition of ESMO's *Gastrointestinal Tract Tumours: Essentials for Clinicians* comes to help any oncologist or oncology-related professional to stay close to optimal clinical care. In line with past publications, this edition has been designed as a "must-have" educational tool to serve and guide oncologists in training and medical students – the future of our profession. By providing a comprehensive update on some of the very latest discoveries within the gastrointestinal (GI) field, spanning a wide range of GI malignancies and, indeed, various perspectives, it will also be of general appeal to colleagues involved in cancer diagnosis or care working across other specialities.

Maintaining the original structure, this second edition is organised in two main sections: "*What every oncologist should know"* and *"More advanced knowledge"*. It includes excellent contributions from internationally renowned leaders in oncology, tackling the "everything you need to know" from the expanding understanding of the molecular basis of GI cancers, diagnosis, staging, tracking of response and interventional radiology of GI tumours, to the latest updates from leading physicians–scientists in oesophageal, gastric, colon, rectal, pancreatic and hereditary colorectal cancer. We sincerely thank all contributors who made this edition possible.

The second section covers essential developments exploring the biology of GI cancer development, treatment of oligometastatic disease, the new opportunities that promise to advance our understanding, molecular subtyping, and tailored treatment of these diseases, as well as an "under the lens" look at rarer GI tumours.

Importantly, we are now in an era of precision medicine against cancer, driven by a multidisciplinary approach, treatment and care, and resources aimed at crucially "lightening the load" for clinicians. Therefore, medical oncologists, researchers and other cancer professionals should seek to report and exchange knowledge on a wide range of topics from different perspectives across tumour types. A final chapter on emerging treatment strategies and new drugs has also been added to fulfil this goal.

It is thanks to the support, dedication and care of the ESMO Publishing department and particularly to Aude Galli and Nicki Peters that you can enjoy this book. It is up to the readers to assess if this book is fulfilling their needs. Our effort and our ambition have been to offer you an educational and pragmatic tool to make real the ESMO theme: Good Science, Better Medicine and Best Practice.

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Andrés Cervantes is Professor of Medicine at the University of Valencia, Spain, and serves as Head of the Department of Medical Oncology at the University Hospital. He is also scientific director of the Institute of Health Research Incliva, in Spain. His main areas of research and clinical interest are gastrointestinal cancer and new drugs development. He is also responsible for a translational research laboratory, mainly working in liquid biopsies and in the molecular classification of gastrointestinal malignancies, as well as in the mechanisms of resistance for HER2 blockade in gastro-oesophageal adenocarcinomas.

Professor Cervantes is the author of more than 300 research articles in peer-reviewed journals. He has been serving the European Society for Medical Oncology (ESMO) in different working groups and committees since 2000 and is currently President-Elect (2020-2022). He is an Associate Editor for Gastrointestinal Cancer in *Annals of Oncology.*

Marcia Hall, MBBS, PhD

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Professor Hall qualified in 1986 from Guy's Hospital in London, UK. She was appointed as a consultant in medical oncology at Mount Vernon Cancer Centre (MVCC) in 1999. Her main area of interest is gynaecological cancers, but she also treated patients with colorectal cancers until 2020.

She is very research-active, being Principal Investigator of many clinical trials at MVCC and Chief Investigator for the UK in three trials currently.

She completed her PhD at the Imperial Cancer Research Fund (now CRUK), working on cyclins and kinases. Since 2015 she has collaborated with colleagues at Brunel University, London. The main focus of her work is the identification and purpose of circulating cancer-associated cells. She was appointed Professor of Translational Oncology in 2018.

Her professional aims are to care effectively for her patients with cancer, using evidence-based medicine where available and offering research trials of novel drugs and/or techniques.

Michalis V. Karamouzis, MD, PhD

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Michalis Karamouzis is currently Associate Professor at the Medical School of the University of Athens, Greece. He is a medical oncologist specialised in treating patients with gastrointestinal cancers. He has also set up a Molecular Oncology Unit in his institution, where his team has been working on cell tissue cultures and animal models.

Professor Karamouzis has authored more than 120 publications in international peer-reviewed journals, achieving up to now more than 3700 citations, with an H-index of 37. He has also served as a reviewer for many peer-reviewed international journals and as evaluator for several scientific project proposals, both at national and international level.

Professor Karamouzis has been a member of the European Society for Medical Oncology (ESMO) since January 2004. In 2011 and 2012 he chaired the ESMO Young Oncologists Committee; currently he holds positions in various ESMO committees and groups, such as the ESMO Educational Publications Working Group.

Josep Tabernero, MD, PhD

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Josep Tabernero holds MD and PhD degrees from the Universitat Autònoma de Barcelona, Spain, and is currently Head of the Medical Oncology Department at the Vall d'Hebron University Hospital, Director of the Vall d'Hebron Institute of Oncology (VHIO) and Professor of Medicine at UVic-UCC (Universitat de Vic – Universitat Central de Catalunya).

Professor Tabernero serves on the Editorial Boards of various top-tier journals including *Annals of Oncology, ESMO Open, Cancer Discovery, Clinical Cancer Research, Cancer Treatment Reviews,* and *Nature Reviews Clinical Oncology*. He has (co-) authored around 500 peer-reviewed papers with an H-Index of 95.

He was the President (2018-2019) and is currently the Past President (2020-2022) of the European Society for Medical Oncology (ESMO). He is also member of the American Association for Cancer Research (AACR) and the American Society of Clinical Oncology (ASCO). He has been a member of the Educational and Scientific Committees of various international meetings, among which ESMO, ASCO and AACR meetings.

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Abbreviations

^{18}FDG-PET	^{18}F-Fluorodeoxyglucose-positron emission tomography
5-FU	5-fluorouracil
AASLD	American Association for the Study of Liver Diseases
ADEX	Aberrantly differentiated endocrine exocrine
AE	Adverse event
AEG	Adenocarcinoma of the oesophagogastric junction
AFAP	Attenuated familial adenomatous polyposis
AFP	Alpha foetoprotein
AJCC	American Joint Committee on Cancer
ALK	Anaplastic lymphoma kinase
AMP	Ampullary (ampulla of Vater) cancer
AP	Adenomatous polyposis
APC	Adenomatous polyposis coli
APR	Abdominoperineal resection
ASC	Active symptom control
ASCC	Anal squamous cell carcinoma
AUC	Area under the curve
BCLC	Barcelona Clinic Liver Cancer
BE	Barrett's oesophagus
bev	Bevacizumab
BMI	Body mass index
BSC	Best supportive care
BTC	Biliary tract cancer
CAPOX	Capecitabine/oxaliplatin
CCA	Cholangiocarcinoma
CDH1	Cadherin
CEA	Carcinoembryonic antigen
CEA-TCB	Carcinoembryonic antigen T-cell bispecific
CgA	Chromogranin A
ChT	Chemotherapy
CIMP-H	CpG island hypermethylation phenotype-high
CIN	Chromosomal instability
CM	Contrast medium
CMS	Consensus molecular subtype
CPS	Combined positive score
CR	Complete response
CRC	Colorectal cancer
CRM	Circumferential resection margin
CRT	Chemoradiotherapy
CT	Computed tomography
CTC	CT colonography
ctDNA	Circulating tumour DNA
CTLA-4	Cytotoxic T-lymphocyte antigen 4
dCCA	Distal cholangiocarcinoma
DCF	Docetaxel/cisplatin/5-FU
DDR	DNA damage repair
DFS	Disease-free survival
dMMR	Deficient mismatch repair
DP	Duodenopancreatectomy
DRE	Digital rectal examination
DWI	Diffusion-weighted imaging
EASL	European Association for the Study of the Liver
EBV	Epstein-Barr virus
eCCA	Extrahepatic cholangiocarcinoma
E-CDH	Epithelial-cadherin
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EMVI	Extramural venous invasion
ERCP	Endoscopic retrograde cholangiopancreatography
ESMO	European Society for Medical Oncology
EUS	Endoscopic ultrasound
FAP	Familial adenomatous polyposis
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FGFR	Fibroblast growth factor receptor
FIGC	Familial intestinal gastric cancer
FISH	Fluorescent *in situ* hybridisation
FLOT	5-FU/leucovorin/oxaliplatin/docetaxel
FOBT	Faecal occult blood test
FOLFIRI	Leucovorin/5-FU/irinotecan
FOLFIRINOX	Leucovorin/5-FU/irinotecan/oxaliplatin
FOLFOX	Leucovorin/5-FU/oxaliplatin
FOLFOXIRI	Leucovorin/5-FU/oxaliplatin/irinotecan
FTD/TPI	Trifluridine/tipiracil
GBC	Gallbladder cancer
gBRCAm	Germline *BRCA1/BRCA2* mutation
GC	Gastric cancer
GEJ	Gastro-oesophageal junction
GEP	Gastroenteropancreatic
GI	Gastrointestinal
GIST	Gastrointestinal stromal tumour
GITSG	Gastrointestinal Tumor Study Group
GORD	Gastro-oesophageal reflux disease
GWAS	Genome-wide association study
H. pylori	*Helicobacter pylori*
HBV	Hepatitis-B virus
HCC	Hepatocellular carcinoma
hCCA	Perihilar cholangiocarcinoma
HDGC	Hereditary diffuse gastric cancer
HER2	Human epidermal growth factor receptor 2
HFSR	Hand-foot-skin reaction
HIAA	Hydroxy-indoleacetic acid
HIV	Human immunodeficiency virus
HNPCC	Hereditary non-polyposis colorectal cancer
HPV	Human papillomavirus
HR	Hazard ratio
iCCA	Intrahepatic cholangiocarcinoma
ICD-O	International Classification of Diseases for Oncology
ICGC	International Cancer Genome Consortium
ICI	Immune checkpoint inhibitor
IDH	Isocitrate dehydrogenase
IHC	Immunohistochemistry
IM	Intestinal metaplasia
IMRT	Intensity-modulated radiotherapy
ITT	Intention-to-treat
JAK2	Janus Kinase 2
KPS	Karnofsky performance status
LA	Locally advanced
LAR	Long-acting release
LAT	Local ablative treatment
LCRT	Long-course radiotherapy
LN	Lymph node
LT	Liver transplantation
MAP	*MUTYH*-associated polyposis
mCRC	Metastatic colorectal cancer
MDCT	Multidetector-row computed tomography
MDT	Multidisciplinary team
MEN-1	Multiple endocrine neoplasia type 1
mFOLFIRINOX	Modified FOLFIRINOX
mIDH1	Mutant IDH1
miRNA	MicroRNA
MMR	Mismatch repair
MNX1	Motor neurone and pancreas homeobox 1
mOS	Median overall survival
mPDAC	Metastatic pancreatic ductal adenocarcinoma
MRCP	Magnetic resonance cholangiopancreatography
MRF	Mesorectal fascia
MRI	Magnetic resonance imaging
MSI	Microsatellite instability
MSI-H	Microsatellite instability-high
MSS	Microsatellite stable
mTOR	Mammalian target of rapamycin
N	Node
nal	Nanoliposomal
NEC	Neuroendocrine carcinoma
NEN	Neuroendocrine neoplasm
NET	Neuroendocrine tumour
NTRK	Neurotrophic tyrosine receptor kinase
OAC	Oesophageal adenocarcinoma
OC	Oesophageal cancer

OGJ	Oesophagogastric junction
OGJC	Oesophagogastric junction cancer
OMD	Oligometastatic disease
ORR	Overall response rate
OS	Overall survival
OSCC	Oesophageal squamous cell carcinoma
PanIN	Pancreatic intraepithelial neoplasia
PARP	Poly (adenosine diphosphate–ribose) polymerase
PC	Pancreatic cancer
pCR	Pathological complete response
PD-1	Programmed cell death protein 1
PDAC	Pancreatic ductal adenocarcinoma
PD-L1	Programmed death-ligand 1
PET	Positron emission tomography
PDX1	Pancreatic and duodenal homeobox 1
PFS	Progression-free survival
pMMR	Proficient mismatch repair
PPI	Proton pump inhibitor
PRRT	Peptide receptor radionuclide therapy
PS	Performance status
PSC	Primary sclerosing cholangitis
PTC	Percutaneous transhepatic cholangiography
pTNM	Pathological Tumour, Node, Metastasis
QoL	Quality of life
R0	Tumour-free resection margins
RECIST	Response Evaluation Criteria in Solid Tumours
RFA	Radiofrequency ablation
RFS	Relapse-free survival
RHO	RAS-homologous
RT	Radiotherapy
SBA	Small bowel adenocarcinoma
SBC	Small bowel cancer
SBRT	Stereotactic body radiotherapy
SCC	Squamous cell carcinoma
SCRT	Short-course radiotherapy
SMA	Superior mesenteric artery
SNP	Single nucleotide polymorphism
T	Tumour
TACE	Transarterial chemoembolisation
TARE	Transarterial radioembolisation
TCGA	The Cancer Genome Atlas
T-DM1	Trastuzumab emtansine
TEM	Transanal endoscopic microsurgery
TGF-β	Transforming growth factor beta
TKI	Tyrosine kinase inhibitor
TME	Total mesorectal excision
TNM	Tumour, Node, Metastasis
TRG	Tumour regression grade
TRK	Tyrosine receptor kinase
UICC	Union for International Cancer Control
ULN	Upper limit of normal
VEGFR2	Vascular endothelial growth factor receptor 2
VHL	von Hippel-Lindau
WHO	World Health Organization

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Andrés Cervantes, Marcia Hall, Michalis Karamouzis and Josep Tabernero

What every oncologist should know

1 Epidemiology, risk factors and pathogenesis

Epidemiology of gastrointestinal tract tumours

Overall, tumours of the gastrointestinal (GI) tract (International Classification of Diseases for Oncology [ICD-O] codes C15-C26) represent about one quarter of all cancers diagnosed in Europe.

In Europe, about 900 000 new cases of tumours of the GI tract were diagnosed in 2018, out of the more than 3.5 million new cases of cancer overall.

Half of GI tract tumours are colorectal cancers (CRCs), followed by cancers of the stomach and pancreas (14% each), and finally liver and oesophageal cancers.

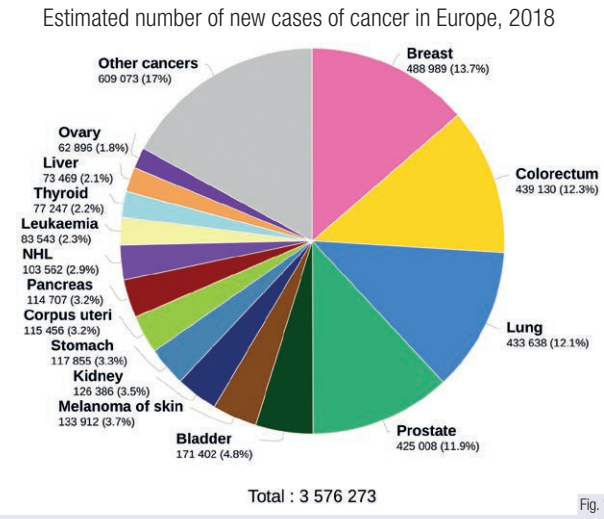


Fig. 1.1

NHL, non-Hodgkin lymphoma.

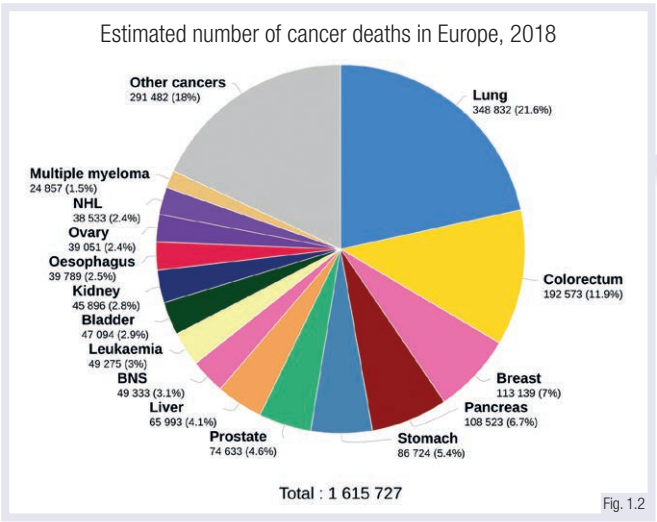


Fig. 1.2

BNS, brain, central nervous system; NHL, non-Hodgkin lymphoma.

GI cancers account for almost one third of all cancer deaths, or about 600 000 deaths out of more than 1.6 million cancer deaths (Europe, 2018).

This relatively high proportion of deaths compared with incidence in GI cancers is due to the fact that these tumours include some cancers with poor prognosis.

CRC deaths account for ~40% of all GI cancer deaths, followed by pancreatic and stomach cancers (21% and 17%, respectively).

Among GI tumours, only those from the colon and rectum have a relatively good prognosis. The 5-year survival is slightly over 60% (average for Europe).

Other tumours within this group show relatively poor prognosis, with 5-year survival below 20%, including pancreatic cancer, where 5-year survival is still below 10%.

CRC survival has increased by ~5% (patients diagnosed in 2010-2014 compared with 2000-2007), but improved only by 1%-1.5% for the remaining GI tumours in the same period.

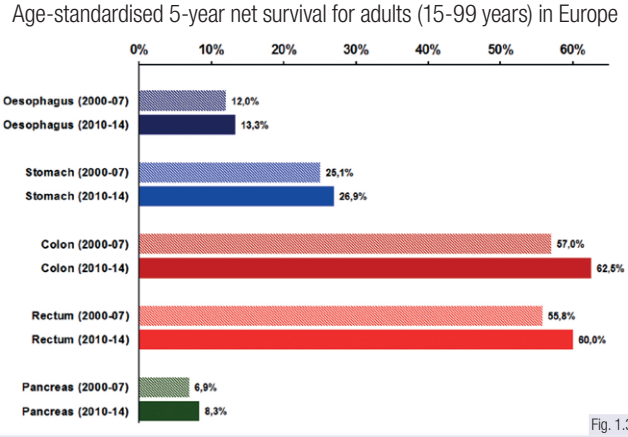


Fig. 1.3

REVISION QUESTIONS

1. What proportion of all cancers diagnosed in Europe represents tumours of the GI tract?
2. Across all tumour types, why is the mortality from GI tumours higher than the incidence?
3. Which tumours of the GI tract have a poor prognosis, according to their survival rates?

Oesophageal cancer

Oesophageal cancer (OC) comprises two distinct diseases: oesophageal squamous cell carcinoma (OSCC) and oesophageal adenocarcinoma (OAC), each with different risk factors and incidence trends.

OC is the eighth most common cancer worldwide. Whereas OSCC incidence is declining, the incidence of OAC is rising in developed countries, such as Canada, USA (White population) and Scotland.

Latin American countries, Asia, and Black populations of the USA have the highest incidence of OSCC, particularly in the 'OC belt' (Northern China to Northern Iran).

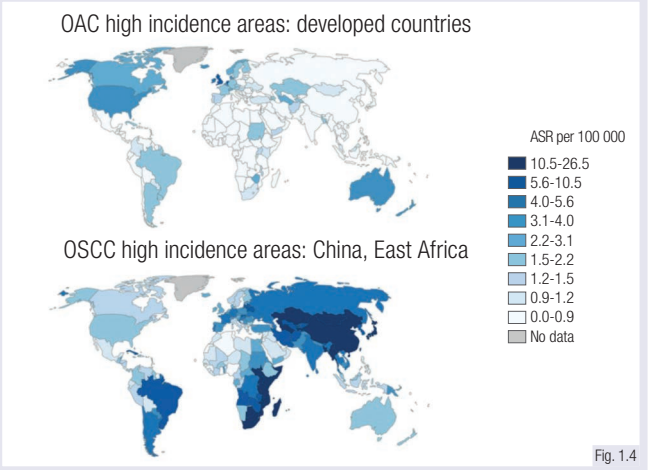
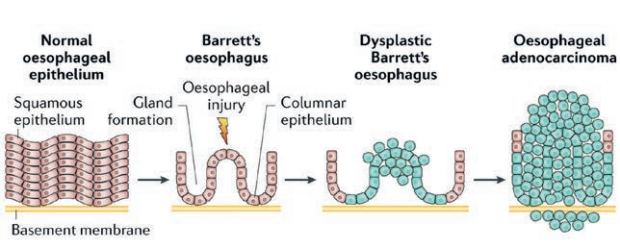


Fig. 1.4

ASR, age-standardised rate; OAC, oesophageal adenocarcinoma; OSCC, oesophageal squamous cell carcinoma.



Development and progression of Barrett's oesophagus. Oesophageal injury, mainly due to gastrointestinal reflux, may lead to Barrett's oesophagus, a lesion that is characterised by replacement of the normal squamous epithelium by columnar epithelium, termed intestinal metaplasia. This pre-malignant condition might progress to dysplasia and oesophageal adenocarcinoma, which may invade the submucosa.

Fig. 1.5

Precursor dysplastic lesions are detectable for OAC/OSCC. Repeated exposure to high-temperature drinks or gastro-oesophageal reflux disease (GORD) may cause inflammation.

Barrett's oesophagus (BE) is a probable intermediate stage between GORD and OAC, in which squamous cells are replaced by columnar epithelial cells, due to chronic injury.

OACs arise from glandular cells at the lower end of oesophagus. OSCCs arise from epithelial cells that are exposed to irritation and carcinogens in foods and drinks.

Smoking, low fruit and vegetable intake and high intake of processed meat increase the risk of both OSCC and OAC. Alcohol consumption only increases the risk of OSCC.

Hot beverages increase the risk of both. Human papillomavirus (HPV) 16 infection may increase the risk of OSCC, while *Helicobacter pylori (H. pylori)* infection may reduce the risk of OAC. Obesity, GORD and BE increase the risk of OAC.

Genome-wide association studies (GWAS) of OSCC in Chinese populations showed associations with different single nucleotide polymorphisms (SNPs). The Cancer Genome Atlas (TCGA) showed genomic amplification of different chromosomes.

Several factors are or may be associated with risk of OSCC and OAC

Factors	OSCC Increases risk	OAC Decreases risk	OAC Increases risk
Tobacco	Smoking		Smoking
Dietary factors	Low fruit intake Low vegetable intake High alcohol intake High intake of processed meat		Low fruit intake Low vegetable intake High intake of processed meat
Infectious agents	HPV 16	*H. pylori* infection	
Hot beverages	Tea, mate		Tea, mate
Body mass index			
Other		Physical activity (1)	Gastro-oesophageal reflux disease Barrett's oesophagus

(1) OAC and OSCC combined.
HPV, human papillomavirus; OAC, oesophageal adenocarcinoma; OSCC, oesophageal squamous cell carcinoma.

Fig. 1.6

REVISION QUESTIONS

1. Are there geographical differences in the distribution of the two histological types of OC?
2. Are there differences in the risk factors associated with OAC and OSCC?
3. Is alcohol consumption associated with the risk of both OAC and OSCC?

Gastric cancer

The high-risk areas for gastric cancer (GC) are Japan, China, Eastern Europe and certain countries in Latin America. Low-risk areas are North America, India, some Western European countries and most of Africa.

About 70% of cases occur in less developed countries, although in Europe there are high-risk areas in Portugal, central areas of Spain and Italy, and Eastern European countries.

Incidence rates have been declining worldwide, except for cardia GC, which has shown an increase in some developed countries, though it is still the fifth most common cancer worldwide.

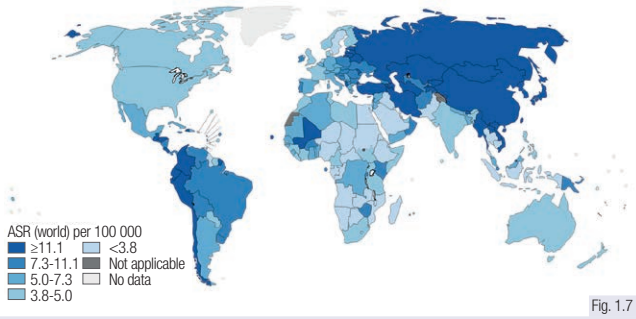


Fig. 1.7

ASR, age-standardised rate.

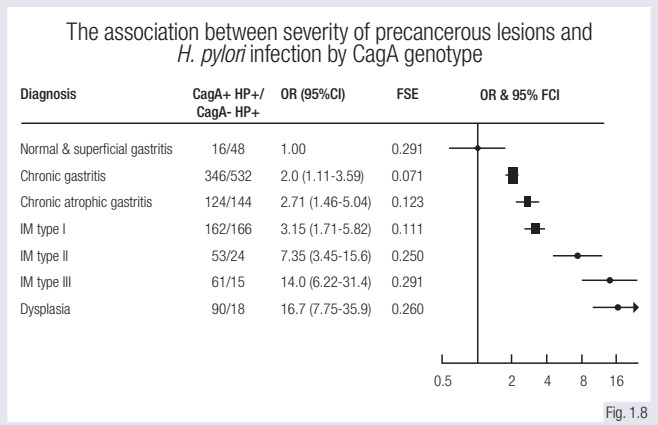


Fig. 1.8

CagA, cytotoxin-associated gene A; CI, confidence interval; FCI, floating confidence interval; FSE, floating standard error on a log scale; *H. pylori*, *Helicobacter pylori*; HP+, *H. pylori*-positive; IM, intestinal metaplasia; OR, odds ratio.

A multifactorial and multistep model of gastric carcinogenesis is currently accepted, with different factors involved at different stages in the cancer process.

The GC development process undergoes a cascade from normal mucosae, through gastritis to atrophic gastritis, complete intestinal metaplasia (IM), incomplete IM, dysplasia and GC.

Pathogenesis differs between cardia and non-cardia GC. *H. pylori* is probably a necessary condition for non-cardia GC, but it is not associated with cardia GC.

Several factors are, or may be, associated with either a decreased or increased risk of GC, including infections, tobacco use, dietary factors, high alcohol intake and body mass index (cardia GC).

SNPs (involved in inflammatory responses, activation of chemical compounds, DNA repair) might modify the effect of environmental exposures and could explain geographical variations.

Germline mutations in *CDH1* and *CTNNA1* cause the rare (1%-3%) familial form of diffuse GC. GWAS in Asia have found a significant association with several genes, the most relevant being *PSCA* and *MUC1*.

Environmental, dietary and lifestyle factors that are or may be associated with gastric cancer risk

Factors	Decreases risk	Increases risk
Infectious factors		*H. pylori* (non-cardia) (virulence factors: GagA, VacA s1, VacA m1, babA2, CagA EPIYA-C) Epstein-Barr virus (EBV)
Tobacco		Smoking
Dietary factors	Green-yellow vegetables Allium vegetables Fruits and citrus fruits Flavonoid Green tea	Salt and salty foods Smoked foods Pickled foods Nitrosamines and nitroso-compounds Alcohol (heavy intake) Red and processed meat (non-cardia) Haem iron (from fresh meat) Grilled meat and fish
Body mass index		Obesity (cardia)
Hormones	Oestrogens (female)	
Anti-inflammatory drugs	Aspirin use	
Occupational exposure		Industrial chemical exposure (rubber, coal mine)
Blood group		Blood group A

H. pylori, *Helicobacter pylori*.

Fig. 1.9

REVISION QUESTIONS

1. Which are the high-risk areas for GC in Europe?
2. Do you agree that *H. pylori* infection is probably a necessary condition of non-cardia GC?
3. What are the main factors that increase and decrease the risk of GC?

Colorectal cancer

CRC is the third most common cancer worldwide, and the second leading cause of cancer death (1.8 million cases and 881 000 deaths in 2018).

Incidence and mortality rates vary geographically, with the highest rates in the most developed countries. These rates are ~25% lower in women than in men.

An overall decline or stabilisation in the risk of CRC has been noted in high-income countries. In contrast, a worrying rise has been observed in patients <50 years old.

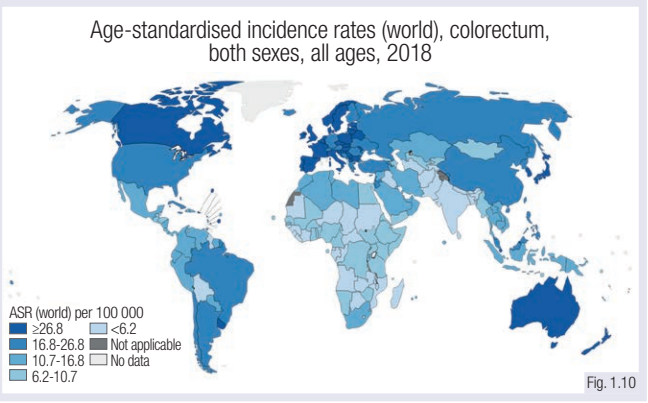


Fig. 1.10

ASR, age-standardised rate.

Lifestyle and environmental factors associated with colorectal cancer risk

Factors	Increases risk	Decreases risk
Body fatness	Both general and abdominal obesity, as marked by body mass index, waist circumference and waist-to-hip ratio	
Physical activity		All types (including occupational and recreational). Restricted to colon; no clear effect for rectal cancer
Processed meat	18% increased risk for each 50 grams per day (IARC group 1 of carcinogens)	
Alcoholic drinks	For alcohol intakes above 30 grams per day (two drinks)	
Tobacco use	Increased risk with cigarettes/day and duration in current smokers; decreased risk in former smokers	
Medication		Long-term use of aspirin and NSAIDs; hormonal therapy in postmenopause
Other diseases	Inflammatory bowel disease (Crohn's disease, ulcerative colitis)	
Dietary factors (evidence less convincing than for processed meat)	Red meat	Dietary fibre, wholegrains, dairy products (all types), calcium intake (dietary and/or supplements)

Fig. 1.11

IARC, International Agency for Research on Cancer; NSAID, non-steroidal anti-inflammatory drug.

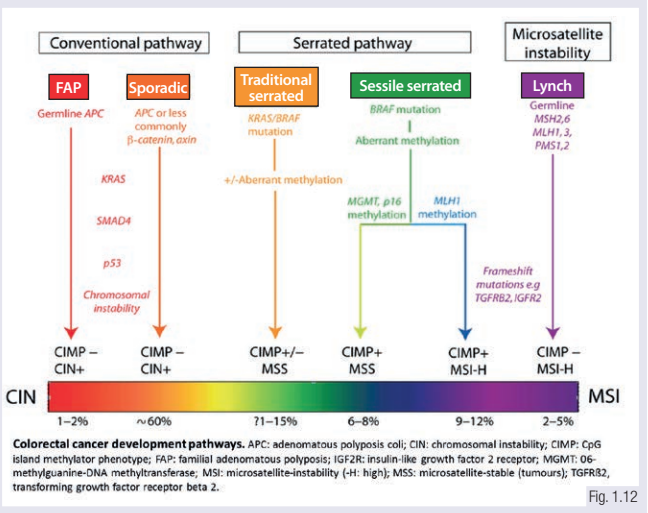
10%-20% of CRCs occur in people with positive family history, with varying risk depending on the number and degree of affected relatives.

About 5%-7% of cases are affected by hereditary conditions. The two major ones are hereditary non-polyposis colorectal cancer (HNPCC) and familial adenomatous polyposis (FAP).

Obesity, lack of physical activity and some dietary factors are the major lifestyle factors contributing to CRC risk, but the underlying causative processes are not defined.

CRC exemplifies stepwise progression as it develops initially as a benign precursor lesion (adenoma), which can progress to an invasive lesion (adenocarcinoma).

The lesion arises from an intestinal clonogenic precursor cell through the accumulation of multiple genetic abnormalities. There are three major precursor lesion pathways: the chromosomal instability (conventional) pathway (~80%), the microsatellite instability pathway (2%-7%) and the sessile serrated (CpG island methylator, ~15%).



Colorectal cancer development pathways. APC: adenomatous polyposis coli; CIN: chromosomal instability; CIMP: CpG island methylator phenotype; FAP: familial adenomatous polyposis; IGF2R: insulin-like growth factor 2 receptor; MGMT: O6-methylguanine-DNA methyltransferase; MSI: microsatellite-instability (-H: high); MSS: microsatellite-stable (tumours); TGFR32, transforming growth factor receptor beta 2.

Fig. 1.12

REVISION QUESTIONS

1. What are the trends in CRC risk in high-income countries?
2. What are the most important modifiable risk factors of CRC?
3. Which is the most common precursor lesion pathway of CRC?

Pancreatic cancer

Cancer of the pancreas is the 12th most common cancer worldwide and the 7th most common cause of cancer death. About 460 000 cases and 430 000 deaths were estimated in 2018.

The risk is higher in men than in women and increases with age; it is mainly a disease of high-income countries. Trends in incidence have remained fairly stable over time.

The early stages do not usually produce symptoms, so the disease is generally advanced when it is diagnosed, which accounts for relatively low survival rates.

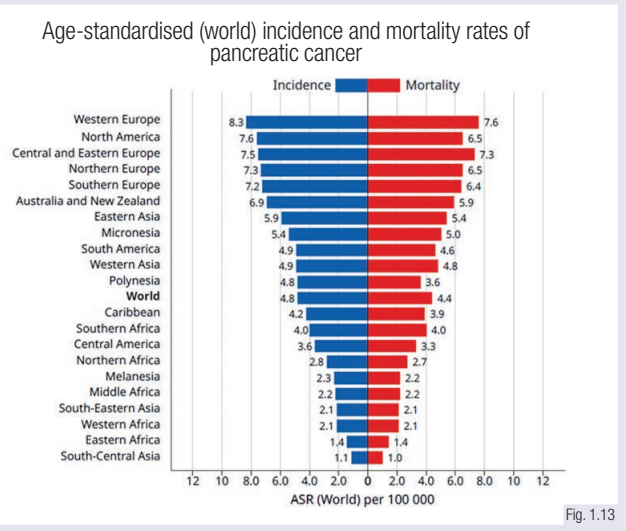


Fig. 1.13

ASR, age-standardised rate.

Risk factors associated with pancreatic cancer risk	
Factors	
Tobacco smoking	Risk increases with intensity (cigarettes/day) and duration, and decreases with time since cessation in former smokers
Body fatness	Greater body mass index, waist circumference, adult weight gain
Other diseases	Diabetes (new-onset type 2 diabetes) and chronic inflammatory pancreatitis
Family history and genetic syndromes	Family history of pancreatic cancer increases risk, particularly when more than one family member is involved. Besides rare germline mutations in susceptibility genes, common variants confer modest risk (i.e. carriers of A or B blood groups relative to group O)
Factors with limited evidence of association with risk of pancreatic cancer	
Dietary factors	High consumption of red meat, processed meat, alcohol, foods containing saturated fatty acids, foods and drinks containing fructose
Other	The role of infection with *H. pylori* is the subject of ongoing research

H. pylori, Helicobacter pylori.

Fig. 1.14

Cigarette smoking is the leading modifiable cause of pancreatic cancer. It is estimated to cause 20%-25% of pancreatic cancers.

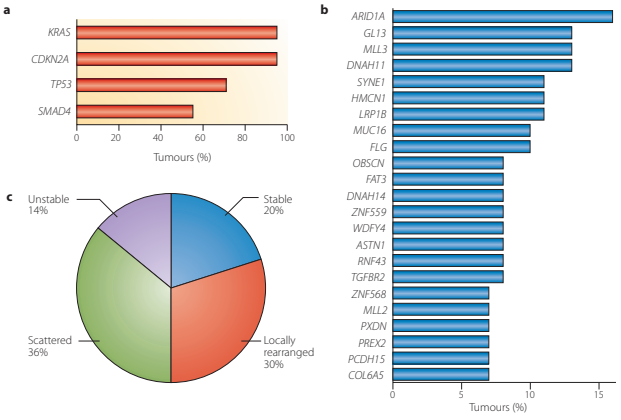
Body fatness, reflected by greater body mass index, including abdominal obesity and adult weight gain, is a cause of pancreatic cancer.

Other risk factors include chronic pancreatitis and diabetes. Family history and rare genetic syndromes (5%-10% of cases) also carry increased risk.

About 95% of pancreatic cancers occur in the exocrine pancreas, the most common being the infiltrating ductal adenocarcinoma. Other pancreatic neoplasms include neuroendocrine tumours.

Intraductal papillary mucinous neoplasms and mucinous cystic neoplasms are curable precursor lesions that can progress to an incurable invasive carcinoma.

The molecular pathology of pancreatic cancer is dominated by activating mutations in *KRAS* and inactivating mutations of *TP53*, *CDKN2A* and *SMAD4*.



Gene alterations in pancreatic cancer. (a) Commonly altered genes; **(b)** less commonly mutated genes; **(c)** pancreatic cancer subtypes proposed based on the number and location of structural rearrangements.

Fig. 1.15

ARID1A, AT-rich interaction domain 1A; CKN2A, cyclin-dependent kinase inhibitor 2A; DNAH11, dynein axonemal heavy chain 11; TGFBR2, transforming growth factor beta receptor 2.

REVISION QUESTIONS

1. Identify the population groups with higher risk of pancreatic cancer according to age, sex and geography.
2. What are the most important modifiable risk factors for pancreatic cancer identified so far?
3. Which are the tumour suppressor genes commonly involved in the pathology of pancreatic cancer?

Summary: Epidemiology, risk factors and pathogenesis

- Taken together, the cancers of the intestinal tract are the most frequent tumours in humans, accounting for around one quarter of all cancer cases and almost one third of all cancer-related deaths. ~50% of these tumours are CRCs
- Except for CRC, with a 5-year survival of 60%, the remainder of GI tumours have a poor prognosis, the worst of which is pancreatic cancer, with 5-year survival <10%
- There are extreme geographical differences in the incidence of OC (more than for any other tumour). Incidence rates vary globally by more than 15-fold in men and almost 20-fold in women
- Smoking, alcohol, low fruit and vegetable intake and low income explain almost 99% of the attributable risk for OSCC in the USA and are strong risk factors in European countries, but tobacco and alcohol are weak risk factors in the highest risk areas of the world (Asian OC belt), where the aetiology of OSCC remains speculative
- *H. pylori* is the most common cause of non-cardia GC, though why *H. pylori* causes GC in only a minority of those infected remains unknown
- Given that GC is a multi-step process, the identification of patients with preneoplastic lesions with a high risk of progression and their periodic endoscopic surveillance represents the most effective method of early GC diagnosis
- There has been a substantial increase in the incidence of CRC in people <50 years old in several high-income countries. However, further studies are needed to establish the causes of this rising incidence and identify potential preventive and early-detection strategies
- CRC may be considered as a *lifestyle* disease: its risk is higher in countries with a diet high in calories and animal fat and a largely sedentary population with increased levels of overweight and obesity. However, there is still a lack of precise knowledge as to how multiple factors interact and contribute to risk
- Pancreatic cancer has one of the poorest prognoses among the major types of GI tumours. The most clearly established modifiable risk factors for pancreatic cancer are tobacco smoking and body fatness
- The carcinogenesis of pancreatic cancer remains largely unknown. However, some potentially curable precursor lesions and a set of significantly mutated oncogenes or tumour suppressor genes have been identified

Further Reading

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2 Diagnosis, staging, response assessment and interventional radiology in gastrointestinal tumours

Technical aspects

Computed tomography (CT), with at least 64 slices, is currently the imaging modality of choice in the study of gastrointestinal (GI) tumours.

New technological developments (including iterative reconstruction algorithms) keep radiation exposure as low as reasonably achievable, while maintaining high image quality.

The use of iodinated contrast medium (CM) injection is mandatory for diagnosing and staging GI tumours.

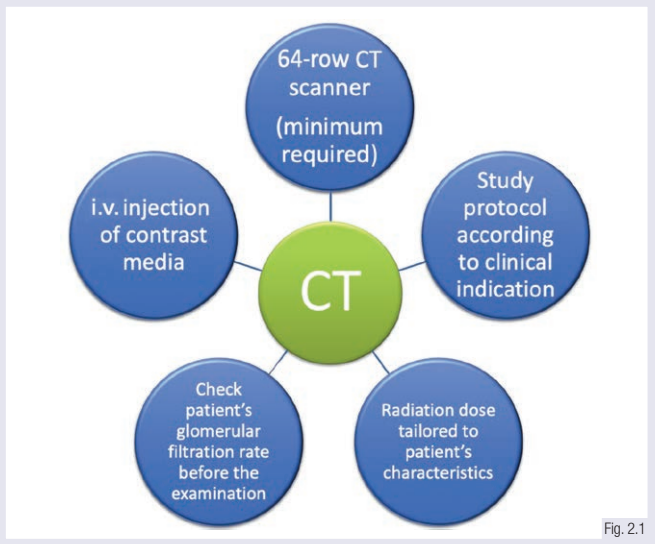


Fig. 2.1

CT, computed tomography; i.v., intravenous.

Fig. 2.2

Magnetic resonance imaging (MRI) offers a multiparametric approach in the evaluation of GI tumours and does not use ionising radiation. This is extremely important in young patients and pregnant women.

Compared with CT, the main drawbacks of MRI include longer imaging protocols and difficult evaluation of poorly collaborative and severely-ill patients.

^{18}F-Fluorodeoxyglucose-positron emission tomography (^{18}FDG-PET)/CT has different roles at the time of cancer diagnosis and during follow-up, depending on the primary tumour.

Advantages of ^{18}FDG-PET/CT are its high sensitivity and whole body coverage. False positives (FDG uptake in inflammatory lesions) and false negatives (absence of uptake in mucinous tumours and concurrent therapy with metformin) must be considered.

In patients with suspected neuroendocrine tumours (NETs), different tracers (e.g. ^{68}Gallium) can be used to improve diagnostic accuracy.

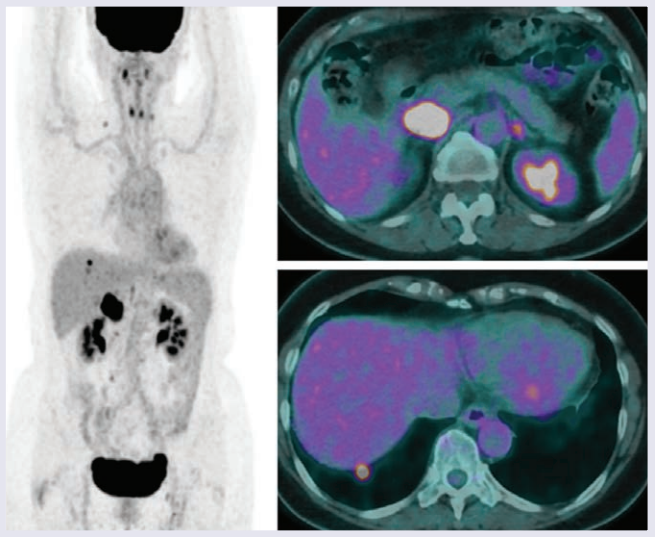


Fig. 2.3

REVISION QUESTIONS

1. What is the imaging test of choice in GI tumours?
2. What are the absolute contraindications to MRI study?
3. What does glucose uptake mean in a PET/CT examination?

Oesophageal cancer

Endoscopy with biopsy is the primary test for the diagnosis of oesophageal cancer.

In patients with alarm symptoms and no immediate access to endoscopy, barium X-ray of the upper GI tract can still be considered a useful imaging examination, although it cannot identify carcinoma *in situ*.

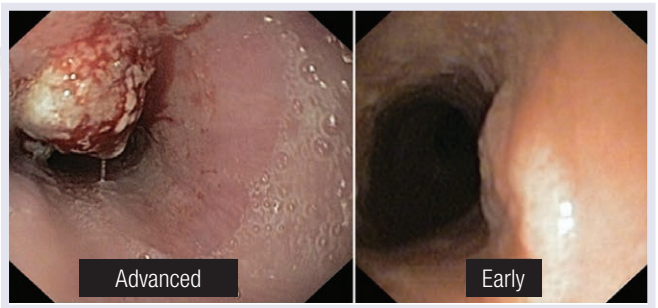


Fig. 2.4

Endoscopic ultrasound (EUS) is important in the initial local staging since it provides information about the depth of tumour (T) invasion and the presence of enlarged lymph nodes (LNs).

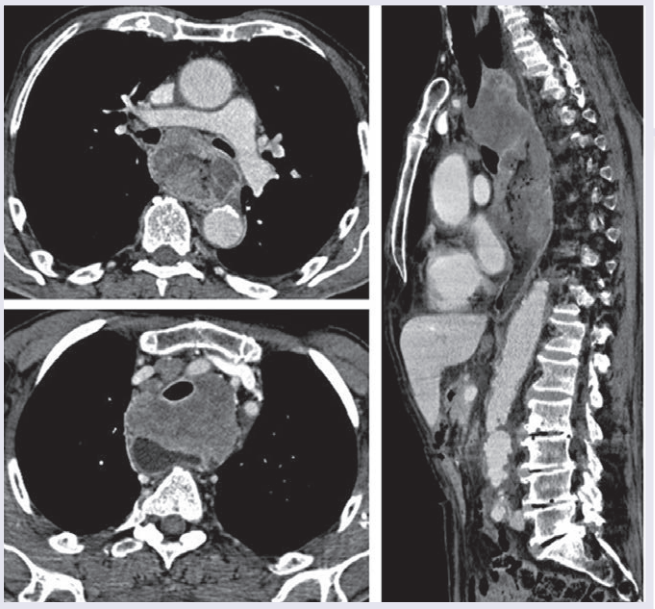


Fig. 2.5

CT of the chest and abdomen is recommended for staging and assessing tumour resectability.

^{18}FDG-PET/CT is an optional test for staging early oesophageal cancer and is recommended for locally advanced tumours. PET/MRI demonstrated acceptable accuracy for T staging compared with EUS, and higher accuracy for N (node) staging compared with PET/CT.

MRI is a problem-solving imaging modality in the case of suspected metastases to the brain, adrenal glands, liver and bones.

CT is the best imaging method to assess post-surgical anatomy and complications.

Response to chemotherapy (ChT) is routinely assessed by evaluation of tumour-related symptoms, endoscopy and CT scan.

Tumour response to ChT may be predicted early by ^{18}FDG-PET/CT. However, according to current evidence, this approach does not change the therapeutic strategy.

In case of either intrinsic or extrinsic oesophageal obstruction, insertion of an endoprosthesis (using fluoroscopic or endoscopic guide) is a valuable palliative treatment.

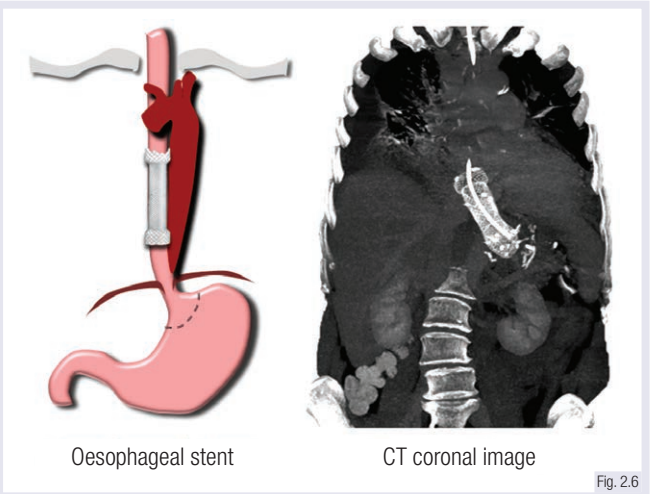


Fig. 2.6

CT, computed tomography.

REVISION QUESTIONS

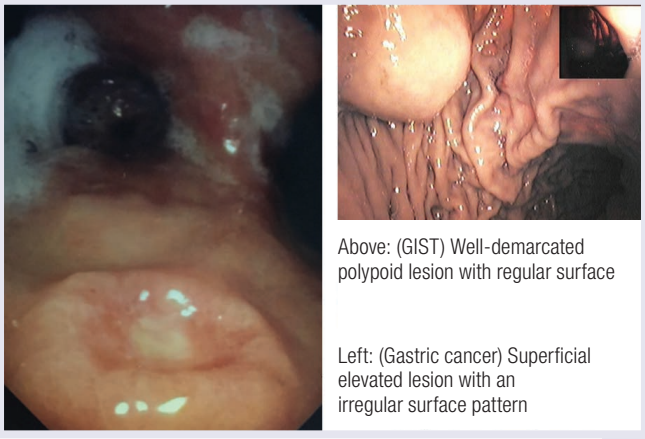
1. What is the most sensitive and specific test to detect oesophageal cancer?
2. What is the role of MRI in staging oesophageal cancer?
3. What is the most common palliative treatment for neoplastic oesophageal obstruction?

Gastric cancer

Endoscopy with biopsy is the most sensitive and specific test to detect gastric cancer.

Sensitivity is close to 98% if multiple biopsy specimens are taken from a suspicious lesion.

Staging using CT scan (chest, abdomen and pelvis) with or without EUS should be performed before surgery to assess disease balance.

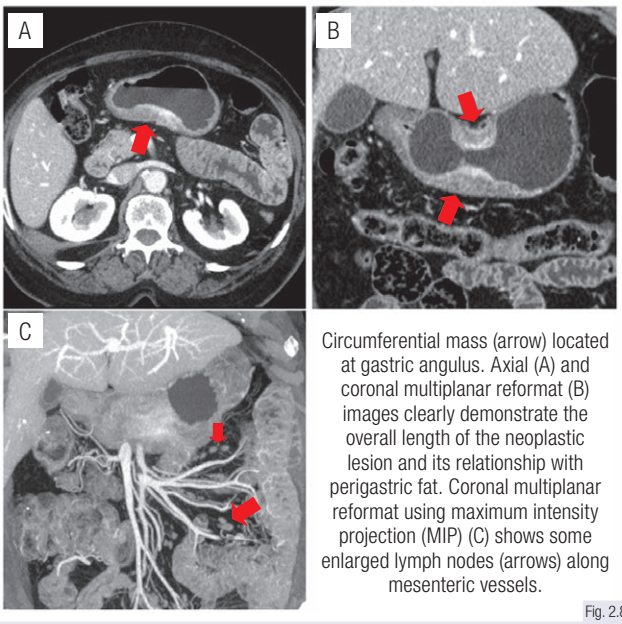


Above: (GIST) Well-demarcated polypoid lesion with regular surface

Left: (Gastric cancer) Superficial elevated lesion with an irregular surface pattern

GIST, gastrointestinal stromal tumour.

Fig. 2.7



Circumferential mass (arrow) located at gastric angulus. Axial (A) and coronal multiplanar reformat (B) images clearly demonstrate the overall length of the neoplastic lesion and its relationship with perigastric fat. Coronal multiplanar reformat using maximum intensity projection (MIP) (C) shows some enlarged lymph nodes (arrows) along mesenteric vessels.

Fig. 2.8

EUS is important in the initial staging, especially in patients who are being considered for endoscopic resection.

Pneumo/hydro-CT has proved to be a useful, safe and accurate technique to identify gastric wall thickening and gastric cancer stage.

^{18}FDG-PET/CT can improve staging through an increased detection of pathological LNs and/or metastatic disease. In diffuse or mucinous tumours, ^{18}FDG-PET/CT may be inconclusive.

CT is the best method to re-stage gastric cancer after neoadjuvant ChT, although its diagnostic accuracy is still under evaluation.

Endoscopy with biopsy of any abnormalities is the best method for postoperative surveillance of local recurrence. The addition of EUS improves sensitivity.

^{18}FDG-PET/CT is accurate and has high positive predictive value in detecting local and distant recurrence in patients with clinical or radiological suspicion after surgical resection.

Percutaneous gastrostomy/jejunostomy and endoscopic placement of self-expandable metallic stents are safe, effective and minimally invasive palliative treatments for patients with luminal obstruction.

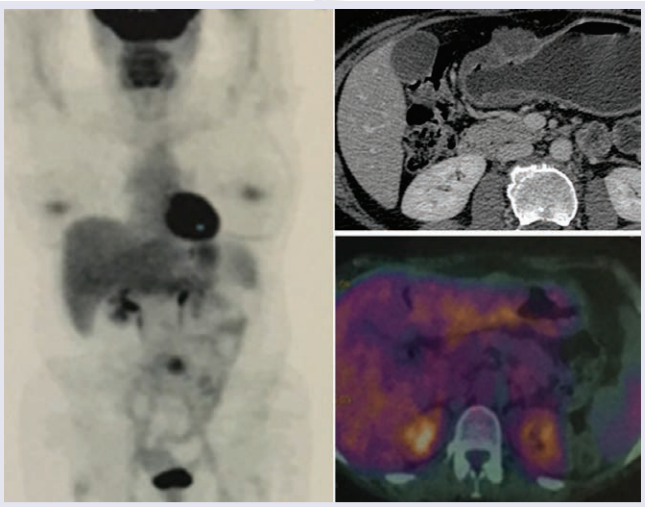


Fig. 2.9

REVISION QUESTIONS

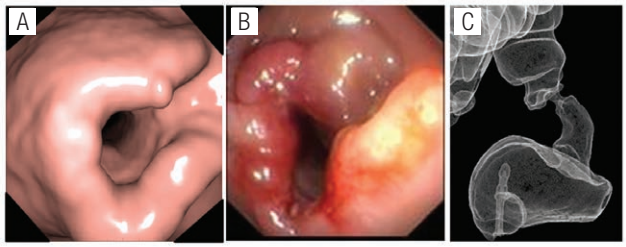
1. What is the initial test for staging gastric cancer?
2. In which case can ^{18}FDG-PET/CT be inconclusive?
3. What is the best imaging method to detect distant metastasis?

Colon cancer

Diagnosis of colon cancer is obtained with colonoscopy and biopsy.

CT colonography (CTC) is a valuable alternative diagnostic method to detect colon cancer in both asymptomatic and symptomatic patients.

The use of barium enema is no longer recommended due to poorer performance compared with colonoscopy and CTC.



Stenosing colon cancer: (A) 3D endoluminal image from CTC, (B) optical colonoscopy and (C) double-contrast barium enema reconstruction from CTC.

Fig. 2.10

CTC, computed tomography colonography.

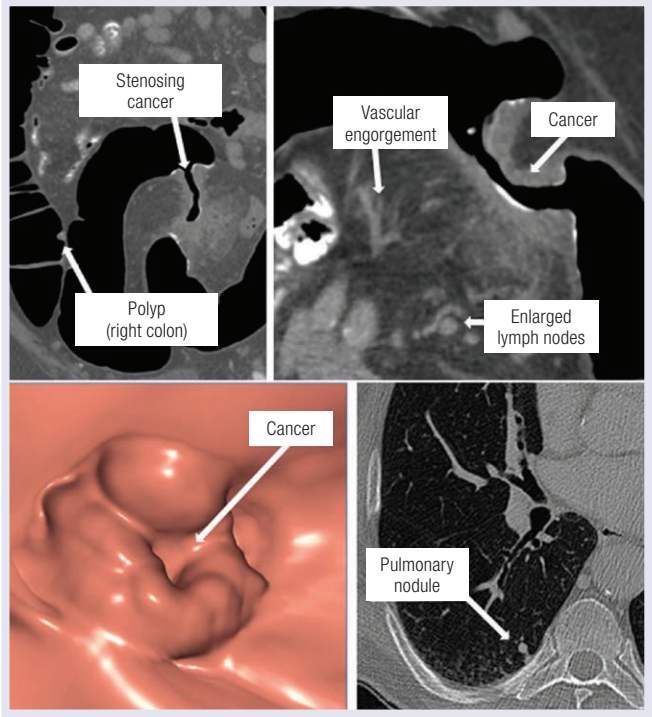


Fig. 2.11

Contrast-enhanced CT of the chest, abdomen and pelvis is appropriate to detect distant metastasis. If initial colonoscopy is incomplete (also due to the presence of a stenosing cancer), contrast-enhanced CTC can be used to stage the patient and to detect synchronous colonic lesions.

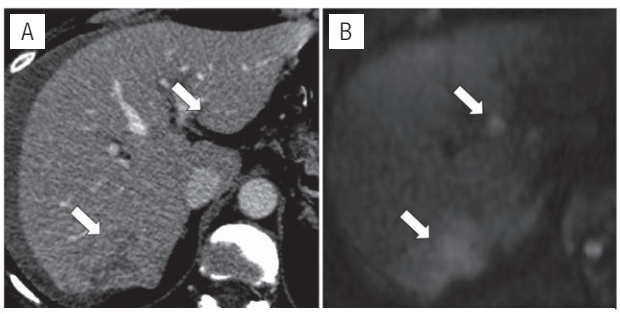
Contrast-enhanced MRI is recommended if CT is contraindicated or if liver lesions require further characterisation.

Routine use of ^{18}FDG-PET/CT is not recommended at the time of initial diagnosis. ^{18}FDG-PET/CT can help clarify abnormal CT findings and improve detection of otherwise unsuspected distant metastases.

CT is the best method to assess early post-surgical complications.

Follow-up includes colonoscopy and a CT scan of the chest, abdomen and pelvis, at different times depending on the patient's risk of recurrence. ^{18}FDG-PET/CT is indicated in patients with equivocal findings at CT and in those with abnormal carcinoembryonic antigen levels and prior negative work-up.

MRI with diffusion-weighted sequences and hepatobiliary contrast agents is the best method to assess the effect of ChT and interventional procedure on liver parenchyma.



Liver metastases from breast cancer after chemotherapy, barely visible on axial image (arrows in A), well defined and easily detectable on axial diffusion-weighted image (arrows in B).

Fig. 2.12

REVISION QUESTIONS

1. Which imaging test can be considered an alternative to colonoscopy in patients with suspected colon cancer?
2. What is the next test to characterise a focal liver lesion equivocal on CT?
3. What is the best method to assess response to ChT of liver lesions?

Rectal cancer

Diagnosis of rectal cancer is based on digital rectal examination (DRE) and endoscopy with biopsy. Tumours with distal extension ≤15 cm from the anal margin are classified as rectal.

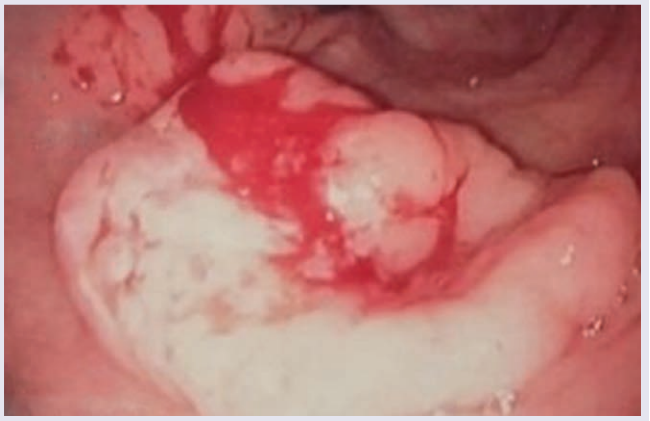
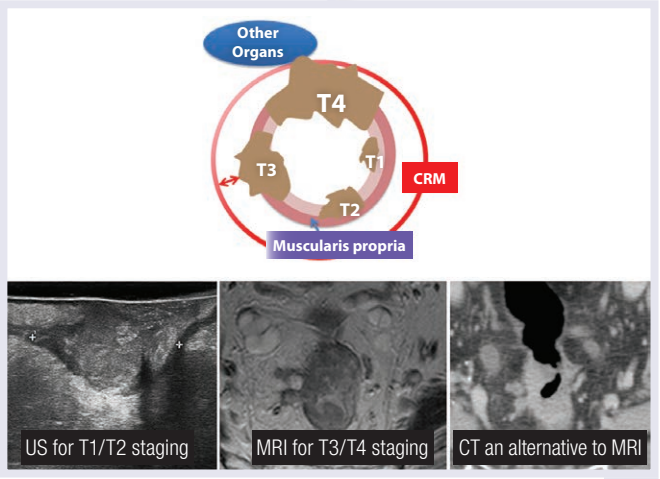


Fig. 2.13

Infiltration of the anal sphincter in low rectal cancer is best assessed by MRI.

EUS can differentiate T1 and T2 tumours, selecting patients for local excision.

MRI is the recommended technique for staging invasive cancer (≥T3). It allows tailored treatment based on evaluation of tumour position, extramural spread, circumferential resection margin (CRM), extramural venous invasion (EMVI) and nodal status.



CRM, circumferential resection margin; CT, computed tomography; MRI, magnetic resonance imaging; US, ultrasound.

Fig. 2.14

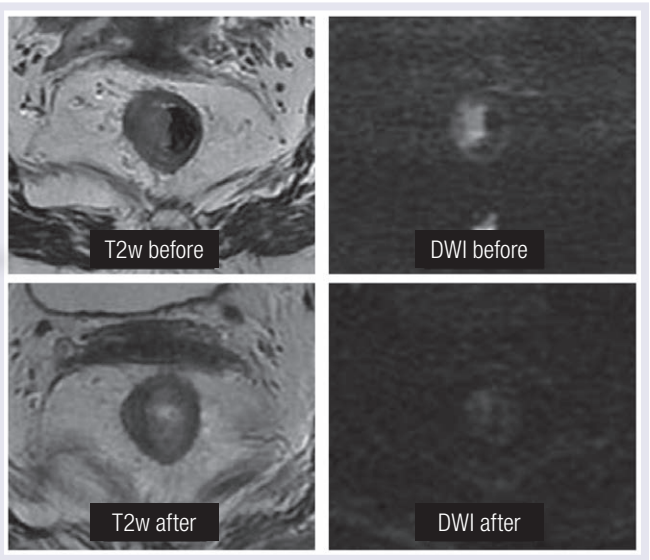
Local staging with CT can be an alternative to MRI in advanced tumours located in the mid-high rectum. CT of the chest, abdomen and pelvis is the best method to detect distant metastases.

^{18}FDG-PET/CT is preferential to CT in the evaluation of distant extrahepatic metastases in locally advanced rectal tumours.

MRI is recommended to assess response after neoadjuvant chemoradiotherapy. Current limitations include difficult assessment of pathological complete response, early identification of non-responders and mucosal healing. The combined use of endoscopy and MRI may overcome these limitations, improving accuracy for rectal cancer restaging.

^{18}FDG-PET/CT can be useful for predicting response to neoadjuvant therapy with a promising role in the early evaluation of response.

Whole-body CT and ^{18}FDG-PET/CT are the best methods for patient follow-up.



DWI, diffusion-weighted imaging; T2w, T2-weighted.

Fig. 2.15

REVISION QUESTIONS

1. What is the most accurate imaging test to select patients for local excision?
2. Which MRI findings are useful for predicting therapy and prognosis of patients with invasive rectal cancer?
3. What is the recommended method to assess response after neoadjuvant therapy?

Pancreatic cancer: Solid and cystic lesions

Pancreatic cancer is occasionally detected at abdominal ultrasound, although its sensitivity is <70%. Body and tail regions are difficult to explore.

CT is the best-validated imaging modality for diagnosing patients with solid pancreatic cancer; the highest lesion conspicuity is achieved during the pancreatic phase of enhancement.

CT allows locoregional and distant staging of pancreatic ductal adenocarcinoma (PDAC). CT is the preferred modality to preoperatively assess patients with unresectable disease (high positive predictive value).

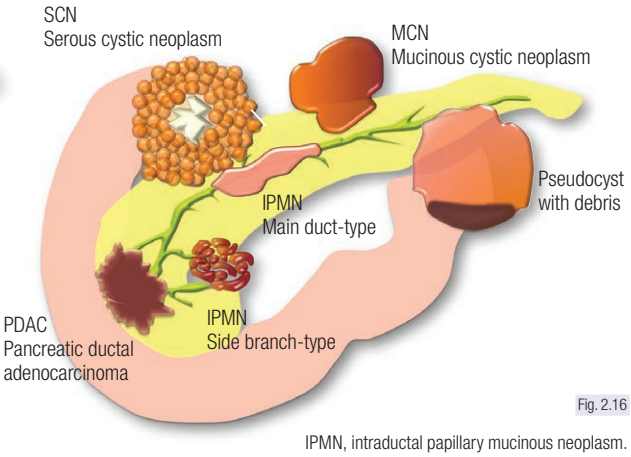
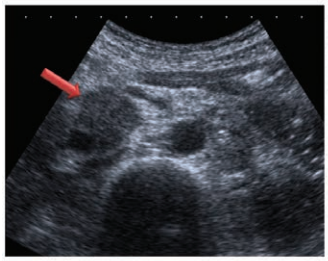
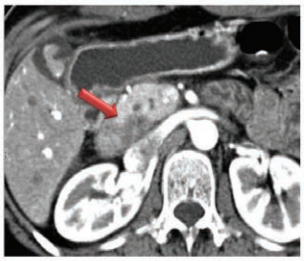


Fig. 2.16

IPMN, intraductal papillary mucinous neoplasm.



Hypoechoic mass, deforming gland contour with common bile duct (CBD) and dilatation



Hypoattenuation solid mass due to desmoplastic fibrotic component

Fig. 2.17

When CT is contraindicated, contrast-enhanced MRI can be used to diagnose and stage pancreatic cancer.

EUS may provide useful information to evaluate small peri-ampullary masses, to assess vascular infiltration and offer a guide for biopsy.

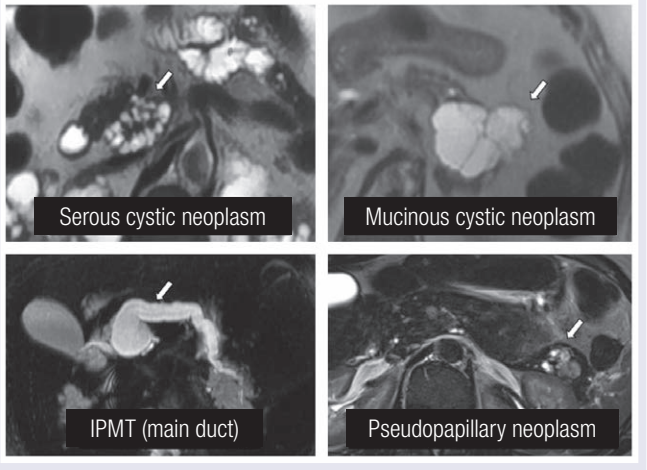
In the case of pancreatic cancer with secondary biliary obstruction, either endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC) can be used for biliary drainage or stent placement.

^{18}FDG-PET/CT is a promising tool to assess response to ChT in locally advanced neoplasia. PET/MRI is still under evaluation.

MRI represents the imaging modality of choice in the characterisation of cystic pancreatic neoplasms.

CT or MRI with magnetic resonance cholangiopancreatography (MRCP) is recommended to check for “high-risk stigmata” or “worrisome features”.

EUS offers the possibility to obtain fluid sample during the procedure. Contrast-enhanced EUS and EUS elastography play a complementary role to conventional EUS.



IPMT, intraductal papillary mucinous tumour.

Fig. 2.18

REVISION QUESTIONS

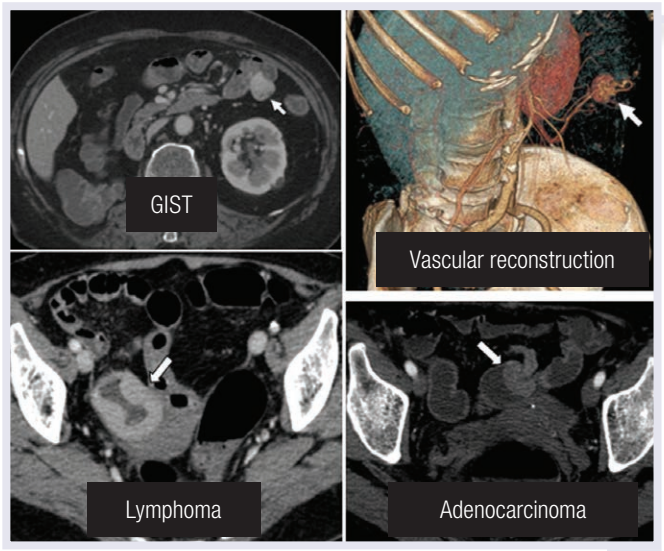
1. What is the first imaging exam in patients with suspected pancreatic cancer?
2. What are the typical cross-sectional imaging findings of PDAC?
3. What is the best imaging examination for preoperative evaluation of PDAC?

Small bowel tumours

Tumours of the small bowel are relatively uncommon. Adenocarcinoma, lymphoma, gastrointestinal stromal tumour (GIST), NET and metastases account for most cases.

Optimal evaluation of the small bowel requires luminal distension, achievable by administration of enteric contrast agent, either orally (enterography) or through a naso-jejunal tube (enteroclysis).

Both MRI and CT have good performance for the diagnosis of small bowel tumours. The use of an intravenous CM is mandatory to assess the bowel wall, lesion enhancement and mesenteric vessels. PET/CT has a primary role for the evaluation of small bowel lymphoma.



GIST, gastrointestinal stromal tumour.

Fig. 2.20

Dedicated software for CT image analysis allows a more comprehensive evaluation of a tumour's relationship with adjacent structures and vessels, important information for surgical planning.

CT is the best method to assess early postsurgical complications.

CT, and PET/CT for lymphoma, are recommended for patient follow-up. In metastatic NETs, ^{68}Gallium-PET can be indicated to detect distant metastases and to assess response to therapy.

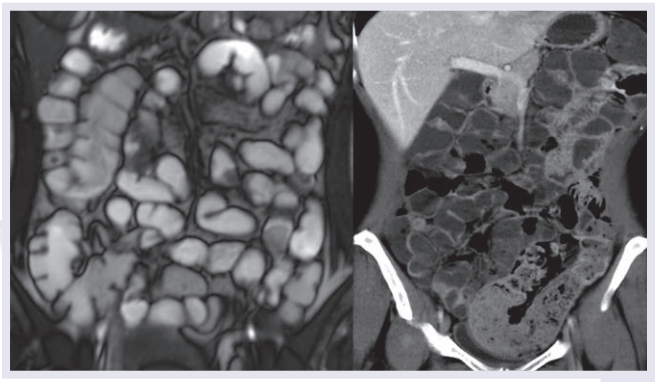


Fig. 2.19

GISTs are more common in the stomach, may present an exophytic or endophytic growth and have a variable tumour enhancement; locoregional lymphadenopathies are extremely unusual.

Lymphoma usually affects the distal ileum. It presents with pseudoaneurysmatic dilatation of the bowel loop without occlusion; locoregional lymphadenopathies are extremely common.

Adenocarcinoma is usually located at the duodenum/jejunum; it presents as a short annular lesion, obstructing the lumen.

NETs have no preferred GI location. They are usually hypervascular, and a desmoplastic reaction in the mesenteric fat adjacent to the affected loop can be detected. Malignant NETs can be metastatic at diagnosis.

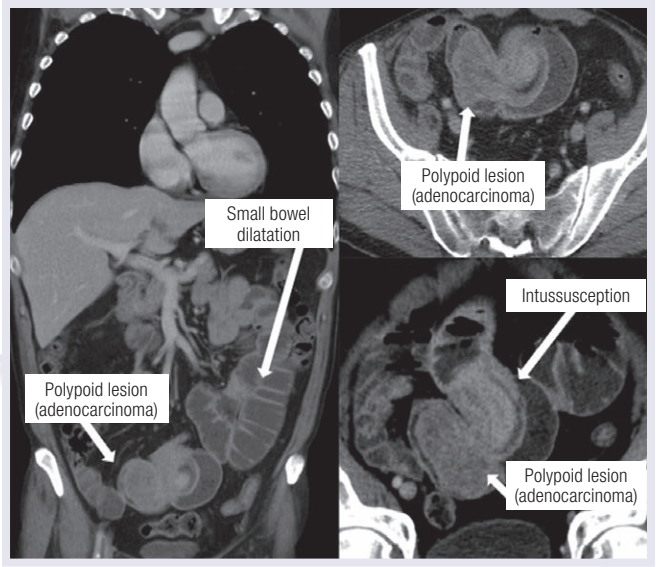


Fig. 2.21

REVISION QUESTIONS

1. What are the best imaging modalities to detect small bowel tumours?
2. What are the main imaging features of GIST?
3. What is the most accurate method to assess complications?

Summary: Diagnosis, staging, response assessment and interventional radiology in gastrointestinal tumours

- Technical aspects:
  - CT is currently the imaging modality of choice in the study of GI tumours
  - MRI offers a multiparametric approach, but it has some potential limitations and a few absolute contraindications
  - ^{18}FDG-PET/CT is an important diagnostic tool at the time of cancer diagnosis and in patient follow-up
- Oesophageal cancer: CT of the chest and abdomen is recommended for staging and assessing tumour resectability
- Gastric cancer: endoscopy with biopsy is the most sensitive and specific test to detect gastric cancer
- Colon cancer: CTC is a valuable alternative diagnostic method to detect colon cancer in both asymptomatic and symptomatic patients
- Rectal cancer: MRI is the recommended technique for staging invasive cancer (≥T3)
- Pancreatic cancer:
  - CT is the best-validated imaging modality for diagnosing and staging patients with solid pancreatic cancer
  - MRI is the imaging modality of choice in the characterisation of cystic pancreatic neoplasms
- Small bowel tumours: a good evaluation of the small bowel requires luminal distension by the administration of enteric contrast agents

Further Reading

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3 Hereditary gastrointestinal cancer syndromes

Classification and identification

Colorectal cancer (CRC) is the third most common malignancy worldwide and the second leading cause of cancer death in both sexes in developed countries.

The majority of CRCs are related to environmental factors and sporadic events, although approximately 30%-35% of CRCs seem to be familial, due to low penetrance genes and environmental factors.

Up to 5% of CRCs are attributed to highly penetrant monogenic germline mutations.

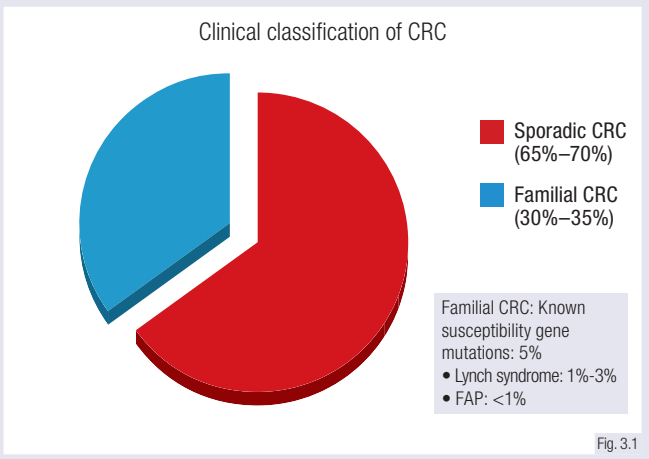
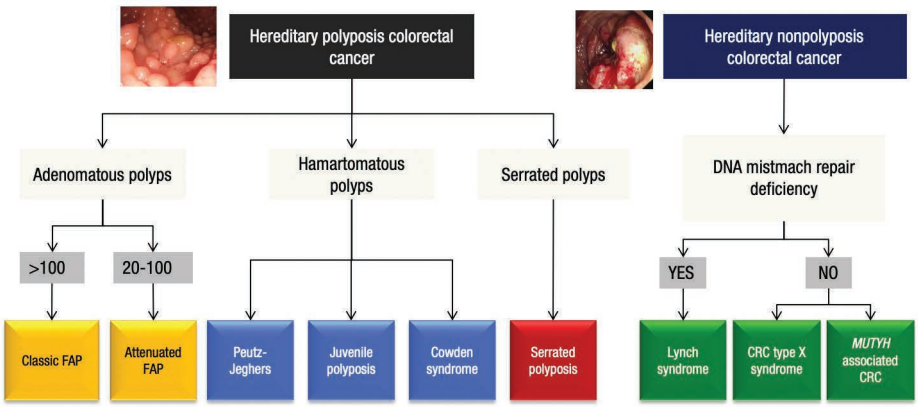


Fig. 3.1

CRC, colorectal cancer; FAP, familial adenomatous polyposis.



CRC, colorectal cancer; FAP, familial adenomatous polyposis.

Fig. 3.2

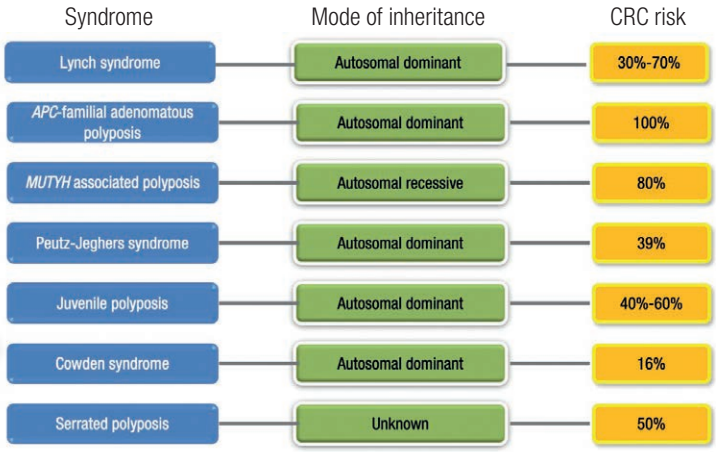
Hereditary CRC syndromes are mainly classified based on the presence of a polyposis phenotype.

Recognising hereditary CRC leads to individualised surveillance recommendations and personalised medicine.

Fig. 3.2 summarises the different hereditary CRC syndromes based on the presence and type of polyposis.

Identification and characterisation of these disorders has allowed modification of their natural history with a substantial decrease in morbidity and mortality among high-risk patients.

Most hereditary CRC syndromes have an autosomal dominant inheritance, as shown in Fig. 3.3, which also describes the specific CRC risk in each syndrome.



APC, adenomatous polyposis coli; CRC, colorectal cancer.

Fig. 3.3

REVISION QUESTIONS

1. What is the relevance of making a diagnosis of a hereditary CRC syndrome?
2. What sort of inheritance do these syndromes have?
3. What is the type of phenotype used to classify the syndromes and which belong to each group?

Non-polyposis CRC syndromes: Lynch syndrome

Lynch syndrome is the most common hereditary CRC syndrome (1%-3% of all CRCs).

It is caused by germline mutations in the mismatch repair (MMR) system genes: *MLH1, MSH2, MSH6, PMS2* or *EPCAM* deletion (which causes epigenetic silencing of *MSH2*).

Deficiency in the MMR system leads to microsatellite instability (MSI). Carcinogenesis is promoted when mismatches occur within the coding region of tumour suppressor genes (*TGF-BRII, BAX, IGF2R, PTEN, CASP5*).

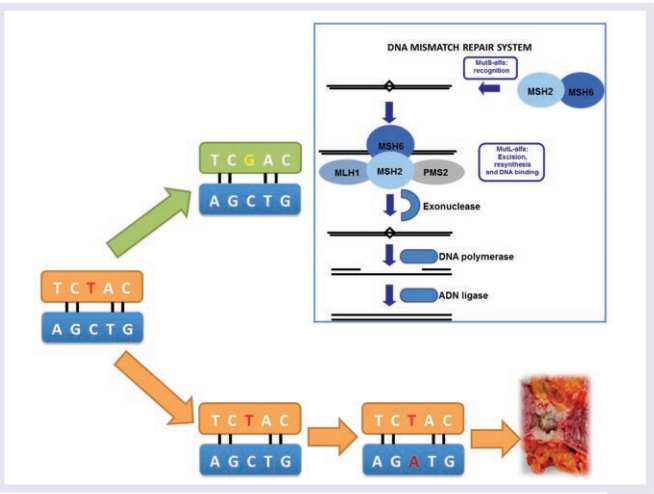
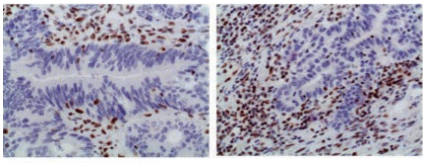


Fig. 3.4

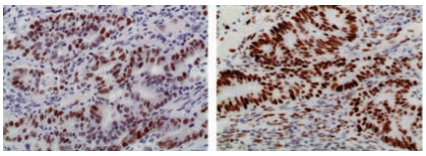
Loss of protein expression:

MLH1 PMS2



Retained protein expression:

MSH2 MSH6



Germline mutated gene	Immunostaining			
	MSH2	MSH6	MLH1	PMS2
MSH2	–	–	+	+
MSH6	+	–	+	+
MLH1	+	+	–	–
PMS2	+	+	+	–

Fig. 3.5

Mutations in the MMR genes lead to loss of protein expression detected by immunohistochemistry (IHC) (with high sensitivity and specificity) and/or MSI.

Up to 15% of all CRCs show MLH1/PMS2 protein loss due to somatic *MLH1* promoter hypermethylation, usually associated with somatic *BRAF* mutations. Germline genetic testing is not required in this situation (sporadic CRC).

Tumour testing with IHC and/or MSI should be considered in all CRC patients. Alternatively, MMR tumour analysis should be completed in patients younger than 70 years, or in those older who fulfil the Revised Bethesda Guidelines.

MLH1 and *MSH2* mutations represent 80%-90% of the total tumour burden. The most frequent *MLH1* mutations are missense and splice-site; frameshift mutations, common in *MSH2*, are frameshift due to small deletions and insertions.

Germline testing includes DNA sequencing and large rearrangement analysis.

There is a genotype-phenotype correlation. *MLH1* mutations are associated with a higher risk of CRC at a young age, *MSH2* with extracolonic cancer, *MSH6* with endometrial cancer and *MSH6* and *PMS2* with later and lower CRC risk.

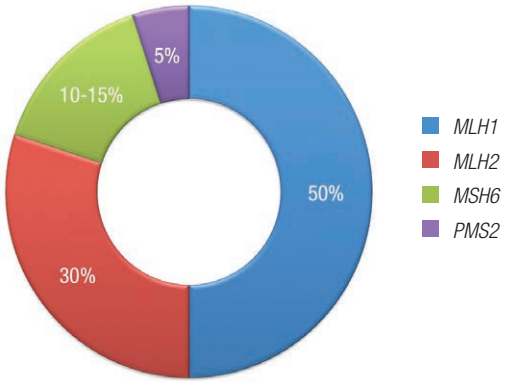


Fig. 3.6

REVISION QUESTIONS

1. What is the main function of the MMR system?
2. When is tumour MMR analysis indicated?
3. What is the correlation between genotype and phenotype?

Non-polyposis CRC syndromes: Lynch syndrome (continued)

Lynch syndrome is characterised by an accelerated carcinogenesis.

Colonoscopy every 1-2 years has been shown to decrease incidence and mortality by >60%. It is recommended to start at 25 years of age for *MLH1/MSH2/EPCAM* and at 35 years for *MSH6/PMS2*. Prophylactic colectomy is usually not recommended.

The risk of a metachronous CRC is 16% at 10 years after initial diagnosis and 41% at 20 years. Besides the risk of CRC, Lynch syndrome carriers are at risk of other malignancies, mainly endometrial cancer in women. The main affected organs are listed in Fig. 3.7.

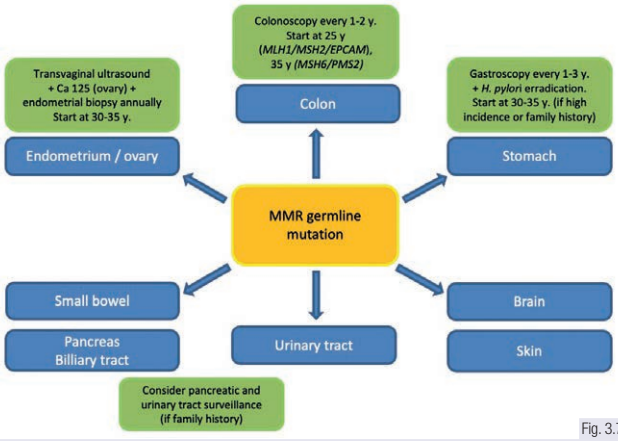


Fig. 3.7

H. pylori, *Helicobacter pylori*; MMR, mismatch repair.

Lynch-like syndrome

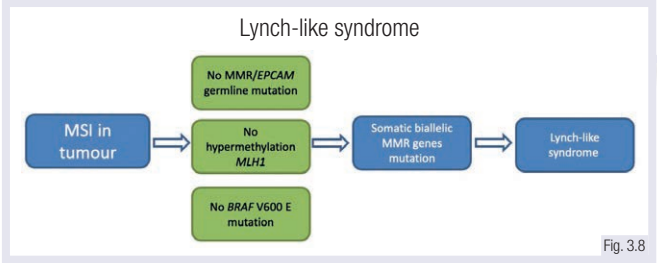


Fig. 3.8

MMR, mismatch repair; MSI, microsatellite instability.

Patients with Lynch-like syndrome show tumour MSI with no MMR or *EPCAM* germline gene alterations, and no hypermethylation of *MLH1* or *BRAF* V600E mutation.

MSI is likely due to somatic biallelic mutations in the MMR genes.

Surveillance with colonoscopy is individualised based on personal and familial CRC history.

CRC in young people

Incidence of CRC in young adults has been increasing in recent years, most of them with no family history. This increase may be influenced by lifestyle factors such as diet.

This group of patients presents different pathological and molecular characteristics. For example, an increased alteration of TP53 and CTNNB1 or an activation of the Wnt/β-catenin pathway are more frequent in young people. Germline susceptibility is heterogeneous.

Further data are needed to optimise treatment options in young adults.

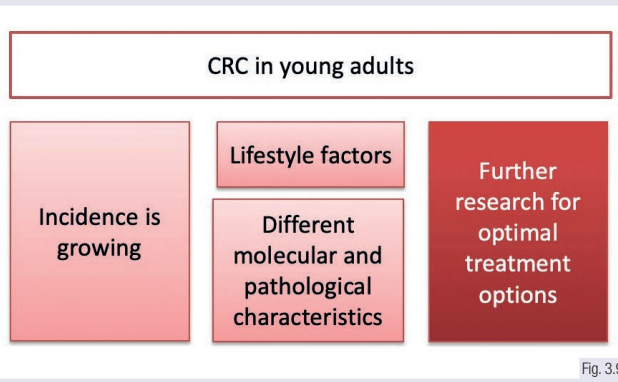


Fig. 3.9

CRC, colorectal cancer.

REVISION QUESTIONS

1. What is the recommended surveillance in Lynch syndrome patients?
2. What is the most common genetic basis of Lynch-like syndrome?
3. What might be a common cause of young-onset CRC?

Gastrointestinal polyposis syndromes: adenomatous polyposis

Adenomatous polyposis (AP) of the colorectum is the most frequent polyposis type and a precancerous condition with a high lifetime risk of CRC, unless detected early.

Currently, at least five different inherited forms can be delineated by molecular genetic analyses: the by-far most frequent types are the autosomal dominant familial adenomatous polyposis (FAP) and the autosomal recessive *MUTYH*-associated polyposis (MAP).

Although all types are defined by multiple adenomas that result in a similar diagnostic and therapeutic approach, a significant clinical variability regarding number, age at onset and benign and malignant extracolonic lesions can be observed.

Familial adenomatous polyposis (FAP)

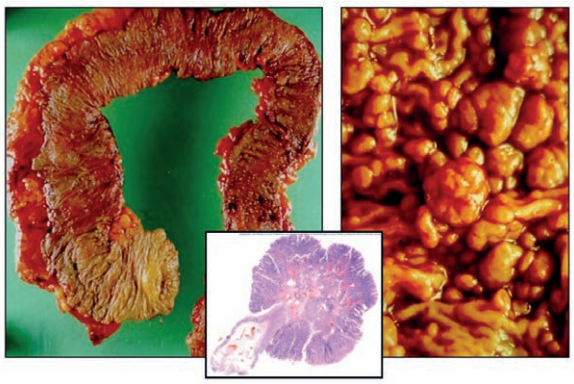


Fig. 3.10

Multi-gene panel testing

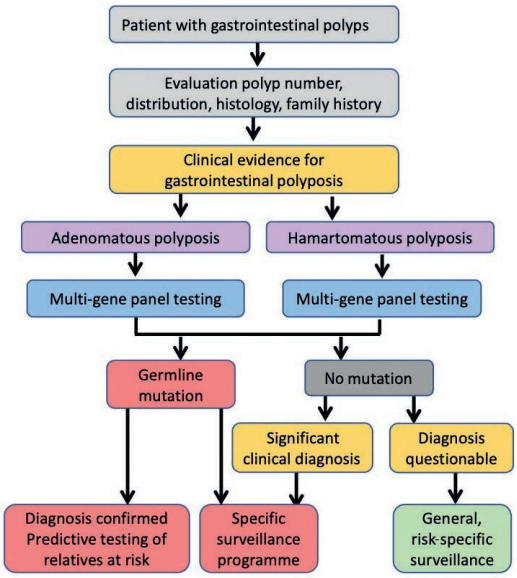


Fig. 3.11

The colorectal phenotype of AP is a biological continuum ranging from a classical, early-onset type, with >100 adenomas (FAP), to an attenuated course (attenuated FAP [AFAP]; MAP) with later onset and fewer (10–100) adenomas.

FAP is caused by heterozygous germline mutations of the tumour suppressor gene *APC* (adenomatous polyposis coli), and MAP by biallelic germline mutations of the DNA repair gene *MUTYH*. Most mutations occur in a single family.

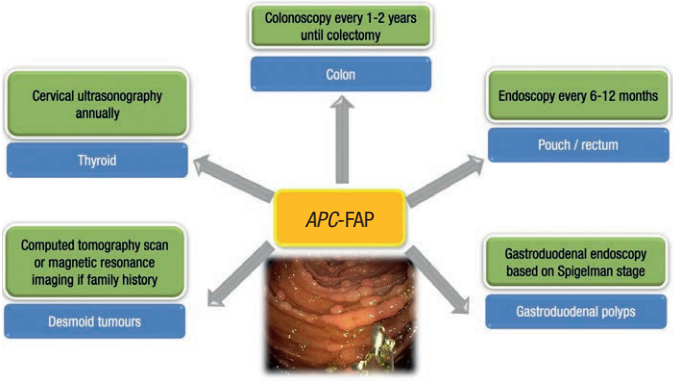
To date, usually multi-gene panel testing, which includes all relevant genes, is applied to identify an underlying germline mutation. In up to 30% of cases no genetic cause can be identified.

Without surveillance and treatment, the risk of CRC is up to 100% at 40-50 years of age in classical FAP, and around 80% at 70 years in AFAP and MAP patients.

Patients with AP and their first-degree relatives/ asymptomatic mutation carriers need specific and intense (endoscopic) surveillance of the gastrointestinal (GI) tract and other organs.

In most patients, colectomy is indicated. Secondary chemoprevention with non-steroidal anti-inflammatory drugs can be considered.

Tumour spectrum and surveillance



APC, adenomatous polyposis coli; FAP, familial adenomatous polyposis.

Fig. 3.12

REVISION QUESTIONS

1. Is surveillance of extracolonic manifestations required in *APC*-related FAP?
2. At what age are colonoscopy and prophylactic colectomy usually recommended in FAP patients?
3. What is the risk of MAP in the offspring of a patient with a heterozygous *MUTYH* mutation?

GI polyposis syndromes: hamartomatous and serrated polyposis syndromes

Hamartomatous polyposis syndromes include several rare conditions characterised by the presence of GI hamartomatous polyps and an increased lifetime risk for CRC. Some are associated with a broad spectrum of extraintestinal lesions.

Depending on the dominant polyp type and the spectrum of extraintestinal lesions, the most common conditions (Peutz-Jeghers syndrome, juvenile polyposis syndrome, PTEN hamartoma tumour syndrome/Cowden syndrome) can be distinguished; however, the differential diagnosis can be challenging.

Patients and high-risk relatives/mutation carriers should be included in syndrome-specific surveillance programmes.

Pedigree of a family with juvenile polyposis caused by a *SMAD4* germline mutation

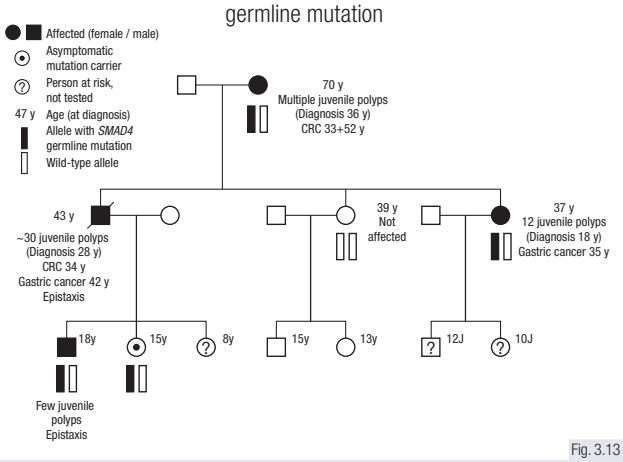


Fig. 3.13

CRC, colorectal cancer.

Peutz-Jeghers syndrome

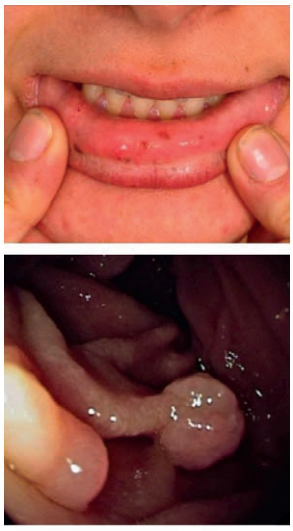


Fig. 3.14

Peutz-Jeghers syndrome, caused by *STK11* mutations, is characterised by Peutz-Jeghers polyps in the GI tract and perioral mucocutaneous pigmentation. It is associated with a high lifetime risk for cancers, in particular of the GI tract, pancreas and breast.

Juvenile polyposis, caused by *SMAD4* or *BMPR1A* mutations, is diagnosed in the presence of multiple juvenile polyps. Polyps can easily be misdiagnosed as hyperplastic or inflammatory. *SMAD4* mutation carriers have a high risk for gastric cancer and hereditary haemorrhagic telangiectasia.

Cowden syndrome, caused by *PTEN* mutations, is characterised by macrocephaly, multiple hamartomas of the skin, mucocutaneous lesions and an increased risk of benign and malignant lesions of the breast, thyroid and endometrium.

Colon polyp and mucocutaneous papillomatous skin lesions in a 63-year-old female with genetically confirmed Cowden syndrome

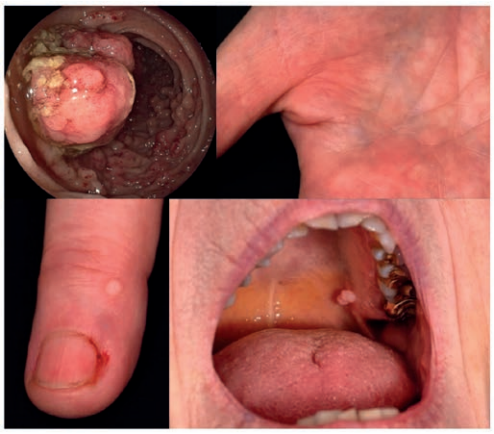


Fig. 3.15

Serrated polyposis syndrome is characterised by the presence of large and/or numerous serrated lesions spreading throughout the colorectum; it is supposed to be one of the most common CRC polyp syndromes.

Serrated lesions include hyperplastic polyps, sessile serrated polyps and traditional serrated adenomas.

The genetic basis is largely unknown as yet. In a few cases, germline mutations in the gene RNF43 have been identified. Differential diagnosis mainly includes MAP, juvenile polyposis and Cowden syndrome.

REVISION QUESTIONS

1. What early-onset symptoms can occur in Peutz-Jeghers syndrome and juvenile polyposis syndrome?
2. How can the different hamartomatous tumour syndromes be distinguished from one another?
3. What is the recommended surveillance in hamartomatous polyposis?

Gastric cancer

Based on Globocan 2019 data, gastric cancer (GC) is the fifth leading cause of cancer worldwide and the third most common cause of cancer-related deaths. *Helicobacter (H.) pylori* infection is the most relevant non-genetic risk factor.

Three main groups of GC can be distinguished: intestinal, diffuse (signet ring cell carcinoma) and the mixed/ indeterminate type.

Approximately 10% of cases present with a positive family history. Around 1%-3% of all gastric malignancies occur due to a genetic predisposition for one of several hereditary tumour syndromes.

Hereditary tumour syndromes with increased risk of gastric cancer

Tumour syndrome	Causative gene
Hereditary diffuse gastric cancer	*CDH1*
Lynch syndrome	*MLH1, MSH2, MSH6, PMS2*
Peutz-Jeghers syndrome	*STK11*
Juvenile polyposis syndrome	*SMAD4, BMPR1A*
Adenomatous polyposis	*APC, MUTYH*
Gastric adenocarcinoma and proximal polyposis of stomach	*APC*
Li-Fraumeni syndrome	*TP53*

APC, adenomatous polyposis coli.

Fig. 3.16

Single focus of signet ring cell carcinoma in patient with prophylactic gastrectomy

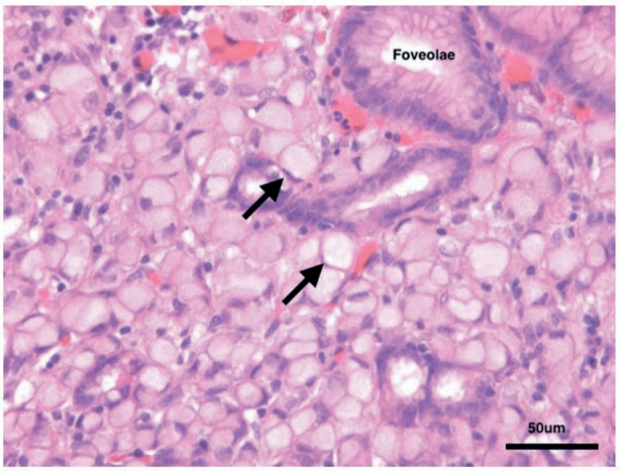


Fig. 3.17

In patients with early-onset disease or strong familial clustering, multi-gene panel testing is recommended to identify the genetic cause in a subset of cases.

The autosomal dominant hereditary diffuse GC (HDGC) is caused by germline *CDH1* mutations and associated with a high lifetime risk for diffuse GC (~80%) and lobular breast cancer in women (~40%).

Familial intestinal GC (FIGC) is defined as familial clustering of intestinal GC where no hereditary cause can be identified by current diagnostic standards.

Prophylactic gastrectomy is the therapeutic option for carriers of *CDH1* pathogenic mutations, even when asymptomatic. Otherwise, annual endoscopy including chromoendoscopy and biopsies are recommended.

Female carriers of a pathogenic *CDH1* germline mutation should consider intense breast cancer surveillance or even prophylactic mastectomy. When another hereditary condition is identified, mutation carriers should follow the syndrome-specific recommendations.

In all other cases, *H. pylori* eradication and frequent gastroscopies might be discussed with high-risk patients, despite the absence of robust evidence of screening efficiency.

Prophylactic gastrectomy in *CDH1* germline mutation carrier

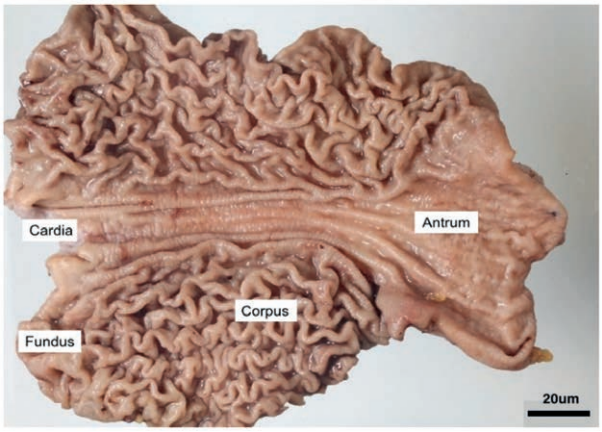


Fig. 3.18

REVISION QUESTIONS

1. Which is the hereditary cancer syndrome with the highest risk for gastric cancer?
2. When, and with what frequency, is screening indicated in high-risk patients?
3. What is the main non-genetic risk factor to control?

Pancreatic cancer

Based on Globocan 2018 data, pancreatic cancer (PC) is the 12th most common cancer worldwide and the 7th cause of cancer-related deaths.

Approximately 10% of patients present with a family history. There are several hereditary cancer syndromes associated with an increased risk of PC.

Risk factors for familial or hereditary pancreatic cancer
Individuals with ≥3 affected relatives with PC, at least 1 affected FDR
Individuals with ≥2 affected FDR relatives
Peutz-Jeghers syndrome patients, regardless of family history of PC
CDKN2A/p16 mutation carriers with one affected FDR
BRCA2 mutation carriers with one affected FDR or two affected family members
PALB2 mutation carriers with one affected FDR
Mismatch repair gene mutation carrier with one affected FDR

Fig. 3.19

FDR, first-degree relative; PC, pancreatic cancer.

Syndrome	Gene	RR
Peutz-Jeghers syndrome	*STK11*	132
Hereditary breast-ovarian cancer syndrome	*BRCA1, BRCA2, PALB2*	4 to 13
Lynch syndrome	*MLH1, MSH2, MSH6, PMS2*	5 to 9
Familial adenomatous polyposis	*APC*	4.46
Familial atypical multiple mole melanoma	*CDKN2A*	7.4 to 47.8
Hereditary pancreatitis	*PRSS1, SPINK1, CTFR, CTRC*	53 to 87

Fig. 3.20

APC, adenomatous polyposis coli; RR, risk ratio.

In most of these cases (80%), a germline genetic alteration is not detected. This is known as familial PC. The risk of PC increases with the number of affected relatives.

Multi-gene panel testing is recommended in families with strong clustering (*BRCA*, MMR genes, *CDKN2A*, *PALB2*, *STK11*).

Despite the absence of robust evidence that screening leads to a decrease in mortality, it is indicated in high-risk patients.

Screening is based on endoscopic ultrasound and/or pancreatic magnetic resonance imaging (MRI).

It is also important to control lifestyle risk factors such as smoking, high body mass index (BMI) and physical inactivity.

When a suspicious lesion is detected, the extent of pancreatic resection is controversial. The decision must be individualised and assessed by a multidisciplinary team.

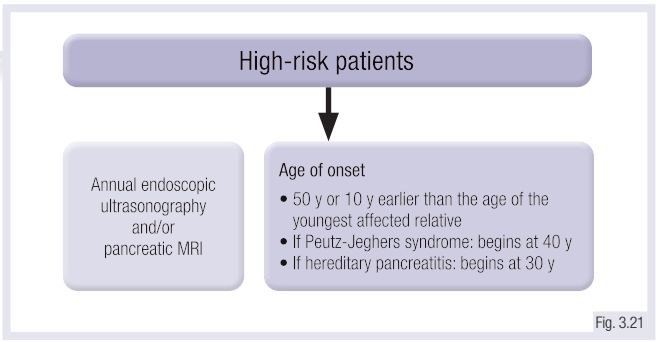


Fig. 3.21

MRI, magnetic resonance imaging.

REVISION QUESTIONS

1. Which is the hereditary cancer syndrome with the highest risk of PC?
2. When, and with what frequency, is screening indicated in high-risk patients?
3. What are the main lifestyle risk factors to control?

Summary: Hereditary gastrointestinal cancer syndromes

- Lynch syndrome is the most common hereditary CRC syndrome (1%-3% of all CRCs). It is an autosomal dominant hereditary syndrome caused by mutations in the DNA MMR genes
- Tumour testing with IHC for the MMR proteins and/or MSI should be considered in all CRCs. Alternatively, perform MMR tumour analysis in patients younger than 70 years or those fulfilling the Revised Bethesda Guidelines
- Screening and surveillance in Lynch syndrome reduce the incidence and mortality of CRC
- AP is suspected in patients with multiple colorectal adenomas (>10-20 synchronous adenomas). FAP and MAP are the most common ones. These patients have a high risk of CRC and other extracolonic tumours (duodenum, thyroid and desmoids)
- In classical FAP, colectomy is indicated due to the almost 100% risk of developing CRC
- Mutations in *APC* and biallelic mutations in *MUTYH* are the most frequent in FAP and MAP
- Hamartomatous polyposis syndromes include several rare conditions with a broad spectrum of extraintestinal benign and malignant lesions. The clinical and histopathological differential diagnosis can be challenging. Hamartomatous polyposis syndromes include Peutz-Jeghers (*STK11*), juvenile polyposis (*SMAD4* or *BMPR1A*) and Cowden syndrome (*PTEN*)
- Serrated polyposis syndromes are common; their genetic basis is largely unknown
- Hereditary PC can be associated with several genes. PC screening with endoscopic ultrasound and/or pancreatic MRI is considered in high-risk individuals, despite the absence of robust evidence on mortality reduction
- HDGC is associated with germline mutations in *CDH1*. Prophylactic gastrectomy and breast cancer surveillance (in females) are usually recommended
- FIGC is defined as familial clustering of intestinal GC where no hereditary cause can be identified. *H. pylori* eradication and frequent gastroscopies can be discussed with high-risk patients
- To identify a causative germline mutation in a patient with a suspected hereditary GI cancer syndrome, a multi-gene panel analysis is usually the method of choice
- Once a germline mutation has been identified in the index case, genetic counselling and predictive testing should be offered to all relatives at risk
- All patients and confirmed mutation carriers should be included in early-onset, intense and syndrome-specific surveillance programmes: one of the most efficient approaches of preventive oncology

Further Reading

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4 Oesophageal cancer

Epidemiology, risk factors, prognosis and classification

Oesophageal cancer is the eighth most common cancer worldwide and the sixth most common cause of cancer-related death. A steep increase in the incidence of adenocarcinoma occurred from 1973 to 2007 but may have reached its plateau.

Oesophageal squamous cell carcinoma (OSCC) comprises the majority of cases worldwide. In contrast, oesophageal adenocarcinoma (OAC) predominantly occurs in more developed countries and is mainly a disease of the male gender.

OSCC carcinogenesis is commonly triggered by exogenous agents. While in Western countries, alcohol and tobacco use is prevalent, in Asia consumption of nitrosamines also plays a role.

Overall incidence trend in oesophageal adenocarcinoma (1973-2006)

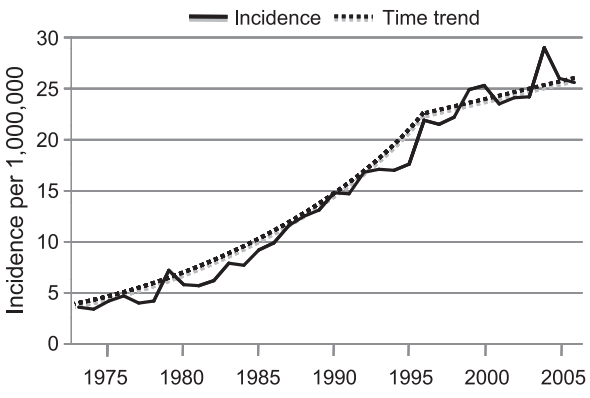
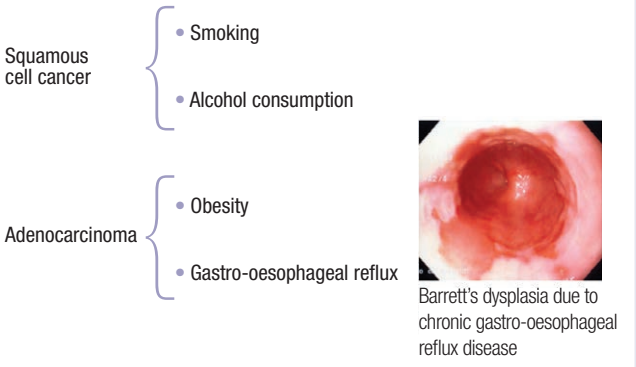


Fig. 4.1



Barrett's dysplasia due to chronic gastro-oesophageal reflux disease

Fig. 4.2

Oesophageal metaplasia is a risk factor for OAC. OAC often develops via metaplasia of the distal oesophagus epithelium. Oesophageal metaplasia (so-called Barrett's mucosa) is induced by chronic gastro-oesophageal reflux. Visceral (male) obesity is a prevalent risk factor.

While OAC is usually located in the distal oesophagus, OSCC can be located in the upper, mid or distal oesophagus. While the median age at diagnosis of OAC is 64 years, OSCC is diagnosed at a median age of 56 years.

Lymphatic spread in oesophageal cancers occurs early, when the submucosal layer is reached. The prognosis of resected tumours is critical. Lymphatic spread is associated with poorer prognosis.

Patients with OSCC often present with comorbid conditions: malnutrition, chronic obstructive lung disease and liver cirrhosis have a high prevalence.

In patients with OAC, obesity, arterial hypertension, diabetes and coronary heart disease are common.

According to the 8th edition of the Tumour, Node, Metastasis (TNM) classification system, two types of adenocarcinoma of the oesophagogastric junction (OGJ) (AEG, type I-II according to Siewert, 1998) are staged as oesophageal cancers, while AEG type III is staged as gastric cancer.

Adenocarcinoma of the oesophagogastric junction (AEG type I-III, Siewert)

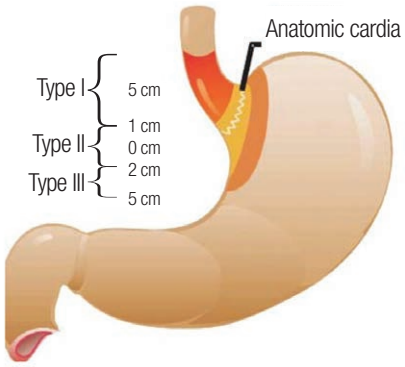


Fig. 4.3

REVISION QUESTIONS

1. How has the incidence of OAC versus OSCC changed over recent decades?
2. What are the major risk factors for OAC and for OSCC?
3. What is the typical location of OAC and of OSCC?

Diagnostic work-up and staging

Endoscopic ultrasound (EUS) is the most accurate method to determine the tumour (T) category. However, the accuracy is operator-dependent and inter-observer variability is significant.

Pooled sensitivity and specificity for T1-T4 staging range between 81.6%–92.4% and 94.4%–99.4%, respectively.

The assessment of nodal involvement (N[node]-category) is more variable with a high sensitivity (up to 91%) but a lower specificity.

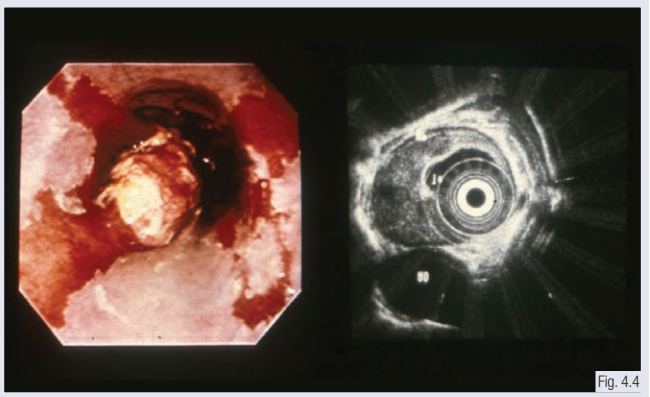


Fig. 4.4

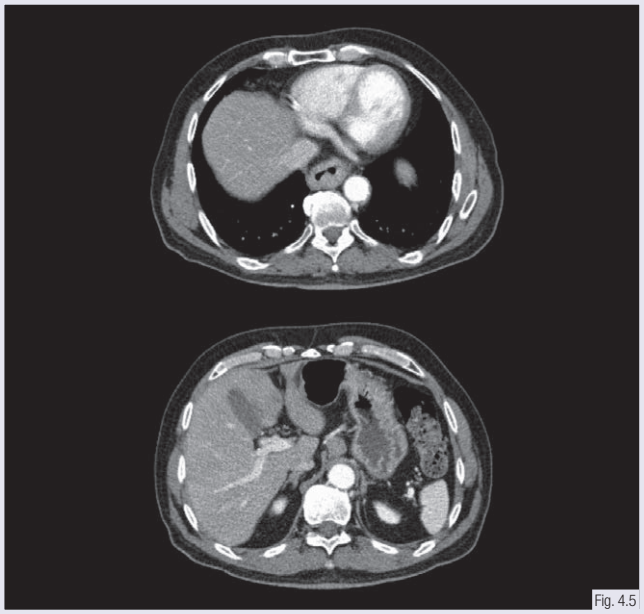


Fig. 4.5

High-resolution multidetector computed tomography (CT) of the thorax and abdomen should be performed to rule out distant metastases and to complement EUS for T- and N-staging.

For proximal tumours, the CT should include the neck region to rule out cervical lymphadenopathy.

The accuracy of CT in determining locoregional nodal involvement is limited. Sensitivity has been observed to be as low as 50%, while specificity was 83%. Staging laparoscopy should be considered for junctional cancers, particularly if there is evidence of intra-abdominal nodal disease.

Positron emission tomography (PET) scanning should be used in combination with CT.

Fluorodeoxyglucose (FDG)/PET adds information for detecting distant metastases. It can thereby help to avoid futile oesophagectomies.

In contrast, the accuracy of FDG/PET to determine N involvement and category is limited. Sensitivity has been observed to be as low as 57%, while specificity was 85%.

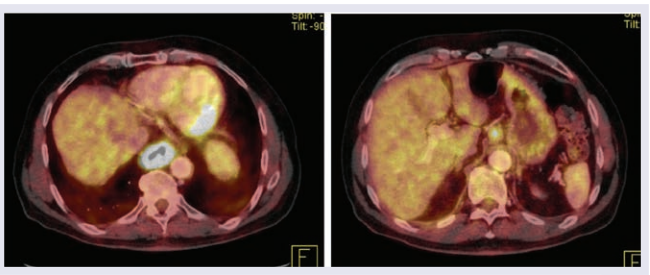


Fig. 4.6

REVISION QUESTIONS

1. What is the most accurate method to determine the T-category?
2. What is the goal of CT in oesophageal cancer?
3. Does FDG/PET add significant information for determining the T- and N-categories?

Surgical treatment

Surgery offers a curative potential in localised oesophageal cancer without distant metastases. There is a strong relationship between lower hospital mortality and increasing surgeon and institutional patient volumes.

Large-volume units consistently report hospital mortalities ≤5%. This reflects careful patient selection and focused multidisciplinary team management with review and audit of outcome.

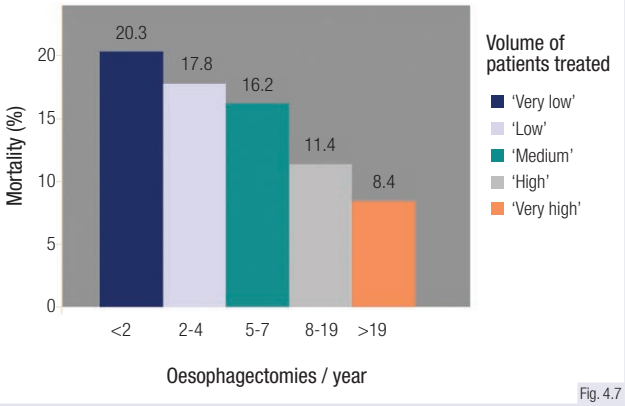
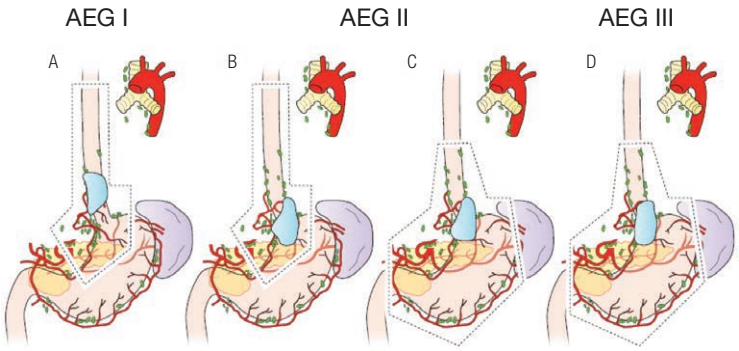


Fig. 4.7

In very early stages, endoscopic resection is recommended over surgery. Due to a 30% rate of lymph node metastases in carcinomas infiltrating the submucosa, endoscopic resection is not recommended in cancers infiltrating beyond the mucosal layer. There is one exception: if infiltration reaches <500 µm deep into the submucosal layer, endoscopic resection can be acceptable.



AEG, adenocarcinoma of the oesophagogastric junction.

Fig. 4.8

Radical oesophagectomy with extended lymphadenectomy is the surgical technique of choice for resection of intrathoracic oesophageal cancers. Nowadays, minimally invasive approaches to the abdominal part of the operation are standard in expert centres. Compared with open surgery, minimally invasive oesophagectomy leads to comparable oncological outcomes and significantly fewer complications.

Transthoracic subtotal oesophagectomy (Ivor Lewis) has been compared with the transhiatal approach and, although there was no overall benefit, there is an advantage for transthoracic surgery for N-positive cancers.

Despite the optimisation of surgical treatment and the development of high-volume centres, outcome following oesophageal resection remains unsatisfactory. Prognosis depends on completeness of resection (R-status) and on T- and N-categories.

The R-status is one of the strongest prognostic factors. Resections without clear margins are not curative.

The probability of achieving an R0 status is associated with the depth of tumour infiltration into the oesophageal wall (T-category). It is between only 50% and 70% in primarily resected T3/T4 tumours.

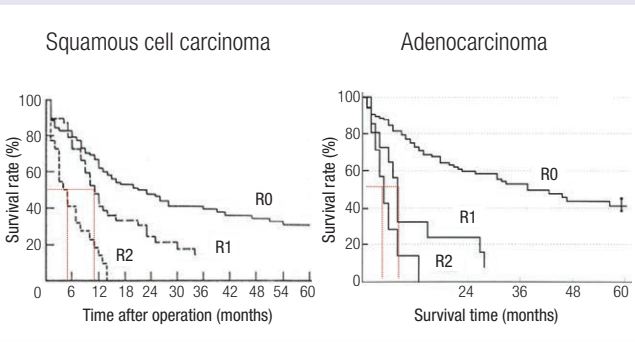


Fig. 4.9

REVISION QUESTIONS

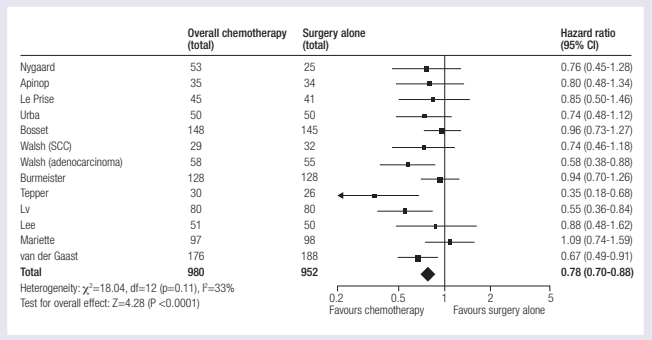
1. On which prognostic factor does post-oesophagectomy mortality particularly depend?
2. What is the recommended resection technique in distal oesophageal adenocarcinoma?
3. What is the probability of an R0 resection in a primarily resected T3/T4 oesophageal carcinoma?

Neoadjuvant treatment

Neoadjuvant treatment is an evidence-based treatment option in oesophageal cancer. The goal of neoadjuvant (preoperative) treatment is to increase the R0 resection rate and improve overall survival.

Neoadjuvant combined chemoradiotherapy (CRT) and perioperative chemotherapy (ChT) alone are effective in locally advanced oesophageal cancer.

For OSCC, neoadjuvant CRT leads to significantly better survival, while ChT alone is only marginally effective. For OAC, both neoadjuvant CRT and ChT lead to significantly improved survival outcomes.



CI, confidence interval; SCC, squamous cell carcinoma. Fig. 4.10

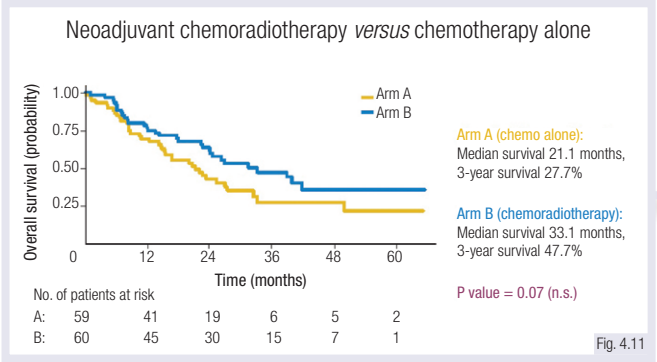


Fig. 4.11

n.s., not significant.

A small randomised study in OAC and OGJ cancer showed a trend towards better survival for neoadjuvant CRT when compared with ChT.

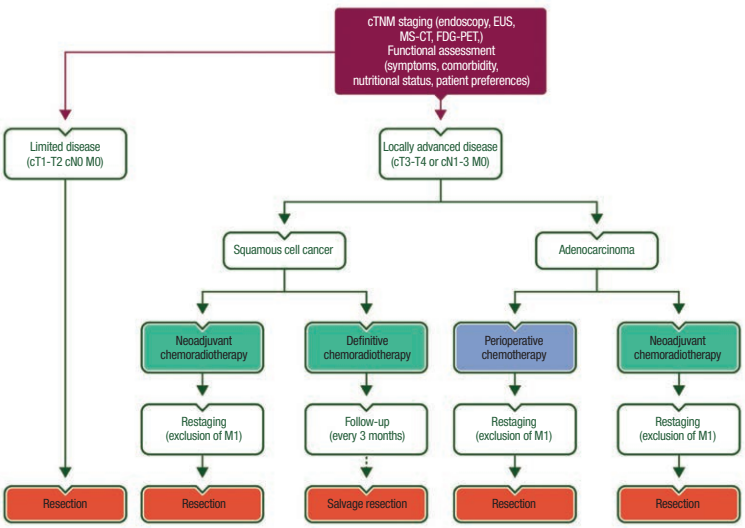
One meta-analysis concluded: "A clear advantage of neoadjuvant CRT over neoadjuvant ChT has not been established".

Ongoing and adequately powered randomised controlled trials (RCTs) are comparing neoadjuvant CRT with ChT.

Current national and international guidelines recommend neoadjuvant treatment for T3 and resectable T4 oesophageal cancers.

The indication for neoadjuvant treatment in T1b/T2 tumours is debated. Nodal involvement is difficult to assess and hence is an unreliable criterion for neoadjuvant treatment outside an RCT.

The decision for neoadjuvant CRT followed by surgery in OSCC must be taken together with the informed patient ('shared decision-making'), as RCTs did not show a clear survival advantage for surgery, compared with definitive CRT.



CRT, chemoradiotherapy; cTNM, clinical tumour, node, metastases classification according to AJCC/UICC (American Joint Committee on Cancer/Union for International Cancer Control); EUS, endoscopic ultrasound; FDG-PET, fluorodeoxyglucose-positron emission tomography; MS-CT, multislice-computed tomography. Fig. 4.12

REVISION QUESTIONS

1. Is neoadjuvant treatment an 'evidence-based' treatment option in locally advanced oesophageal cancer?
2. Is the effect of neoadjuvant CRT and neoadjuvant ChT equivalent in OSCC?
3. Is there a clearly established advantage for neoadjuvant CRT over neoadjuvant ChT in oesophageal cancer?

Chemoradiotherapy

The randomised Dutch CROSS study reinforced the value of neoadjuvant CRT in localised oesophageal cancer.

The CROSS study included 363 patients: 75% with OAC, 25% with OSCC, >80% with T3/T4 tumours and >60% with a positive nodal status.

The experimental arm contained CRT with a radiation dose of 41.4 Gy (1.8 Gy per fraction) plus concomitant carboplatin AUC2 (area under the curve 2) and paclitaxel 50 mg/m^2 given once weekly (x 5).

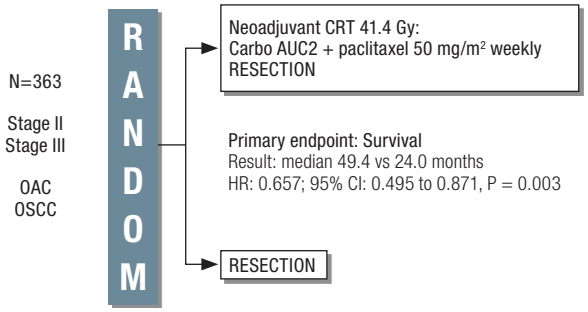


Fig. 4.13

AUC, area under the curve; Carbo, carboplatin; CI, confidence interval; CRT, chemoradiotherapy; HR, hazard ratio; OAC, oesophageal adenocarcinoma; OSCC, oesophageal squamous cell carcinoma.

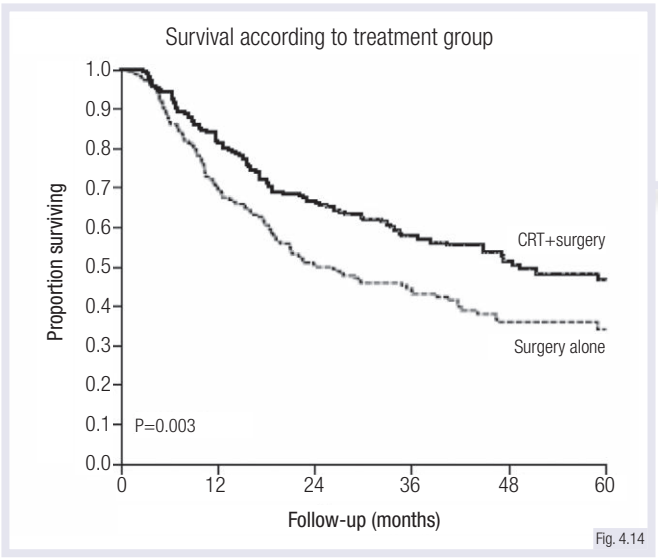


Fig. 4.14

CRT, chemoradiotherapy.

CROSS showed a significant survival advantage in favour of neoadjuvant CRT: median survival 49.4 months vs 24.0 months, hazard ratio (HR): 0.647, p = 0.003.

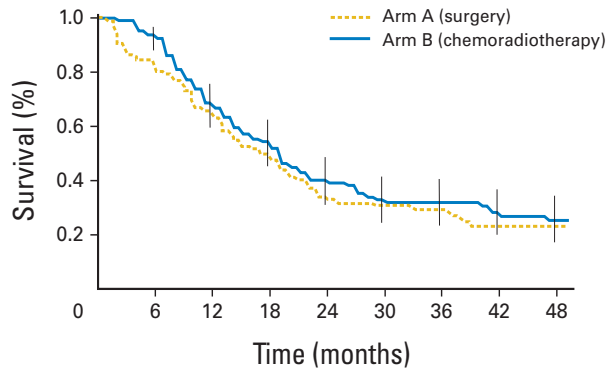
However, the benefit seemed to be greater for OSCC (HR: 0.453) compared with OAC (HR: 0.732).

Of note, with modern radiation planning and optimised interdisciplinary coordination, no increased postoperative mortality was observed (4% in both arms).

Neoadjuvant CRT followed by surgery was previously compared with definitive CRT in OSCC.

Two randomised studies (one in France [89% OSCC] and one in Germany [100% OSCC]) observed improved local tumour control with surgery, but did not show a significant survival advantage for surgery.

Therefore, definitive radiotherapy combined with platinum +5-fluorouracil (5-FU) ChT is an alternative option for patients with locally advanced OSCC.



	CRT	Surgery	P
Mortality	1%	9%	0.002
Stent	27%	13%	0.005
Median survival	19.3 months	17.7 months	n.s.

CRT, chemoradiotherapy; n.s., not significant.

Fig. 4.15

REVISION QUESTIONS

1. Patients with which histologies and which tumour stages were included in the randomised CROSS study?
2. Did the CROSS study show a significant survival advantage for neoadjuvant CRT?
3. Is definitive CRT equivalent to neoadjuvant CRT followed by oesophagectomy in localised OSCC?

Chemotherapy, targeted therapy and immunotherapy for palliation

While mediastinal relapses have become rarer in oesophageal cancer patients treated with neoadjuvant therapies plus oesophagectomy and lymphadenectomy, haematogenous relapses remain a significant problem.

Oesophageal cancer is often diagnosed primarily with distant (haematogenous and/or lymphatic) metastases. Therefore, effective ChT is clearly warranted.

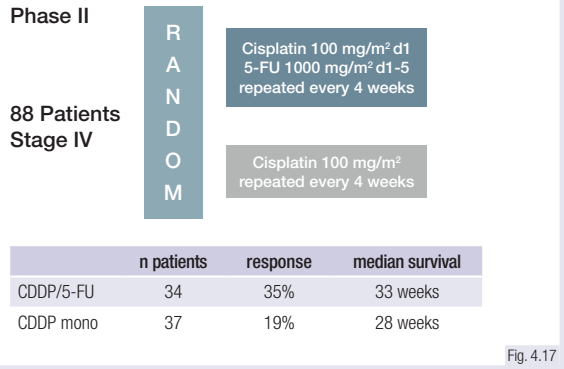
Very few trials have been conducted in advanced oesophageal cancer. The evidence on how to best treat advanced oesophageal cancer is rather weak.

Relapses following curative treatment with CRT + resection

Relapse	After resection (n=161) n	%	After CRT + resection (n=213) n	%	HR	P-value
Mediastinal	33	20.5%	15	7.0%	0.29	<0.001
Haematogenous	57	35.4%	61	28.5%	0.67	0.03

CRT, chemoradiotherapy; HR, hazard ratio.

Fig. 4.16



	n patients	response	median survival
CDDP/5-FU	34	35%	33 weeks
CDDP mono	37	19%	28 weeks

Fig. 4.17

5-FU, 5-fluorouracil; CDDP, cisplatin.

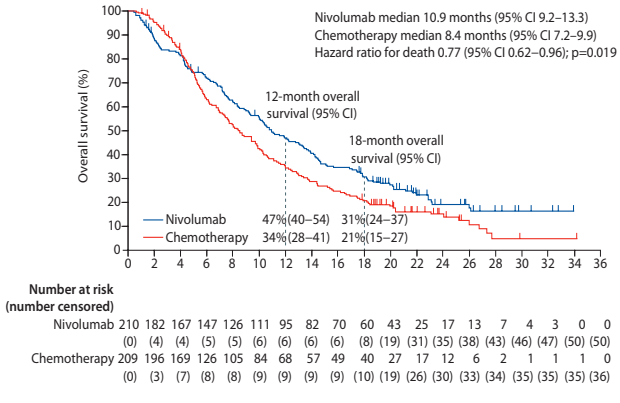
Many physicians are treating advanced oesophageal cancer like advanced gastric cancer, but it is not clear whether this pragmatic approach is justified.

"The severe side-effects induced by the combination suggest that, currently, no standard chemotherapy can be recommended for patients with advanced squamous cell oesophageal cancer…" (Bleiberg, 1997).

Newly identified molecular targets and targeted therapies may allow for better and more efficacious treatment in oesophageal cancer.

Human epidermal growth factor receptor 2 (HER2), which is expressed in about 20% of patients with AEG, is an established drug target. Trastuzumab, an anti-HER2 monoclonal antibody, improved outcomes in advanced HER2-positive gastric and OGJ cancer.

Oesophageal cancer, especially OSCC, is sensitive to immunotherapy. Nivolumab was associated with a significant improvement in overall survival and a favourable safety profile compared with ChT (paclitaxel or docetaxel) in previously treated patients with advanced OSCC, and might represent a new standard second-line treatment option for these patients.



CI, confidence interval.

Fig. 4.18

REVISION QUESTIONS

1. What is more common after neoadjuvant therapy and oesophagectomy: locoregional or distant relapse?
2. Which treatment is regarded as standard-of-care for first-line treatment of patients with metastatic oesophageal cancer?
3. Which biomarker should be assessed for selecting the most efficacious treatment for patients with metastatic AEGs?

Summary: Oesophageal cancer

- While the incidence of OSCC has decreased in some parts of the Western world, the incidence of OAC has increased dramatically over the past 4 decades
- Treatment of oesophageal cancer is stage-dependent
- Diagnostic work-up should comprise endoscopy and EUS (for T-categorisation), CT and, if available, FDG/PET (for exclusion of distant metastases). Nodal staging is inaccurate
- Neoadjuvant treatment has proven benefit in the locally advanced stages of oesophageal cancer, especially for T3 and resectable T4 cancers
- In OAC, both neoadjuvant ChT or neoadjuvant CRT can be recommended before surgery
- In OSCC, neoadjuvant CRT followed by surgery produces similar results to definitive CRT. Surgery after definitive CRT should be considered for those with residual disease or local relapse, but will also be determined by patient factors
- There is no standard ChT regimen for the treatment of advanced oesophageal cancer. Pragmatically, many physicians treat advanced oesophageal cancer like advanced gastric cancer

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Gastric cancer

Epidemiology and clinical presentation

Gastric cancer is the fourth most commonly diagnosed tumour type worldwide. However, its incidence, particularly in the corpus/antral location, is decreasing in Western countries.

Gastric cancer with corpus and antral location is related to *Helicobacter pylori* (*H. pylori*) infection as a causative agent.

In Western countries, tumours located around the gastro-oesophageal junction (GEJ), are increasing in prevalence, mainly in men, smokers and the overweight. GEJ adenocarcinoma is strongly linked to a history of reflux and the presence of Barrett's oesophagus.

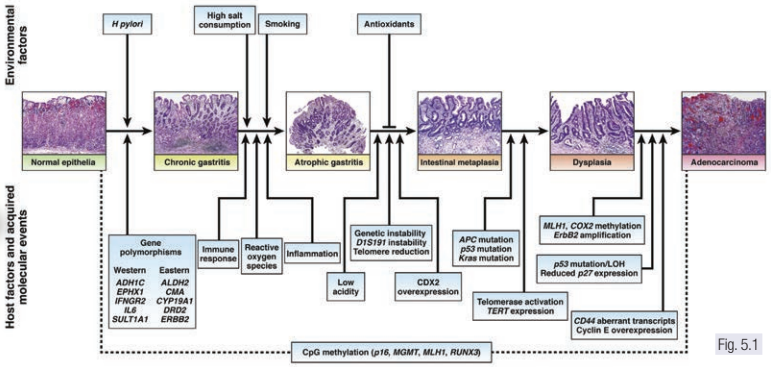


Fig. 5.1

APC, adenomatous polyposis coli; *H. pylori*, *Helicobacter pylori*; LOH, loss of heterozygosity; MGMT, O-6-methylguanine-DNA methyltransferase; MLH1, MutL homologue 1; TERT, telomerase reverse transcriptase.

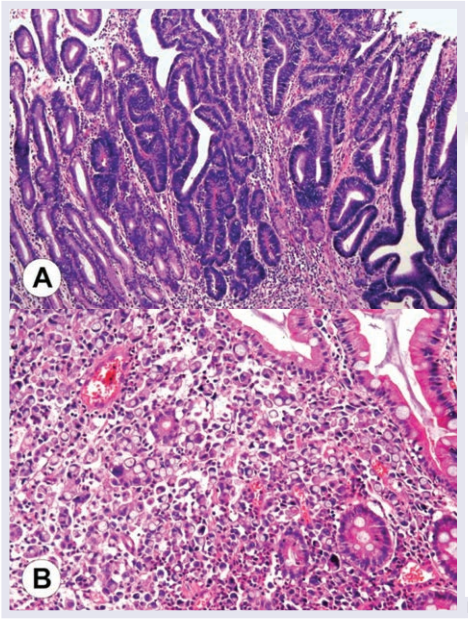


Fig. 5.2

Gastric cancer, according to the Lauren classification, can be defined as intestinal (A) or diffuse (B).

The World Health Organization (WHO) classification recognises four major histological patterns: tubular, papillary, mucinous and poorly cohesive (including signet ring cell carcinoma), plus uncommon histological variants.

Less than 10% of gastric cancers are hereditary. Mutations in *p53* (Li–Fraumeni), *STK11* (Peutz–Jeghers), familial *APC* (adenomatous polyposis coli) or mismatch repair genes (Lynch), are the most common. Hereditary diffuse gastric cancer is related to *CDH1* mutations.

Gastric cancer can cause vague symptoms until an advanced stage. Abdominal pain, weight loss, dysphagia, dyspepsia, vomiting, bleeding, early satiety and/or iron-deficiency anaemia may be observed.

Palpable epigastric mass, jaundice, periumbilical masses, left supraclavicular nodes and acanthosis nigricans are generally late events indicating metastatic disease.

Diagnosis should be made from a gastroscopic or surgical biopsy, reviewed by an experienced pathologist. Histology should be reported according to the WHO criteria and the Lauren classification.

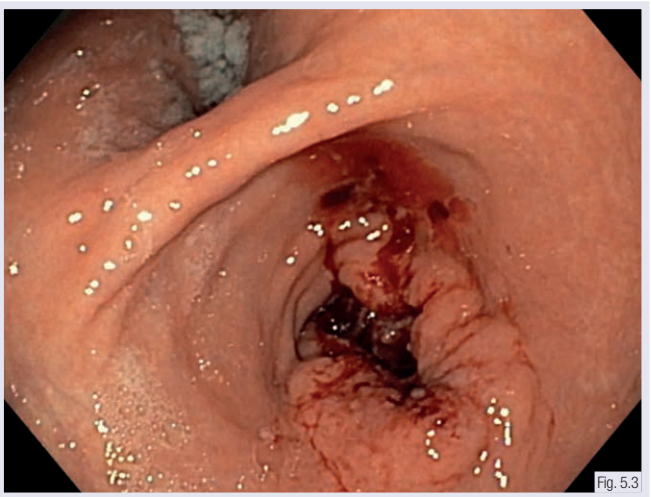


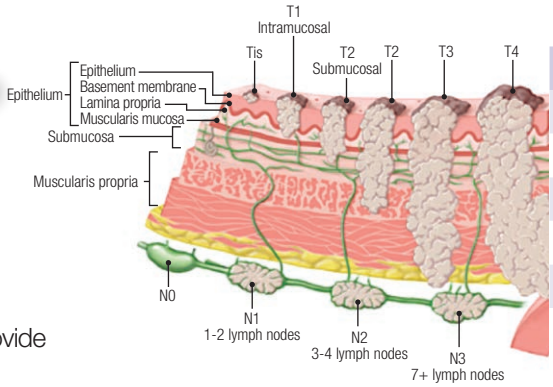
Fig. 5.3

REVISION QUESTIONS

1. What is the role of *H. pylori* in gastric cancer carcinogenesis?
2. What are the main subtypes of gastric cancer according to the Lauren classification?
3. Which subtype is related to *CDH1* mutations?

Diagnostic work-up, staging and surgery for localised disease

Clinical staging is performed according to the Tumour, Node, Metastasis (TNM) classification (8th edition) of the Union for International Cancer Control (UICC)–American Joint Committee on Cancer (AJCC) staging manual.



	T	N	M
STAGE I	T1-2	N0	M0
STAGE IIA	T1-2	N1-3	M0
STAGE IIB	T3-4a	N0	M0
STAGE III	T3-4a	N1-3	M0
STAGE IVA	T4b	N1-3	M0
STAGE IVB	Any T	Any N	M1

Fig. 5.4

Tis, carcinoma *in situ*.

A computed tomography (CT) scan of the thorax and abdomen is mandatory to search for distant metastasis.

Endoscopic ultrasound (EUS) can be performed to provide more accurate information on T (tumour) and N (node) status of the tumour. Laparoscopy plus peritoneal washings may be useful to rule out peritoneal carcinomatosis. Fluorodeoxyglucose-positron emission tomography (FDG-PET) CT can detect 'CT-occult' metastases in ~15% of patients.

Location and grading of the lymph nodes D1 resection

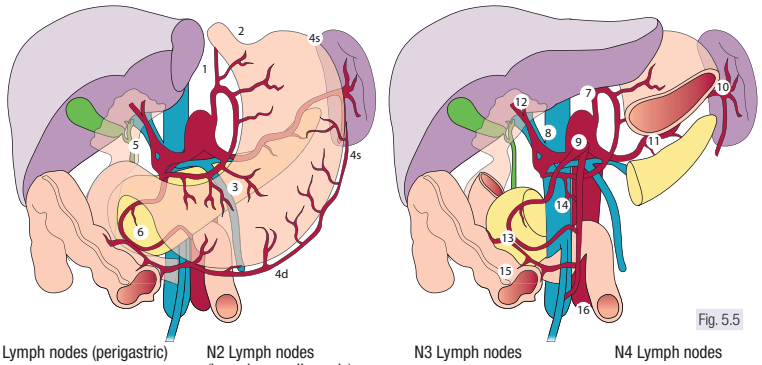


Fig. 5.5

N1 Lymph nodes (perigastric)
1 Right cardiac nodes
2 Left cardiac nodes
3 Nodes along the lesser curvature
4d Lymph nodes along the short gastric and the left gastroepiploic vessels
4s Lymph nodes along the right gastroepiploic vessels
5 Suprapyloric nodes
6 Infrapyloric nodes

N2 Lymph nodes (branches coeliac axis)
7 Nodes along root left gastric artery
8 Nodes along common hepatic artery
9 Nodes around coeliac axis
10 Nodes at splenic hilum
11 Nodes along splenic artery

N3 Lymph nodes
12 Nodes at the hepatoduodenal ligament
13 Retropancreatic (periduodenal) nodes
14 Nodes at the root of the mesentery

N4 Lymph nodes
15 Nodes along the middle colic vein
16 Para-aortic nodes

Surgery is the only curative modality to treat localised gastric cancer. For reliable pathological TNM staging, a minimum of 15 recovered and examined lymph nodes is required.

Radical gastrectomy is indicated for resectable stage IB-III disease. Subtotal gastrectomy may be carried out if a macroscopic proximal margin of 5 cm can be achieved between the tumour and the GEJ.

A margin of 8 cm is advocated for diffuse-type cancers. Otherwise, a total gastrectomy is indicated.

D2 lymphonodal dissection is considered the standard surgical approach for localised gastric cancer patients. It comprises the removal of perigastric (D1) and coeliac lymph nodes.

Surgery for gastric cancer should be carried out in specialised, high-volume centres.

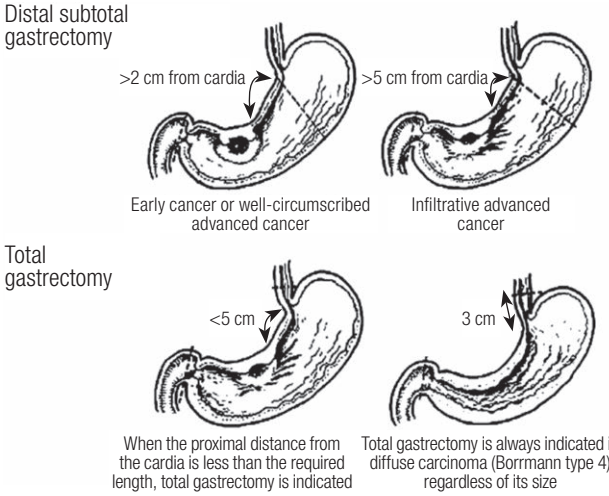


Fig. 5.6

REVISION QUESTIONS

1. What is the most appropriate diagnostic tool to define locoregional disease?
2. What could be considered the most relevant approach for localised gastric cancer?
3. Which kind of lymphadenectomy could be considered the standard of care?

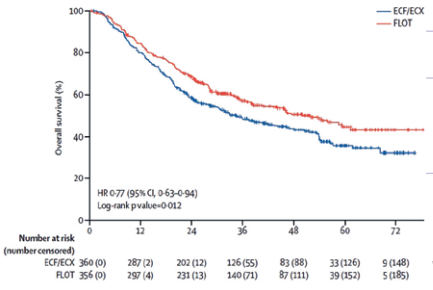
Chemotherapy in locally advanced and metastatic disease

Perioperative chemotherapy (ChT) with FLOT (5-fluorouracil [5-FU]/leucovorin/oxaliplatin/docetaxel) is the preferred approach for treating localised resectable gastric cancer in Europe. Alternative platinum/fluoropyrimidine combinations can be considered if patients are ineligible for FLOT.

Gastric cancer patients with microsatellite instability (MSI) do not benefit from adjuvant or neoadjuvant ChT.

Post-operative radiotherapy does not result in any benefit when added to perioperative ChT.

5-FU/leucovorin/oxaliplatin/docetaxel vs ECF/ECX as preoperative chemotherapy for gastro-oesophageal adenocarcinoma: The FLOT-4 Study – Results on overall survival



	ECF/ECX	FLOT
mOS	35 months [27-46]	50 months [38-na]
HR	0.77 [0,63 – 0,94] p=0.012 (log rank)	

OS rate*	ECF/ECX	FLOT
2y.	59%	68%
3y.	48%	57%
5y.	36%	45%

*projected OS-rates

Fig. 5.7

5-FU, 5-fluorouracil; CI, confidence interval; ECF, epirubicin/cisplatin/5-FU; ECX, epirubicin/cisplatin/capecitabine; FLOT, 5-FU/leucovorin/oxaliplatin/docetaxel; HR, hazard ratio; mOS, median overall survival; OS, overall survival.

Overall survival estimate after any chemotherapy or surgery alone truncated at 10 years

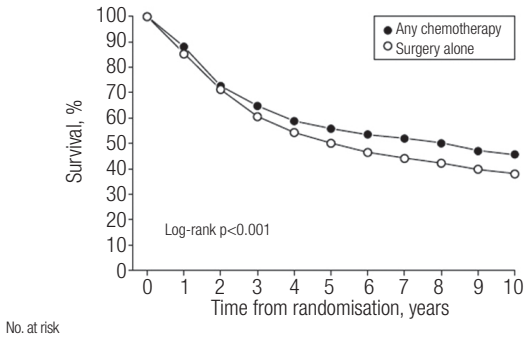


Fig. 5.8

Patients treated with primary surgery may benefit from adjuvant ChT or postoperative chemoradiotherapy (CRT). Based on the CROSS trial, the use of preoperative CRT should be limited to GEJ adenocarcinomas.

The use of perioperative trastuzumab vs trastuzumab/pertuzumab is under investigation for human epidermal growth factor receptor 2 (*HER2*)-amplified tumours but it is not standard practice in early stage cancers.

The role of preoperative CRT after preoperative ChT in patients with resectable gastric and GEJ cancer can still be considered experimental.

Patients diagnosed with stage IV disease should be considered for palliative ChT, due to its ability to improve survival and quality of life.

Recommended drug combinations are a platinum/fluoropyrimidine doublet or a taxane-containing triplet. Doublets are preferred for most patients. Triplets (e.g. docetaxel/cisplatin/5-FU [DCF]) should be restricted to patients with excellent performance status. Irinotecan-based combinations may also be used.

Oxaliplatin may substitute cisplatin and has a better toxicity profile, while capecitabine can be used instead of infusional 5-FU if the patient can swallow tablets. Anthracyclines are no longer recommended.

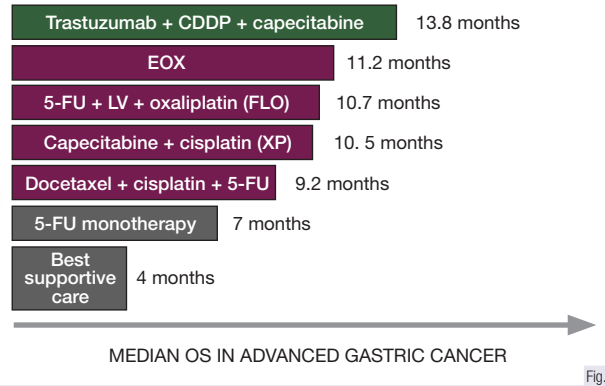


Fig. 5.9

5-FU, 5-fluorouracil; CDDP, cisplatin; EOX, epirubicin/oxaliplatin/capecitabine; LV, leucovorin; OS, overall survival.

REVISION QUESTIONS

1. What is the best treatment strategy for patients diagnosed with locally advanced disease?
2. Why should patients diagnosed with metastatic disease be considered for systemic treatment?
3. What are the most active chemotherapeutic agents approved in the first-line setting?

Targeted agents in first-line for advanced/metastatic disease

HER2 is an important biomarker and key driver of tumourigenesis in gastric cancer patients. *HER2* is amplified or overexpressed in 15%-20% of gastric cancers.

The status of *HER2* amplification (by fluorescent *in situ* hybridisation [FISH] or immunohistochemistry [IHC]) must be determined in all advanced gastric and gastro-oesophageal cancer patients before starting first-line therapy.

HER2 overexpression is more often found in intestinal-type (30%) than in diffuse-type (5%) gastric cancer.

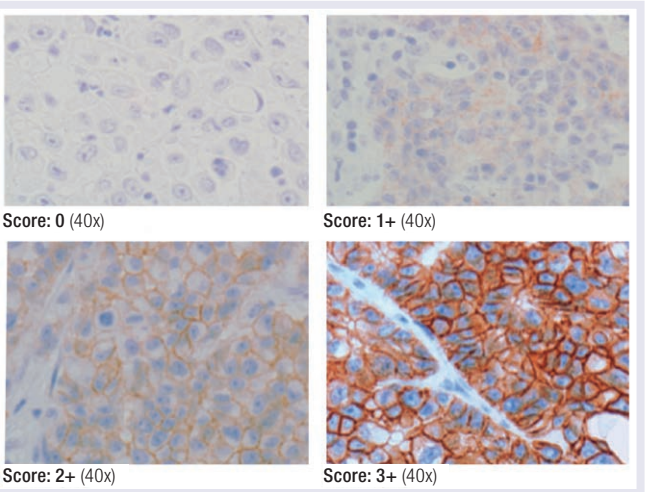


Fig. 5.10

Phase III trials on HER2 blockade for *HER2*-amplified advanced gastro-oesophageal adenocarcinomas

Trial	Chemotherapy backbone	Line of therapy number	HR OS	P value	Response rate
ToGA	Cisplatin+5-FU/ capecitabine	First 584	0.74	0.04	51% vs 37% p=0.0017
LOGiC	Oxaliplatin/capecitabine +/-lapatinib	First 545	0.91	0.35	53% vs 39% p=0.031
TyTAN	Paclitaxel+/-lapatinib	Second 261	0.84	0.20	27% vs 9% p=0.001
GATSBY	T-DM1 vs taxane	Second 345	1.15	0.85	NR
JACOB	Cisplatin+5-FU/ capecitabine/trastu +/- pertuzumab	First 780	0.84	0.056	56% vs 48% p=0.026

5-FU, 5-fluorouracil; HR, hazard ratio; HER2, human epidermal growth factor receptor 2; NR, not reported; OS, overall survival; T-DM1, trastuzumab emtansine.

Fig. 5.11

Trastuzumab added to cisplatin/fluoropyrimidine ChT in first-line *HER2*-amplified gastric cancer patients (ToGA trial) led to a significant improvement in response rate, progression-free survival (PFS) and overall survival (OS).

Heterogeneity of HER2 expression is an important feature in gastric cancer, leading to potential sampling error and to decreased efficacy of trastuzumab. Multiple biopsies are required to accurately confirm HER2 status.

Other anti-HER2 blocking strategies such as lapatinib, the addition of pertuzumab to trastuzumab and the use of trastuzumab emtansine (T-DM1) failed to improve survival for gastric cancer patients.

Antiangiogenics, anti-EGFR (epidermal growth factor receptor) antibodies and MET inhibitors failed to show a survival benefit for patients with advanced gastric adenocarcinoma in first-line.

Checkpoint inhibitors (anti-programmed cell death protein 1 [PD-1] and cytotoxic T-lymphocyte antigen 4 [CTLA-4] antibodies) are under investigation in the first-line setting for gastric cancer.

Phase III trials with targeted therapies in first-line treatment for advanced gastro-oesophageal adenocarcinomas

TRIAL	Chemotherapy	Biological	HR OS	P value	Change in median survival over control arm
ToGA	Cisplatin+5-FU/ capecitabine	Trastuzumab	0.74	0.04	+2.8 months
AVAGAST	Cisplatin+ capecitabine	Bevacizumab	0.87	0.10	+2.0 months
AVATAR	Cisplatin+ capecitabine	Bevacizumab	1.11	0.55	-0.9 months
RAINFALL	Cisplatin+5-FU/ capecitabine	Ramucirumab	0.96	0.68	+0.5 months
EXPAND	Cisplatin+ capecitabine	Cetuximab	1.00	0.95	-1.3 months
REAL-3	Oxaliplatin+epi- + capecitabine	Panitumumab	1.37	0.013	-2.5 months
RILOMET-1	Cisplatin+epi- + capecitabine	Rilotumumab	--	--	Stopped in futility analysis
METGastric	FOLFOX6	Onartuzumab	1.06	0.83	-0.6 months

5-FU, 5-fluorouracil; epi, epirubicin; FOLFOX6, leucovorin/5-FU/oxaliplatin; HR, hazard ratio; OS, overall survival.

Fig. 5.12

REVISION QUESTIONS

1. Which is the most relevant and targetable biomarker to be identified in metastatic gastric cancer patients?
2. In which subtype is *HER2* amplification most represented?
3. Apart from HER2-blocking agents, are there other targeted agents approved for metastatic gastric cancer?

Treatment beyond first-line for advanced/metastatic disease

Second-line ChT with single-agent irinotecan, docetaxel or paclitaxel is associated with better survival and quality of life and is therefore recommended for fit patients.

Single-agent therapy with ramucirumab, a monoclonal antibody targeting vascular endothelial growth factor receptor 2 (VEGFR2), led to improved survival compared with supportive care. Ramucirumab also increased survival when combined with weekly paclitaxel.

Trifluridine/tipiracil given as third-line therapy can prolong survival over best supportive care.

Second-line chemotherapy and targeted agent trials comparing with BSC or active treatment

Trial author	Year	Patients random (n)	Treatment	HR OS	P value	Gain in median survival
Thuss-Patience, et al.	2011	40 1:1	Irinotecan	0.48	0.0023	2.4 months
Kang, et al.	2012	193 2:1	Irinotecan Docetaxel	0.65	0.004	1.3 months
Ford, et al.	2014	168 1:1	Docetaxel	0.67	0.01	1.6 months
Otshu, et al.	2013	656 2:1	Everolimus	0.90	0.124	0.9 months
Fuchs, et al.	2014	355 2:1	Ramucirumab	0.77	0.047	1.4 months

BSC, best supportive care; HR, hazard ratio; OS, overall survival. Fig. 5.13

Nivolumab (an anti-PD-1 antibody) showed improved survival compared with placebo in an Asian trial of chemo-refractory (third-line) gastric cancer (ATTRACTION-2); however, it is not licensed in Europe yet.

Pembrolizumab (an anti-PD-1 antibody) is licensed in the USA for patients with chemo-refractory (third-line and beyond) gastric cancer who express programmed death-ligand 1 (PD-L1). However, pembrolizumab did not improve survival when compared with paclitaxel in a second-line trial or when combined with cisplatin/fluoropyrimidine in a second-line trial. The anti-PD-L1 antibody avelumab did not improve survival compared with ChT for chemorefractory gastric cancer patients.

Gastro-oesophageal adenocarcinomas: Third- or further-line therapy randomised trials comparing with BSC or active treatment

Trial author	Year	Patients random (n)	Treatment	HR OS	P value	mOS and gain in median survival
Shitara, et al. TAGS Third-line	2018	507 2:1	Trifluridine/ tipiracil vs BSC	0.69	0.0003	5.7 vs 3.6 2.1 months
Bang, et al. JAVELIN 300 Third or further lines	2018	371 1:1	Avelumab vs investigator's choice of chemotherapy	1.10	ns	4.6 vs 5.0 -0.4 months
Kang, et al. ATTRACTION-2 Third or further lines	2017	493 2:1	Nivolumab vs BSC	0.63	0.0001	5.26 vs 4.14 1.12 months

BSC, best supportive care; HR, hazard ratio; mOS, median OS; OS, overall survival. Fig. 5.14

The Cancer Genome Atlas (TCGA) project used a comprehensive evaluation of molecular alterations in gastric cancer by somatic copy number analysis, whole exome sequencing, DNA methylation profile, messenger RNA and microRNA sequencing and reverse phase protein array.

TCGA divides gastric cancer into four genomic subtypes: Epstein-Barr virus (EBV)-related tumours, MSI tumours, genomically stable tumours and chromosomally unstable tumours.

Each molecular subtype is enriched with distinct genomic features, suggesting the possibility to personalise treatment.

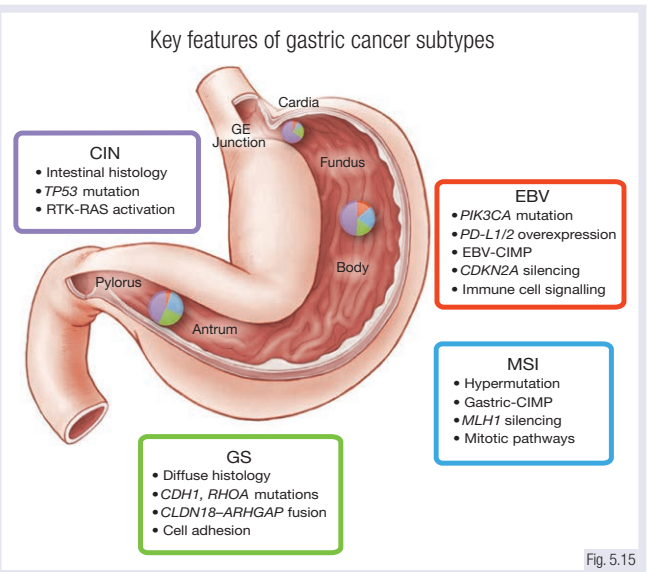


Fig. 5.15

CIMP, CpG island methylator phenotype; CIN, chromosomal instability; EBV, Epstein-Barr virus; GE, gastro-oesophageal; GS, genomically stable; MSI, microsatellite instability; PD-L1, programmed death-ligand 1; RTK, receptor tyrosine kinase; MLH1, MutL homologue 1.

REVISION QUESTIONS

1. What benefit can be derived from administering treatment beyond first-line?
2. How many genomic subtypes have been identified by the TCGA project?
3. Which biomarkers can predict response to immunotherapy?

Summary: Gastric cancer

- A diagnosis of gastric cancer should be made from gastroscopic or surgical biopsy reviewed by an experienced pathologist
- All gastric cancer patients should undergo comprehensive local and systemic staging
- Surgical resection is the basis for a curative approach in patients with localised disease
- Perioperative treatment with FLOT represents the preferred approach for treating locally advanced disease. Neoadjuvant CRT can be considered for localised tumours of the GEJ
- Patients with metastatic disease should be considered for palliative ChT
- All patients with advanced/metastatic disease should be tested for *HER2* status
- Trastuzumab associated with platinum-based ChT as first-line treatment improves survival and quality of life in *HER2*-positive tumours
- Second-line and third-line treatment should be recommended in patients with good performance status
- The need for biomarkers able to predict response or resistance to checkpoint inhibitors is urgent

Further Reading

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Colon cancer – Treatment of early-stage disease

Diagnosis and primary treatment

Colorectal cancer (CRC) is the second most frequently diagnosed malignancy in Europe, with about 75% occurring in the colon and 25% in the rectum.

Approximately 4.3% of men and women will be diagnosed with CRC at some point in their lifetime, based on 2012-2014 data.

Due to the high incidence of CRC, national screening programmes with FOBTs (faecal occult blood tests) followed by colonoscopy appear to be cost-effective for people older than 50 years.

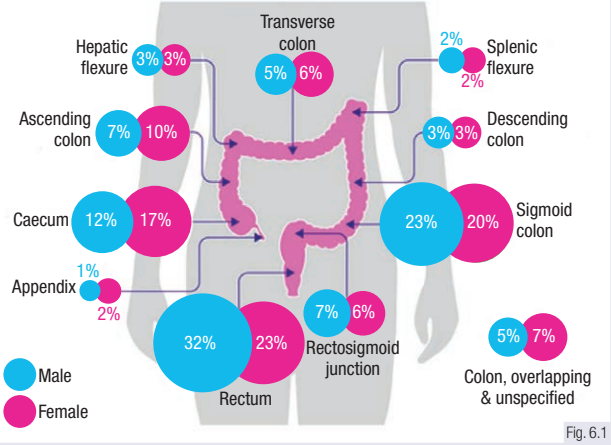


Fig. 6.1

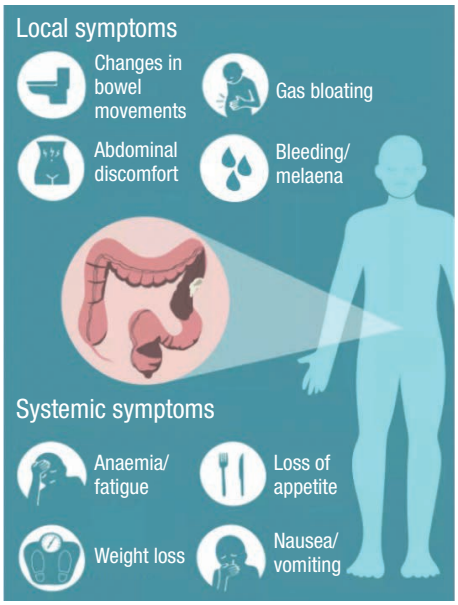


Fig. 6.2

Common signs and symptoms of CRC are: change in bowel habits, abdominal discomfort, melaena/anaemia, fatigue, abdominal mass, ascites. Bowel obstruction or tumour perforation may arise as acute presentations.

Twenty-five percent of patients are metastatic at the time of diagnosis. Diagnosis and staging examinations include: pancolonoscopy with biopsy, chest/abdomen computed tomography (CT) scan, pelvic magnetic resonance imaging (MRI) in rectal cancer, CEA (carcinoembryonic antigen); other (positron emission tomography [PET] scan, MRI, etc.) if clinically indicated.

Subsequently, the treatment plan must be discussed by a multidisciplinary team including a gastroenterologist, gastrointestinal (GI) surgeon, medical oncologist, radiologist and pathologist.

If localised, the primary tumour should be resected by a trained GI surgeon. Curative surgery consists of partial colectomy and resection of at least 12 lymph nodes (LNs). For T1 tumours, local excision by endoscopy may be discussed.

Once surgery has been performed, the pathology report is crucial to stratify risk of relapse and consequently decide the best strategy for each patient.

It should mention depth of bowel wall infiltration (pT-status), number of affected LNs (pN-status), resection margins clearance, degree of differentiation, lymphovascular/ perineural invasion and microsatellite instability (MSI) status. For stage I tumours treated by surgical/endoscopic local excision, the depth of submucosal invasion (in µm) should be specified along with the resection margins.

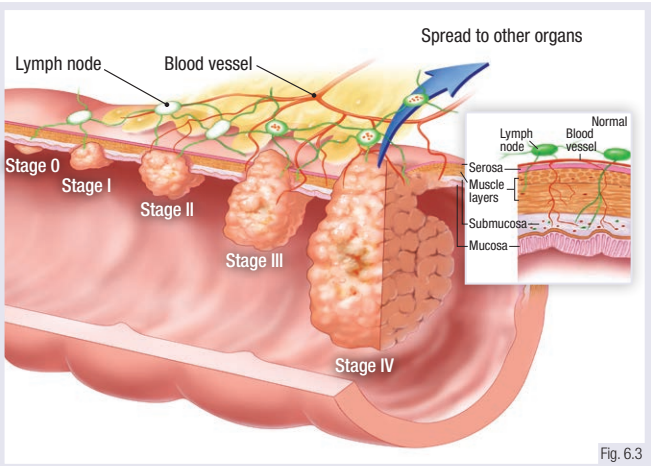


Fig. 6.3

REVISION QUESTIONS

1. What percentage of CRCs are localised in the rectosigmoid?
2. What are the correct examinations to diagnose and stage CRC?
3. Which parameters should be mentioned in a pathology report?

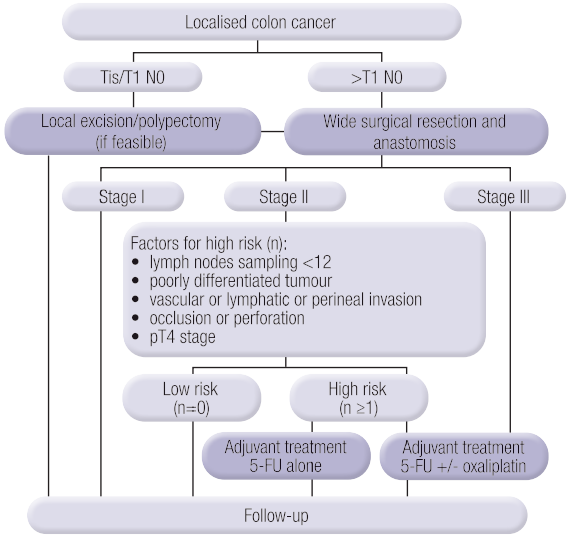
Risk of recurrence and principles of adjuvant treatment

The pTNM (pathological Tumour, Node, Metastasis) status has a strong prognostic impact on survival, and should therefore be used for postoperative decision-making.

After primary colon cancer removal, recurrence occurs in 50% of patients with nodal involvement (stage III), and 25% when there is a T3-4 tumour without nodal involvement (stage II), due to micro-metastatic spreading.

For stage I disease, long-term disease-free survival (DFS) is ≥90% and no adjuvant therapy is recommended. For stage IV, adjuvant perioperative or postoperative therapy may be indicated.

Treatment algorithm for early colon cancer



5-FU, 5-fluorouracil; N, node; T, tumour; Tis, carcinoma *in situ*. Fig. 6.5

Only 20% of stage III patients will really benefit from adjuvant ChT. Adjuvant treatment has thus always to be balanced with the patient's age and comorbidities.

FOLFOX (leucovorin/5-fluorouracil/oxaliplatin) or CAPOX (capecitabine/oxaliplatin) are the two standard regimens for stage III patients. Recent debated publications suggest oxaliplatin only benefits patients ≤70 years.

Molecular scores and markers such as BRAF, MSI, RAS, CDX2 have been shown to be highly prognostic but are not validated for treatment guidance. Circulating tumour DNA (ctDNA) may also be a good surrogate of minimal residual disease in CRC, which may guide treatment in stage II and III disease in the future.

UICC/AJCC TNM Classification and staging of colorectal cancer (8th edition)

Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
	T2	N0	M0
IIA	T3	N0	M0
IIB	T4a	N0	M0
IIC	T4b	N0	M0
IIIA	T1-T2	N1/N1c	M0
	T1	N2a	M0
IIIB	T3-T4a	N1/N1c	M0
	T2-T3	N2a	M0
	T1-T2	N2b	M0
IIIC	T4a	N2a	M0
	T3-T4a	N2b	M0
	T4b	N1-N2	M0
IVA	Any T	Any N	M1a
IVB	Any T	Any N	M1b
IVC	Any T	Any N	M1c

AJCC, American Joint Committee on Cancer; M, metastasis; N, node; T, tumour; Tis, carcinoma *in situ*; UICC, Union for International Cancer Control. Fig. 6.4

Chemotherapy (ChT) regimens based on fluoropyrimidines have been proven effective in deleting the minimal residual/micro-metastatic disease.

The addition of oxaliplatin improves survival mainly in stage III patients, with a long-term absolute increase ranging from 2.7% to 6% over fluoropyrimidines alone in three randomised clinical trials.

ChT should ideally begin within 8 weeks of surgery. The longer the delay, the lower the benefit: 12% increase in risk of death for every 4 weeks of delay in a meta-analysis of >14 000 patients in 10 trials. Thus, starting ChT more than 4-5 months after surgery is probably useless.

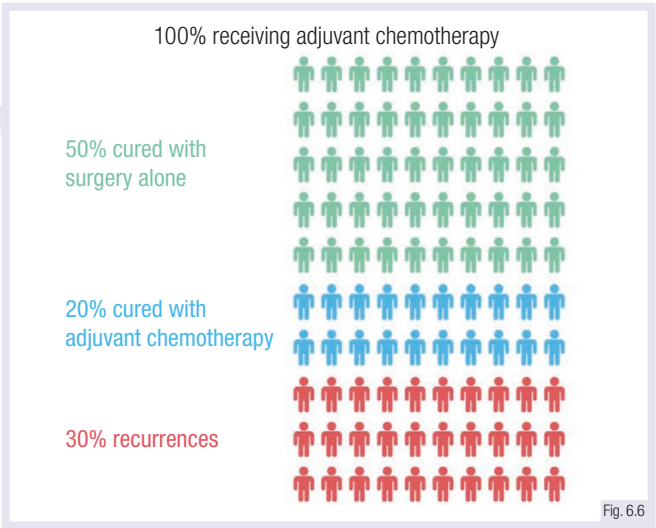


Fig. 6.6

REVISION QUESTIONS

1. Which CRC stages need adjuvant therapy after surgery?
2. How many patients benefit from adjuvant treatment?
3. What are the main drugs used for adjuvant treatment?

Adjuvant treatment in stage II

For pT3-4N0 (stage II) CRC, studies have found only small improvements in survival with the addition of ChT. This must be weighed up against the possible side effects from the ChT treatment.

Adjuvant ChT is not consensual but may be beneficial in cases of high-risk features, particularly retrieval of less than 12 LNs for analysis and pT4-stage (especially pT4b).

Less significant prognostic factors in which adjuvant ChT may be discussed are:

- Poorly differentiated tumour
- Vascular, lymphatic or perineural tumour invasion
- Bowel obstruction or tumour perforation.

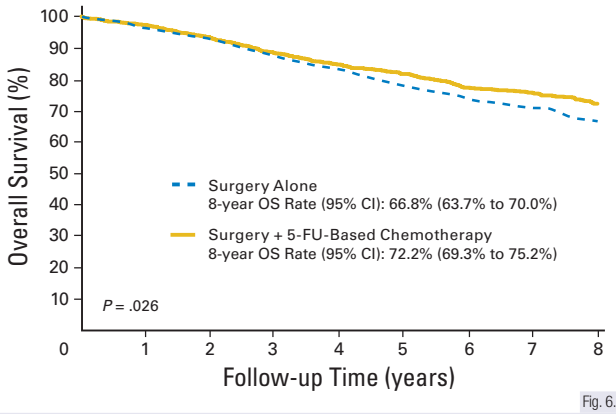


Fig. 6.7

CI, confidence interval; 5-FU, 5-fluorouracil; OS, overall survival.

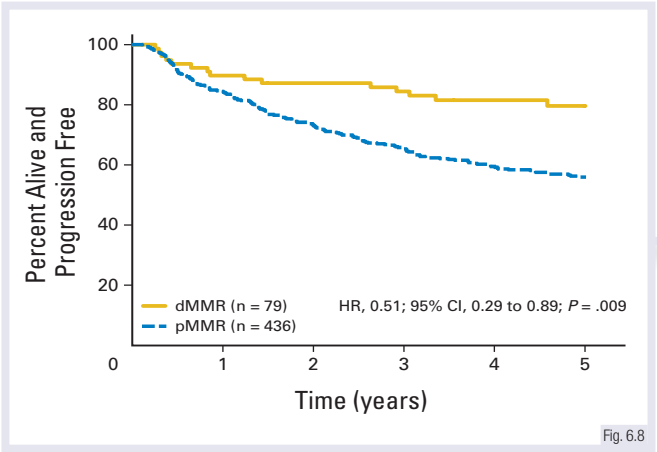


Fig. 6.8

CI, confidence interval; dMMR, deficient mismatch repair; HR, hazard ratio; pMMR, proficient mismatch repair.

MSI-high (MSI-H) status is associated with a deficiency or mutations of the DNA mismatch repair (MMR) genes. MSI-H represent 20% of stage II and 10% of stage III CRC patients.

MSI-H (i.e. deficient MMR [dMMR] status) has been found to confer an improved overall survival (OS) over microsatellite-stable (i.e. proficient MMR [pMMR]) colon cancers as well as a reduced incidence of LN spread and metastasis.

In MSI stage II colon cancer having a very good prognosis, adjuvant ChT is not recommended after primary tumour removal.

No other molecular factors have been validated as strongly prognostic or predictive of benefit from adjuvant treatment in colon cancer, including stage II.

Clinical factors and MSI status are thus the only determinants of prognosis useful in daily practice to define adjuvant ChT indication.

At the time of publication, validation of molecular biomarkers is needed and they are not recommended to guide treatment. The choice of adjuvant treatment for stage II patients needs to be a careful balance between the potential treatment benefits and toxicities.

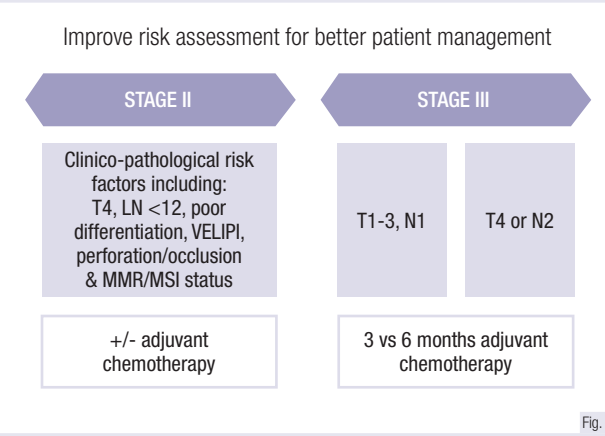


Fig. 6.9

LN, lymph node; MMR, mismatch repair; MSI, microsatellite instability; VELIPI, vascular emboli, lymphatic invasion and perinervous invasion.

REVISION QUESTIONS

1. How does the pT influence the treatment of stage II colon cancer?
2. What is the clinical impact of MSI status?
3. Are there any other validated tumour biomarkers to predict adjuvant ChT benefit in stage II?

Treatment duration

Despite being beneficial, adjuvant ChT can induce several adverse effects that need to be considered.

Cumulative sensory neuropathy induced by oxaliplatin must be carefully followed up; oxaliplatin must be discontinued in case of grade >1 neuropathy, and the treatment changed to 5-fluorouracil or capecitabine alone.

Shortening treatment duration, if not detrimental to efficacy, could improve risk/benefit balance.

Cumulative sensory neuropathy induced by adjuvant oxaliplatin for 6 months

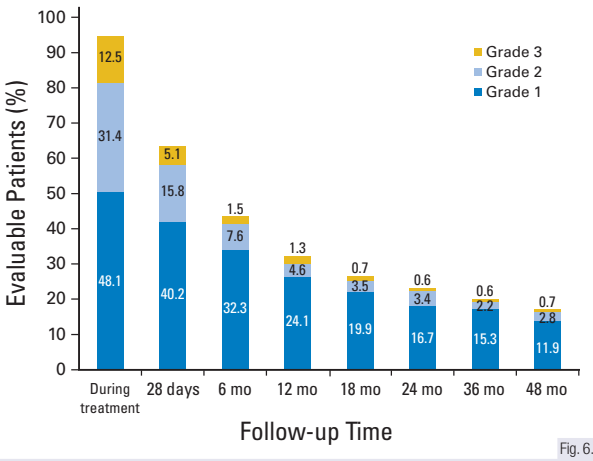


Fig. 6.10

IDEA trial: study design

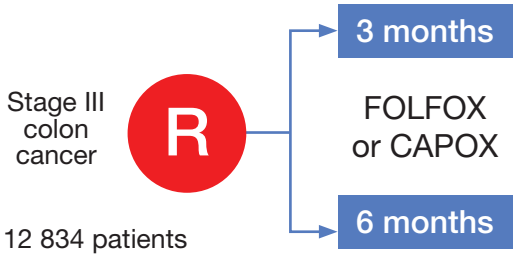


Fig. 6.11

CAPOX, capecitabin/oxaliplatin; FOLFOX, leucovorin/5-fluorouracil/oxaliplatin; R, randomised.

Treatment duration of 3 vs 6 months has been explored by six randomised studies, pooled in the IDEA international non-inferiority trial, aiming to reduce side effects without giving up too much anticancer efficacy.

As agreed by patient advocates and oncologists, shorter duration of therapy should not sacrifice >12% of the benefit of adjuvant treatment.

Toxicity was lower in the 3-month arm, with small absolute difference for cycle-dependent effects such as diarrhoea or neutropaenia, but a markedly lower rate of acute, on-treatment, cumulative neurotoxicity.

The IDEA study was not able to confirm the 3-year DFS non-inferiority of 3 months vs 6 months of oxaliplatin-containing adjuvant ChT.

The absolute difference in 3-year DFS between the two treatment arms (0.9%), while statistically significant, may not be clinically meaningful.

Treatment duration depends on the regimen chosen and the disease risk subgroup, with 3 months CAPOX being enough for T1-3/N1 patients and 6 months FOLFOX generally preferred for T4 and/or N2 patients.

Results of the IDEA international pooled non-inferiority analysis

3 yr DFS rate (%) and HR by regimen and risk group		Regimen								
		CAPOX			FOLFOX			CAPOX/FOLFOX combined		
		3 yr DFS, % (CI)		HR (95% CI)	3 yr DFS, % (CI)		HR (95% CI)	3 yr DFS, % (CI		HR (95% CI)
		3 m	6 m		3 m	6 m		3 m	6 m	
Risk group	Low-risk (T1-3 N1) ~60%	85.0 (83.1-86.9)	83.1 (81.1-85.2)	0.85 (0.71-1.01)	81.9 (80.2-83.6)	83.5 (81.9-85.1)	1.10 (0.96-1.26)	83.1 (81.8-84.4)	83.3 (82.1-84-6)	1.01 (0.90-1.12)
	High-risk (T4 or N2) ~40%	64.1 (61.3-67.1)	64.0 (61.2-67.0)	1.02 (0.89-1.17)	61.5 (58.9-64.1)	64.7 (62.2-67.3)	1.20 (1.07-1.35)	62.7 (60.8-64.4)	64.4 (62.6-66.4)	1.12 (1.03-1.23)
	Risk groups combined	75.9 (74.2-77.6)	74.8 (73.1-76.6)	0.95 (0.85-1.06)	73.6 (72.2-75.1)	76.0 (74.6-77.5)	1.16 (1.06-1.26)	P-value interaction test: Regimen: 0.0061 Risk group: 0.11		

Non-inferior | Not proven | Inferior

Fig. 6.12

CAPOX, capecitabin/oxaliplatin; CI, confidence interval; DFS, disease-free survival; FOLFOX, leucovorin/5-fluorouracil/oxaliplatin; HR, hazard ratio.

REVISION QUESTIONS

1. What is the most frequent toxicity of oxaliplatin-based adjuvant ChT?
2. What was the aim of the IDEA trial?
3. Which subgroup of patients may benefit from 3 months of adjuvant ChT?

Follow-up and resectable stage IV colon cancer treatment

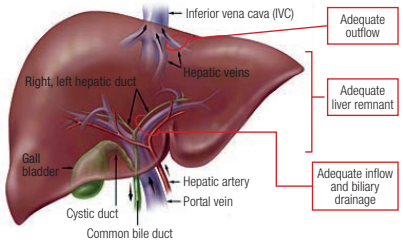
Despite adjuvant treatment, ~25%-30% of radically resected colon cancer patients will develop distant metastases.

In stage II-III patients, an advantage for more intensive follow-up has been demonstrated in several prospective studies and three meta-analyses of randomised controlled studies.

A 20%-33% relative reduction of risk of death, with an absolute difference reaching 7%, is linked to early detection of disease relapse.

Criteria for CRC liver metastases resectability

- Remaining liver without any lesion
- Preservation of at least one of the three sus-hepatic veins
- With the homolateral portal vein
- Free margins
- Remaining liver volume ≥25% of initial functional parenchyma



20% of patients have (potentially) resectable liver metastases

Fig. 6.13

CRC, colorectal cancer.

Kaplan-Meier plots of disease-specific survival stratified by low clinical risk score (CRS; top curve) and high CRS (bottom curve)

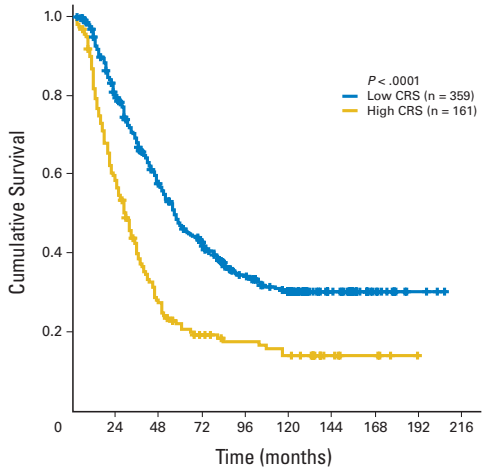


Fig. 6.14

Radical resection of oligometastatic disease is the only long-term curative treatment of stage IV colon cancer.

Five-year survival rates in resected patients range from 20% to 50%, compared with <10% in non-resected patients.

Multidisciplinary discussion is warranted to assess the risk/benefit balance of surgical removal of metastases.

In good-prognosis, easily resectable disease, or if there is a risk of missed lesions after induction ChT, upfront surgery may be considered.

In bad-prognosis, not easily resectable disease, oxaliplatin-based perioperative treatment should be preferred.

No advantage with epidermal growth factor receptor (EGFR) inhibitors or antiangiogenic drugs has been observed in this setting.

All randomly assigned patients

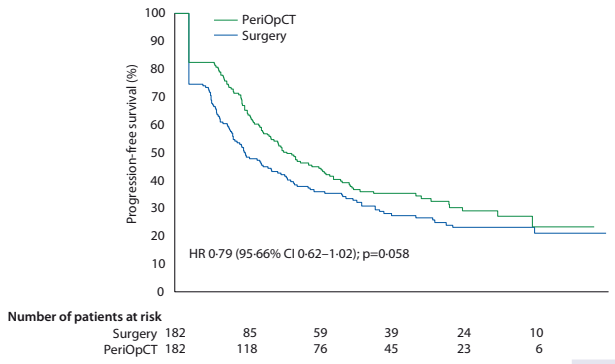


Fig. 6.15

CI, confidence interval; HR, hazard ratio; PeriOpCT, perioperative chemotherapy.

REVISION QUESTIONS

1. What is the aim of follow-up in colon cancer?
2. Is metastases resection beneficial?
3. Should ChT always be administered before metastases removal?

Summary: Colon cancer – Treatment of early-stage disease

- CRC is the second most frequently diagnosed malignancy in Europe
- National screening programmes with FOBTs followed by colonoscopy should be implemented
- CRC treatment strategy should be discussed by a multidisciplinary team
- After curative surgery, recurrence occurs in 50% of stage III and 25% of stage II patients, due to micrometastatic disease
- Adjuvant ChT can induce ~40% reduction in risk of relapse
- Adjuvant ChT should begin within 8 weeks of surgery
- Fluoropyrimidines and oxaliplatin regimens are preferred in stage III, giving an absolute OS gain of ~8%
- Indication for adjuvant ChT in stage II patients depends on evaluation of prognostic factors
- No major survival benefit is obtained with the addition of oxaliplatin in stage II patients
- The IDEA study provided strong evidence for individualising the duration of adjuvant therapy in stage III colon cancer

Further Reading

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Colon cancer – Treatment of metastatic disease

First-line therapy

Around 25%-35% of patients with colorectal cancer (CRC) present with synchronous metastases, whereas about 25% will develop metachronous metastases, the liver being the most common site of spread.

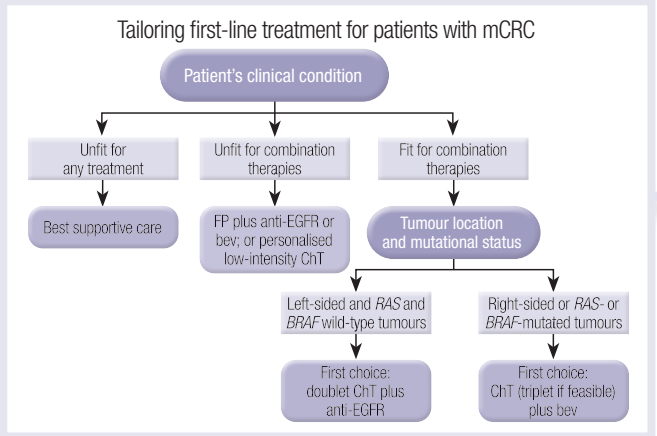
The median overall survival (OS) of patients affected by metastatic CRC (mCRC) has notably increased in the past decades: >30 months in *RAS* wild-type cases and 25-28 months in *RAS* mutants.

The availability of a growing amount of surgical, locoregional and systemic options makes the current treatment of mCRC patients a personalised *continuum of care*.

Approved systemic drugs for treatment of mCRC	
Cytotoxic agents	**Targeted agents**
5-fluorouracil[a]	Bevacizumab[b]
Capecitabine[a]	Panitumumab[c]
Oxaliplatin	Cetuximab[c]
Irinotecan	Aflibercept[d]
Trifluridine/tipiracil	Ramucirumab[e]
-	Regorafenib[f]
-	Encorafenib[g]
Recommended chemotherapy (ChT) combined regimens	
Doublet ChT	**Triplet ChT**
FOLFOX (leucovorin/5-fluorouracil/oxaliplatin)	FOLFOXIRI (leucovorin/5-fluorouracil/ oxaliplatin/irinotecan)
CAPOX (capecitabine/oxaliplatin)	
FOLFIRI (leucovorin/5-fluorouracil/irinotecan)	

Fig. 7.1

[a]: Fluoropyrimidines; [b]: anti-vascular endothelial growth factor A (VEGF-A) monoclonal antibody; [c]: anti-epidermal growth factor receptor (EGFR) monoclonal antibodies; [d]: decoy receptor targeting VEGF-A and -B and placental growth factor (PlGF); [e]: anti-VEGF receptor 2 monoclonal antibody; [f]: multikinase inhibitor; [g]: BRAF inhibitor.
mCRC, metastatic colorectal cancer.



Bev, bevacizumab; ChT, chemotherapy; EGFR, epidermal growth factor receptor; FP, fluoropyrimidine (capecitabine or 5-fluorouracil); mCRC, metastatic colorectal cancer.

Fig. 7.2

Initial and on-treatment therapeutic decisions for each patient diagnosed with mCRC should be taken within a multidisciplinary team (MDT).

The choice of the optimal upfront treatment should be based on the key drivers listed below.

Patient's clinical condition: eligibility for any therapy should be determined according to a comprehensive assessment of general conditions including age, performance status, organ function, comorbidities, attitude and expectations.

Treatment intent: cytoreduction, to allow resection of metastases or palliation of symptoms; or disease control, to delay clinical and tumour progression.

Tumour molecular profile: *RAS* mutations predict resistance to anti-EGFR (epidermal growth factor receptor) agents. *BRAF* V600E mutation has a negative prognostic impact and predicts benefit from the combination of BRAF (encorafenib) and EGFR (cetuximab) inhibitors.

Primary tumour site: in *RAS* wild-type cases, left-sidedness is associated with better prognosis and benefit from anti-EGFRs, whereas right-sidedness predicts poor clinical outcome and a limited impact of these agents.

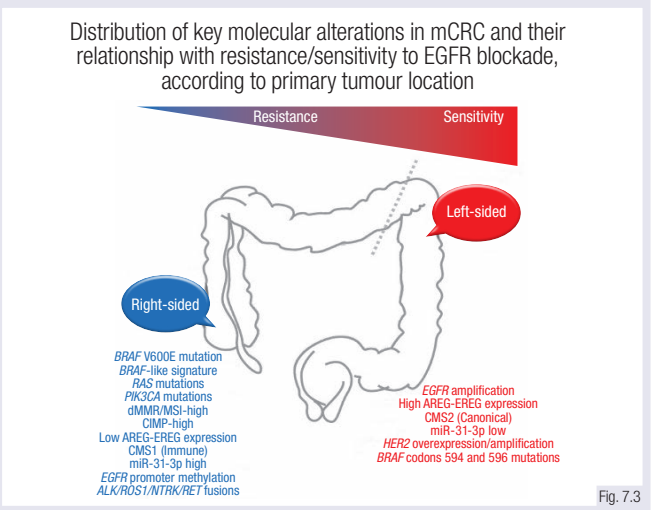


Fig. 7.3

ALK, anaplastic lymphoma kinase; AREG, amphiregulin; CIMP, CpG island methylator phenotype; dMMR, deficient mismatch repair; EGFR, epidermal growth factor receptor; EREG, epiregulin; HER2, human epidermal growth factor receptor 2; mCRC, metastatic colorectal cancer; MSI, microsatellite instability; NTRK, neurotrophic tyrosine receptor kinase.

REVISION QUESTIONS

1. What is the role of an MDT?
2. Which molecular markers predict intrinsic resistance to anti-EGFR drugs?
3. Is there a site of origin of CRC with a negative prognostic impact?

First-line therapy (continued)

The standard first-line therapy includes a chemotherapy (ChT) backbone plus targeted agent: bevacizumab (bev) or an anti-EGFR antibody.

In patients fit for combined ChT regimens, doublets (leucovorin/5-fluorouracil [5-FU]/oxaliplatin [FOLFOX], leucovorin/5-FU/irinotecan [FOLFIRI], capecitabine/oxaliplatin [CAPOX]) or the triplet FOLFOXIRI (leucovorin/5-FU/oxaliplatin/irinotecan) can be used with bev, regardless of *RAS* and *BRAF* status. Anti-EGFRs can be adopted only with 5-FU-based doublets and in *RAS* wild-type tumours.

Patients deemed unfit for combination therapies are candidates for a fluoropyrimidine with the addition of bev.

Individual patient data meta-analysis of FOLFOXIRI plus bev versus doublets plus bev as initial therapy of unresectable mCRC. Overall survival results according to treatment

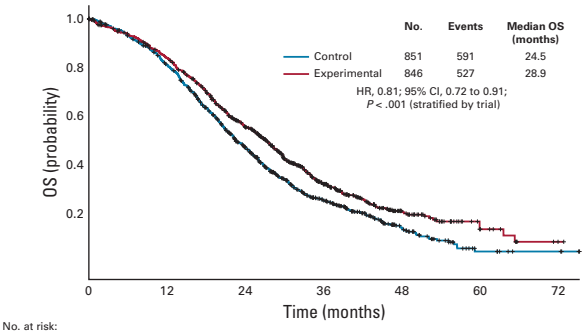


Fig. 7.4

Control: doublet plus bev; Experimental: FOLFOXIRI plus bev.
Bev, bevacizumab; CI, confidence interval; FOLFOXIRI, leucovorin/5-fluorouracil/oxaliplatin/irinotecan; HR, hazard ratio; mCRC, metastatic colorectal cancer; OS, overall survival.

Results of progression-free survival of mCRC patients receiving maintenance therapy with fluoropyrimidine plus bevacizumab, bevacizumab alone or no treatment in the phase III AIO-KRK 0207 trial

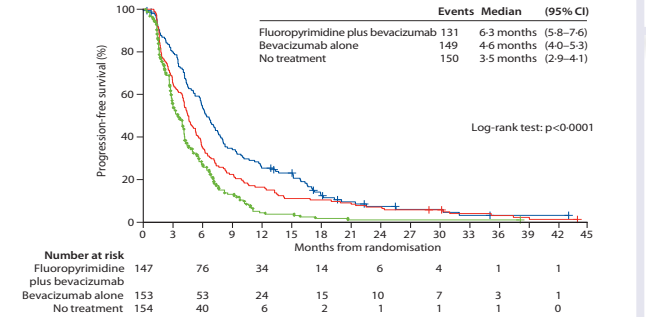


Fig. 7.5

CI, confidence interval; mCRC, metastatic colorectal cancer.

After a 4-6 month bev-based induction treatment, continuing bev plus a fluoropyrimidine is the recommended maintenance regimen. The role of maintenance following an anti-EGFR-based induction and the optimal regimen are not well established, but continuing anti-EGFR and 5-FU can be considered.

Therapeutic management of liver metastases

In one third of patients, the liver is the only site of CRC metastases. The MDT has a crucial role in assessing the resectability of liver disease and to properly integrate systemic and locoregional therapies based on both 'oncological' (prognostic) and 'technical' (surgical) criteria.

Surgery is the gold standard, since the radical resection of liver metastases contributes to a long-term survival benefit and may be curative.

Other ablative treatments are available: chemo- and radio-embolisation, stereotactic radiotherapy, intra-arterial ChT, radiofrequency and microwave ablation.

For technically easy-to-resect liver disease, both upfront surgery and perioperative ChT (3 months before and after surgery) are potential options according to prognostic criteria.

An upfront regimen able to induce tumour shrinkage, allow radical surgery and potentially prevent relapse is recommended when the purpose is converting initially unresectable liver metastases to resectable.

Summary of controlled trials investigating *conversion* therapies in mCRC patients with initially unresectable liver-limited disease

Trial	Study interventions (No. of pts)	ORR (%)	R0 Resection rate (%)	mPFS (mos)
CELIM[a]	FOLFOX+cet (n = 56) vs FOLFIRI+cet (n = 39)	68 vs 57	38 vs 30	12.1 vs 11.5[b]
OLIVIA	FOLFOXIRI+bev (n = 41) vs FOLFOX+bev (n = 39)	81 vs 62	49 vs 23	18.6 vs 11.5
Ye et al, 2013[b]	ChT+cet (n = 70) vs ChT alone (n = 68)	57 vs 29	26 vs 7	10 vs 6
PLANET-TTD[c]	FOLFOX+pan (n = 27) vs FOLFIRI+pan (n = 26)	78 vs 73	26 vs 54[d]	13 vs 15
ATOM[c]	FOLFOX+bev (n = 57) vs FOLFOX+cet (n = 59)	65 vs 85	25 vs 22	11.5 vs 14.8

Fig. 7.6

[a]: in molecularly unselected patients; [b]: only *KRAS* exon 2 wild-type patients; [c]: *RAS* wild-type patients; [d]: R0+R1 resection rate.
bev, bevacizumab; cet, cetuximab; ChT, chemotherapy; FOLFIRI, leucovorin/5-fluorouracil/irinotecan; FOLFOX, leucovorin/5-fluorouracil/oxaliplatin; FOLFOXIRI, leucovorin/5-fluorouracil/oxaliplatin/irinotecan; mCRC, metastatic colorectal cancer; mPFS, median progression-free survival; ORR, overall response rate; pan, panitumumab.

REVISION QUESTIONS

1. Which patients are the best candidates for FOLFOXIRI plus bev?
2. How and when should you deintensify a first-line bev-containing induction treatment?
3. What are the objectives of an optimal conversion therapy?

Second-line therapy

After failure of the upfront treatment, a second-line therapy should be proposed to patients with adequate clinical conditions and organ function. The choice of the ChT backbone and targeted agent is mainly driven by the previous regimen administered and its outcome.

A standard option is the switch from an upfront oxaliplatin-based regimen to a second-line irinotecan-based regimen, and *vice versa*. Reintroduction of an initially successful and well-tolerated induction regimen (both doublets or triplet FOLFOXIRI) can also be considered following a maintenance strategy or a treatment holiday.

Both anti-angiogenic drugs and anti-EGFR antibodies may be combined with ChT.

Anti-angiogenic agents approved in the second-line setting of mCRC treatment and their mechanism of action

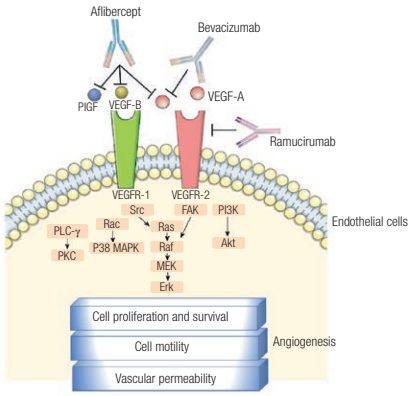


Fig. 7.7

mCRC, metastatic colorectal cancer; PlGF, placental growth factor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

Summary of phase III randomised trials investigating second-line angiogenesis inhibition in patients treated with a bevacizumab-based regimen in first-line

Trial	Study interventions (No of pts)	OS (HR)	PFS (HR)	ORR (%)	Safety
TML	ChT+bev (n = 409) vs ChT alone (n = 411)	HR: 0.81 *p*=0.0062	HR: 0.68 *p*<0.0001	5.4 vs 3.9 *p*=0.31	No unexpected AEs
BEBYP	ChT+bev (n = 92) vs ChT alone (n = 92)	HR: 0.77 *p*=0.04	HR: 0.70 *p*=0.001	21 vs 17 *p*=0.57	No unexpected AEs
VELOUR[a]	FOLFIRI+afl (n = 612) vs FOLFIRI (n = 614)	HR: 0.82 *p*=0.0032	HR: 0.76 *p*<0.0001	19.8 vs 11.1 *p*=0.0001	Increased ChT-related AEs
RAISE	FOLFIRI+ram (n = 536) vs FOLFIRI (n = 536)	HR: 0.84 *p*=0.0005	HR: 0.79 *p*=0.0005	13.4 vs 12.5 *p*=0.65	Increased ChT-related AEs

Fig. 7.8

[a]: only 30% of patients received first-line bevacizumab-based therapy.
AE, adverse event; afl, aflibercept; bev, bevacizumab; ChT, chemotherapy; FOLFIRI: leucovorin/5-fluorouracil/irinotecan; HR, hazard ratio; mCRC, metastatic colorectal cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; ram: ramucirumab.

Patients who received an anti-EGFR-containing upfront treatment should be switched to an antiangiogenic agent. Continuing the antiangiogenic strategy is recommended for patients who started with a bev-based regimen, regardless of *RAS* status.

Bev can be used in second-line in combination with oxaliplatin- or irinotecan-based schedules, both in bev-naïve and pretreated patients.

Aflibercept and ramucirumab can be used only with FOLFIRI in patients pretreated with an oxaliplatin- and bev-based (only for ramucirumab) regimen.

All the available antiangiogenic agents demonstrated similar efficacy in bev-pretreated patients, with less favourable safety profiles for aflibercept and ramucirumab.

Studies evaluating the addition of an anti-EGFR to second-line ChT did not demonstrate a survival benefit. The phase II randomised CAPRI study could not demonstrate any survival advantage by the continuation of cetuximab beyond progression.

Trials comparing bev beyond progression vs anti-EGFR agents in second-line did not provide conclusive results.

Results of progression-free survival of mCRC patients[a] receiving second-line FOLFOX with or without continuation of cetuximab in the phase II randomised CAPRI trial

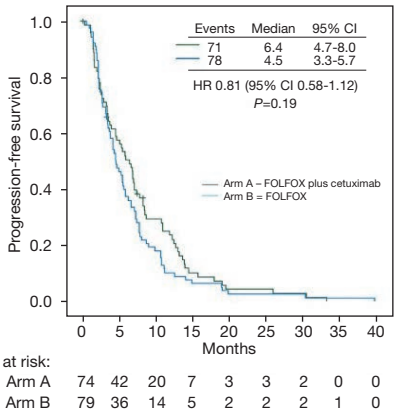


Fig. 7.9

[a]: only KRAS exon 2 wild-type patients.
CI, confidence interval; HR, hazard ratio; FOLFOX, leucovorin/5-fluorouracil/oxaliplatin; mCRC, metastatic colorectal cancer.

REVISION QUESTIONS

1. What factors influence the choice of drugs to be used after first-line failure?
2. Which targeted agent is efficacious also beyond first-line disease progression?
3. Is the continuation of anti-EGFR beyond progression a standard option?

Beyond second-line therapy

Due to a *'funnel effect'*, only 30%-40% of mCRC patients are able to receive a third or further line of therapy.

Prolonging survival and preserving an adequate quality of life are the treatment aims in this purely palliative setting.

Potential options are cetuximab, alone or combined with irinotecan, or panitumumab alone, only in patients with *RAS* (and *BRAF*) wild-type mCRC not previously treated with anti-EGFR agents.

Results of overall survival of refractory mCRC patients randomised to receive regorafenib or placebo in the phase III CORRECT trial

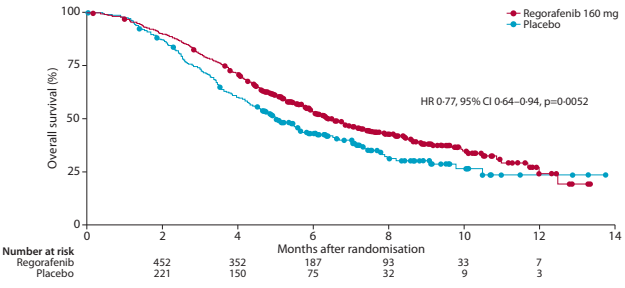


Fig. 7.10

CI, confidence interval; HR, hazard ratio; mCRC, metastatic colorectal cancer.

Results of overall survival of refractory mCRC patients randomised to receive trifluridin/tipiracil or placebo in the phase III RECOURSE trial

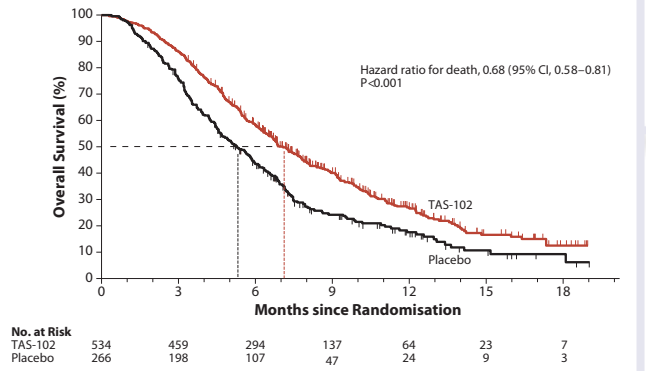


Fig. 7.11

CI, confidence interval; mCRC, metastatic colorectal cancer.

When mCRC becomes refractory to standard therapies (fluoropyrimidines, irinotecan and oxaliplatin, anti-angiogenic and anti-EGFR agents for wild-type tumours), the use of regorafenib or trifluridine/tipiracil (FTD/TPI) should be considered. Regorafenib is an oral multikinase inhibitor and FTD/TPI an oral anti-metabolite.

Both improved survival of refractory mCRC patients when compared with placebo, with a similar magnitude of benefit, but different safety profiles.

While adverse events (AEs) associated with FTD/TPI are mainly due to bone marrow suppression, regorafenib-related AEs include hand-foot-skin reaction (HFSR), fatigue and diarrhoea. Patient's condition, preferences and drug-tolerability profile are drivers in this choice.

Re-administering the same agents used in previous lines of therapy is not supported by a proper level of evidence, but can be considered in selected patients who previously responded and then progressed after the agents were interrupted.

Recent phase II trials highlight signals of activity for anti-EGFR rechallenge in *RAS* and *BRAF* wild-type patients initially sensitive but becoming resistant to a first-line anti-EGFR-based regimen. The analysis of circulating tumour DNA in liquid biopsy may serve as a useful predictor of benefit from this approach, which is still under investigation.

Most commonly reported (≥25%) adverse events for trifluridine/tipiracil and regorafenib in phase III RECOURSE and CORRECT trials, respectively

Trifluridine/tipiracil (n=533)			Regorafenib (n=500)		
	Overall	Grade ≥3		Overall	Grade ≥3
Leucopenia	77	21	Hand-foot skin reaction	47	17
Anaemia	77	18	Fatigue	47	9
Neutropaenia	67	38	Diarrhoea	34	7
Nausea	48	2	Anorexia	30	3
Thrombocytopaenia	42	5	Voice changes	29	<1
Decreased appetite	39	4	Hypertension	28	7
Fatigue	35	4	Oral mucositis	27	3
Diarrhoea	32	3	Rash/desquamation	26	6

All data are shown as %.

Fig. 7.12

REVISION QUESTIONS

1. Are patients with *RAS*-mutant mCRC eligible for anti-EGFR agents in later lines?
2. Do regorafenib and FTD/TPI differ in terms of efficacy?
3. Which are the most common AEs related to FTD/TPI?

Molecular markers in mCRC

In the precision medicine scenario, testing tumour molecular markers is a standard practice to guide treatment choices in mCRC patients.

RAS mutations (involving *KRAS* and *NRAS* codons 12, 13, 59, 61, 117 and 146) are detected in approximately 50%-55% of mCRCs and predict resistance to anti-EGFR agents.

RAS testing is mandatory at the time of diagnosis of mCRC. Patients with a *RAS*-mutated tumour must be excluded from receiving anti-EGFR antibodies.

RAS and *BRAF* mutations in MAPK pathway in CRC

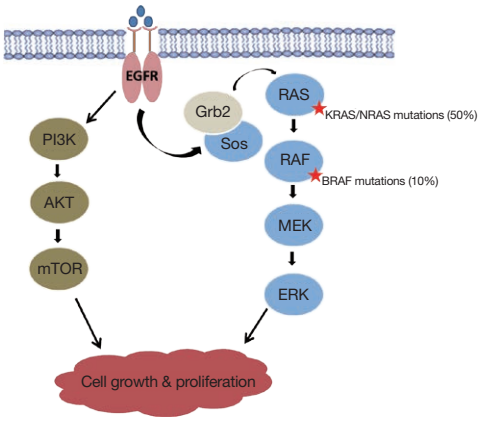


Fig. 7.13

Mutations in *RAS* and *BRAF* cause constitutive activations of the signalling cascade, resulting in uninhibited cellular proliferation and tumour growth. These effects occur downstream of the EGFR receptor, rendering these mutant tumours resistant to anti-EGFR therapies.
CRC, colorectal cancer; EGFR, epidermal growth factor receptor; mTOR, mammalian target of rapamycin.

BRAF V600E mutation occurs in 8%-10% of mCRCs and is mutually exclusive with *RAS* mutations.

BRAF testing is recommended for prognostic stratification (negative impact on survival) and to identify patients candidate for BRAF + EGFR inhibition. The presence of *BRAF* V600E mutation rules out the risk of Lynch syndrome in microsatellite instability (MSI)-high patients with *MLH1* loss of expression.

Results of progression-free (A) and overall survival (B) of refractory mCRC patients treated with pembrolizumab (anti-PD-1) according to MMR status

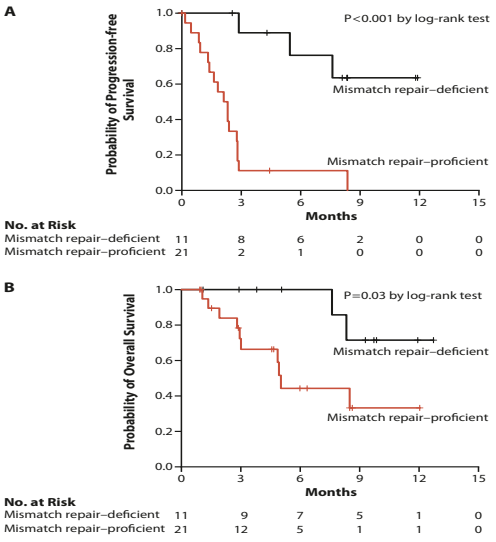


Fig. 7.14

mCRC, metastatic colorectal cancer; MMR, mismatch repair; PD-1, programmed cell death protein 1.

MSI testing is recommended for identifying patients at risk of Lynch syndrome. MSI-high/dMMR (deficient mismatch repair) status (around 5% in mCRC) predicts benefit from immune checkpoint inhibitors.

mCRC bearing gene fusions involving *NTRK1-3* (neurotrophic tyrosine receptor kinase) (prevalence <1%) can be targeted with oral TRK inhibitors.

HER2 (human epidermal growth factor receptor 2)-targeted strategies provided a benefit in *HER2*-amplified mCRC (prevalence up to 5%).

A comprehensive molecular landscape of mCRC: genomic biomarkers and their prevalence

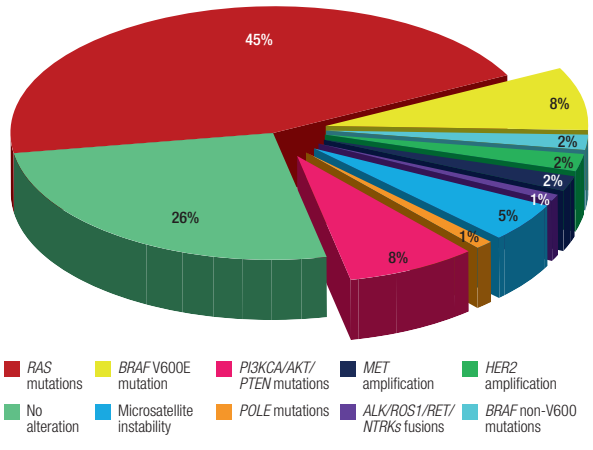


Fig. 7.15

ALK, anaplastic lymphoma kinase; HER2, human epidermal growth factor receptor 2; mCRC, metastatic colorectal cancer; NTRK, neurotrophic tyrosine receptor kinase.

REVISION QUESTIONS

1. Which genomic alterations are more frequent in mCRC?
2. Why is the assessment of MSI useful in the management of mCRC patients?
3. Is *BRAF* non-V600E mutational status testing mandatory in daily clinical practice?

Summary: Colon cancer – Treatment of metastatic disease

- Survival of patients affected by mCRC has notably increased in the past decades, as a fruitful consequence of the availability of more systemic treatments, the development of new surgical techniques, the awareness of locoregional options and, not least, the discussion of patient cases in the context of MDTs
- The correct integration of systemic and surgical +/- other locoregional treatments offers a chance of cure to some mCRC patients, mainly those with liver-limited disease
- The choice of the first-line treatment is of paramount importance in the therapeutic route of initially unresectable mCRC patients, as it paves the way for further interventions. Both patient- and disease-related characteristics drive this decision
- Some steps forward have been made within the 'precision medicine' perspective: a more comprehensive characterisation of tumour-specific molecular alterations is increasingly crucial not only to exclude patients from receiving inefficacious treatments, but also to tailor targeted treatments, thus shifting the paradigm towards a 'positive selection' approach

Further Reading

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Rectal cancer

Epidemiology and clinical presentation

Colorectal cancer (CRC) is the third most commonly diagnosed cancer in males and the second in females. Approximately 55% of cases occur in more developed regions.

Risk factors: age >50 years, high-fat/low-fibre diet, obesity, sedentary lifestyle, smoking, alcohol intake, adenomas, inflammatory bowel disease and familial history of CRC.

Symptoms: bleeding, proctalgia, changed bowel habits with obstructive defecation or increased frequency, abdominal pain, weight loss, asthenia, nausea, vomiting.

Endoscopy and biopsy of rectal cancer

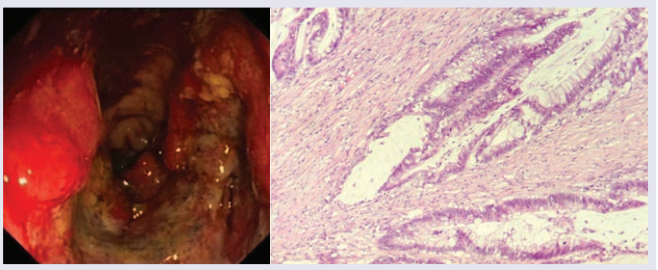


Fig. 8.1

Diagnostic work-up and staging

Diagnostic work-up in primary rectal cancer	
Parameter	**Method of choice**
Location (distance from anal verge)	DRE/palpation Rigid sigmoidoscopy (flexible endoscopy)
Morphological verification	Biopsy
cT stage Early Intermediate/advanced	 ERUS MRI MRI (ERUS)
Sphincter infiltration	MRI (ERUS, palpation, EUA)
cN stage	MRI (CT, ERUS)
M stage	CT, MRI (or US) of the liver/abdomen CT of the thorax PET-CT if extensive EMVI for other sites
Evaluation for all patients	MDT discussion

Methods within brackets are less optimal.
CT, computed tomography; DRE, digital rectal examination; EMVI, extramural vascular invasion; ERUS, endorectal ultrasound; EUA, examination under anaesthesia; MDT, multidisciplinary team; MRI, magnetic resonance imaging; PET, positron emission tomography; US, ultrasound.

Fig. 8.2

Histological biopsy is needed to confirm diagnosis. Fig. 8.2 shows diagnostic work-up. Clinical staging should be reported according to the Tumour, Node, Metastasis (TNM) classification.

Pelvic magnetic resonance imaging (MRI): involvement of mesorectal fascia (MRF), peritoneum, extramural spread >5 mm, venous invasion, (extra)mesorectal nodal involvement and invasion of adjacent structures.

MRI accuracy to define involvement of lymph nodes is ~60%. Endorectal ultrasound may help determine T-stage, particularly in early tumours, but has limitations in stenotic or upper-third tumours.

Multidisciplinary team approach

A multidisciplinary team (MDT) approach is essential to achieve optimal results in the treatment of rectal cancer, even in the presence of metastases.

The MDT should at least include a gastroenterologist, a dedicated colorectal surgeon, a pelvic MRI-experienced radiologist, a radiation oncologist, a medical oncologist, a pathologist and a stoma therapist.

MDT weekly (suggested) meeting: discuss new cases, MRI review, selection for preoperative therapy (if indicated), review of pathology reports of operated patients, discussion of any relapse.

Pelvic MRI of a rectal cancer with mesorectal fascia invasion and extramesorectal lymph nodes

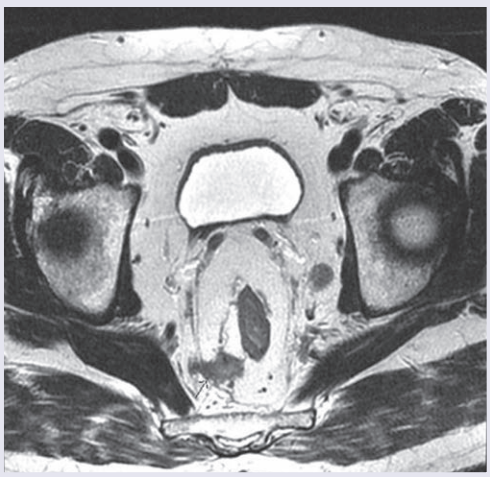


Fig. 8.3

MRI, magnetic resonance imaging.

REVISION QUESTIONS

1. What is the role of pelvic MRI for local staging and decision-making in rectal cancer?
2. What are the implications of MRF involvement as predicted by MRI?
3. What are the MRI-defined high risk features for localised rectal cancer?

Patient grouping and recommendations for treatment of localised or locally advanced disease

Rectal tumours are classified into three groups as described in Fig. 8.4. For Group 1, total mesorectal excision (TME) as a single approach is recommended.

For Group 2, preoperative short-course radiotherapy (RT) or preoperative chemoradiotherapy (CRT) followed by TME is recommended.

For Group 3, preoperative CRT is recommended.

Risk-based groups in localised rectal cancer: Locally agreed treatment policy for rectal cancer within the MDT

Treatment group	MRI features	Treatment strategy
1	T1-T2/T3 <5 mm, N0/N1, predicted CRM -ve	Surgery alone (TME)
2	T3 ≥5 mm/T4, N2, predicted CRM -ve	Preoperative CRT
3	Predicted CRM +ve	Preoperative CRT

Fig. 8.4

+ve, positive; -ve, negative; CRM, circumferential resection margin; CRT, chemoradiotherapy; MDT, multidisciplinary team; MRI, magnetic resonance imaging; TME, total mesorectal excision.

Surgery for localised rectal cancer

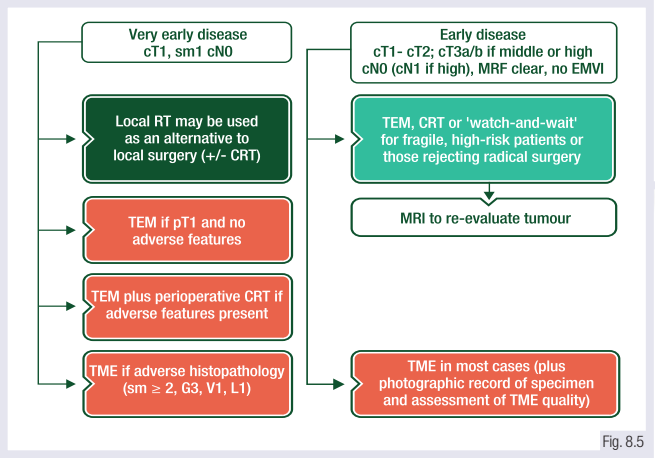


Fig. 8.5

CRT, chemoradiotherapy; EMVI, extramural vascular invasion; MRF, mesorectal fascia; MRI, magnetic resonance imaging; RT, radiotherapy; TEM, transanal endoscopic microsurgery; TME, total mesorectal excision.

Very early tumours (cT1N0, no adverse pathological factors): indicated local therapy (transanal endoscopic microsurgery [TEM] or mucosectomy).

If the tumour involves muscular layer (cT2), the risk of positive lymph nodes (LNs) is 15%–20%, and local excision alone is inappropriate.

Surgical technique: TME. Complete excision of mesorectal tissue to the level of the levators. Adequate clearance of the rectal mesentery reduces the risk of local relapse.

Surgery for locally advanced rectal cancer

TME is the gold standard for middle and lower-third rectal cancers. The pathologist should assess the surgical planes as mesorectal, intramesorectal or muscularis propria.

Lower third: standard TME for abdominoperineal resection follows MRF onto sphincters. Most important area of resection: pelvic floor (limited access).

Lower third: High intraoperative perforation rate and circumferential resection margin (CRM) involvement. Dissection from below, outside sphincteric plane, avoids 'coning effect' and prevents positive CRM.

Surgical specimens of total mesorectal excision, anterior resection or abdominoperineal amputation according to the surgical planes: mesorectal (A), intramesorectal (B) and muscularis propria (C).

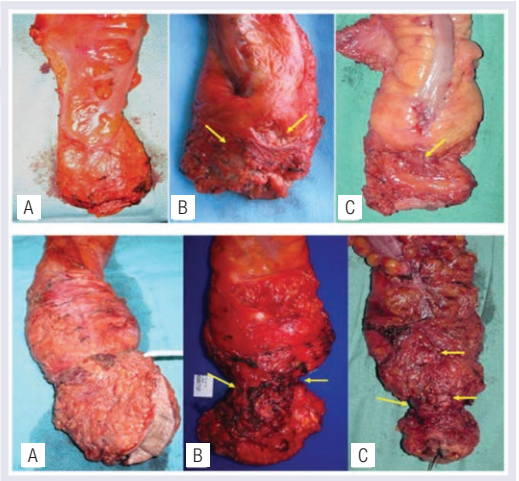


Fig. 8.6

REVISION QUESTIONS

1. Should all localised rectal cancers be treated with neoadjuvant (C)RT?
2. What is the impact of the proximity of mesorectal LNs to the MRF?
3. How important is the assessment of the mesorectal plane?

Radiotherapy for localised rectal cancer

Intermediate-stage resectable (group 2): preoperative short-course RT (SCRT) or long-course RT (LCRT) followed by TME is recommended. Preoperative CRT is superior to postoperative CRT and less toxic.

Preoperative treatment: both SCRT (5 Gy x 5 days) or LCRT (45–50.4 Gy) are valid in Group 2 rectal cancers.

Prolonged LCRT is preferred for patients with MRF involvement or close to the tumour front or other high-risk features (Group 3). SCRT followed by delayed surgery is under evaluation.

Short-course vs long-course RT		
	Short-course RT	Long-course RT
Total radiation dose (Gy)	25	45-50.4
Fraction size (Gy) / number of fractions	5 / 5	1.8-2 / 23-28
Duration (weeks)	1	4.5-5.5
Concomitant chemotherapy	No	Yes
Early toxicity, % G3-4	3.2%	18.2%, P <0.001
Long-term toxicity, % G3-4	5.8%	8.2%, P: non-significant
Downstaging	Depends on timing of surgery*	Yes
Recommended timing for surgery after end of RT	7-10 days*	6-8 weeks

Fig. 8.7

*Some recent extensive studies show downstaging when short-course RT is given and surgery is performed 6 to 12 weeks thereafter.

RT, radiotherapy.

Chemoradiotherapy for localised rectal cancer

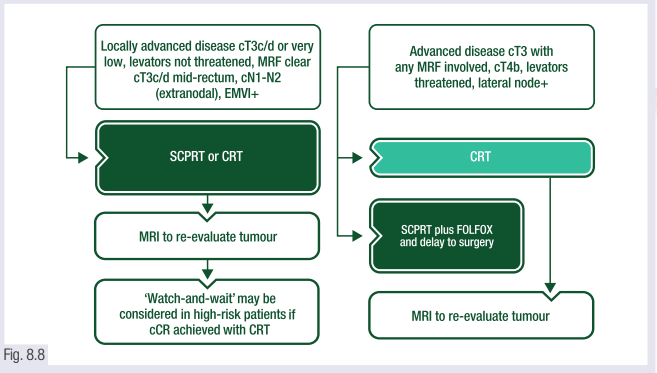


Fig. 8.8

cCR, clinical complete response; CRT, chemoradiotherapy; EMVI, extramural vascular invasion; FOLFOX, leucovorin/5-fluorouracil (5-FU)/oxaliplatin; MRF, mesorectal fascia; MRI, magnetic resonance imaging; SCPRT, short-course preoperative radiotherapy.

Group 3 and some Group 2 patients: preoperative LCRT, including RT (50-54 Gy) + 5-fluorouracil (5-FU)-based chemotherapy (ChT). Goal: increase R0 resectability. Extended surgery can be considered for R0 resection.

Concomitant ChT during LCRT: improves local control, increases downsizing and downstaging; 5-FU most often used, oral capecitabine has a similar effect.

Combinations with other cytotoxics (oxaliplatin, irinotecan, targeted drugs, etc.) are considered experimental. Adding oxaliplatin to LCRT increases toxicity.

Adjuvant/neoadjuvant chemotherapy

Postoperative adjuvant ChT has not been shown to improve survival in phase III trials compared with no adjuvant ChT, although it is routinely considered in patients with pathologically involved LNs, based on colon cancer data.

Some trials showed a benefit of adjuvant oxaliplatin-based ChT over fluoropyrimidines alone in patients without downstaging after preoperative CRT, or even for all patients after preoperative CRT.

Induction or consolidation ChT (before or after preoperative [C]RT) is gaining acceptance because of increased downstaging and pathological complete response (pCR) rates, but has not been validated in phase III trials.

Disease-free survival of rectal cancer patients receiving adjuvant chemotherapy with fluropyrimidines +/- oxaliplatin

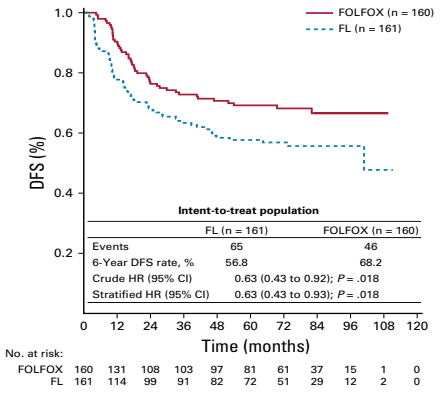


Fig. 8.9

CI, confidence interval; DFS, disease-free survival; FL, 5-FU/leucovorin; FOLFOX, leucovorin/5-fluorouracil (5-FU)/oxaliplatin; HR, hazard ratio.

REVISION QUESTIONS

1. What is the preferred RT approach as preoperative treatment for patients with locally advanced rectal cancer with MRF involvement?
2. Should adjuvant ChT be given to all operated rectal cancer patients after SCRT or neoadjuvant CRT?
3. Are neoadjuvant ChT regimens considered standard of care?

The role of the pathologist

The pathologist's role is critical. Reports should include TNM staging and assessment of the quality of mesorectal surgery. Achieving an optimal plane significantly reduces local recurrence.

CRM involvement predicts local recurrence and survival. Accurate reporting requires serial cross-sectioning of tumour, visual inspection and histological sampling of suspicious areas.

Tumour regression grade (TRG) after preoperative treatment is prognostic. Amount of viable tumour vs fibrosis determines degree of regression. Downstaging implies lower recurrence risk.

Measurement of distance from tumour to circumferential resection margins

A: Slices of a surgical specimen. B: Distance from a lymph node to the resection margin. C: Distance from the primary tumour to the resection margin. D: Microscopic view of a rectal slice.

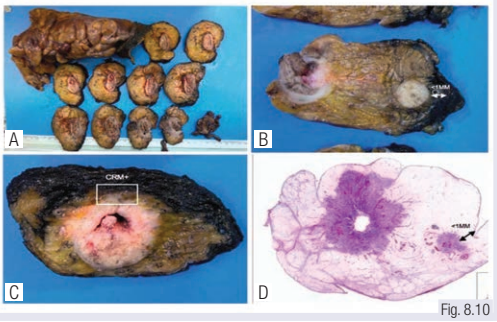
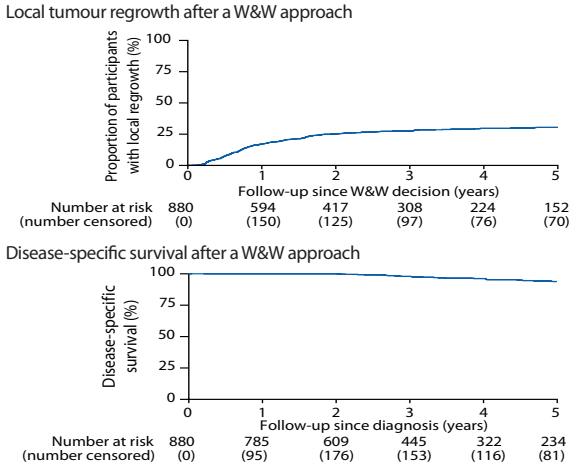


Fig. 8.10

CRM, circumferential resection margin.

The watch and wait approach for localised rectal cancer



W&W, watch & wait.

Fig. 8.11

Surgery of some lower-third tumours implies anal amputation and permanent stoma. After neoadjuvant treatment, a complete response may be achieved, especially on less advanced tumours.

A thorough assessment is needed to ensure the completeness of response. When this is achieved, avoiding surgery or delaying it with close observation may be an alternative in selected cases.

In international registries, 25% of patients presented with local regrowth, mainly in the first 2 years, mostly detected endoscopically. In case of local regrowth, curative-intent surgery should be performed.

Concomitant presentation of locally advanced rectal cancer and metastatic disease limited to liver or lungs

Locally advanced rectal cancer with limited single organ (liver/lung) metastases: consider a curative approach (if metastases are [potentially] resectable after induction ChT). Optimal timing of resection is essential.

If primary tumour symptoms (e.g. bleeding, pain) are prominent, SCRT or LCRT may facilitate complete R0 resection of the primary, if feasible. SCRT may promptly solve local symptoms, therefore not delaying systemic ChT.

A biological agent could be added to ChT to achieve a higher chance of response. Determination of *N*- and K-*RAS* mutational status is required for optimal treatment selection.

Synchronous liver metastases in a patient with locally advanced rectal cancer

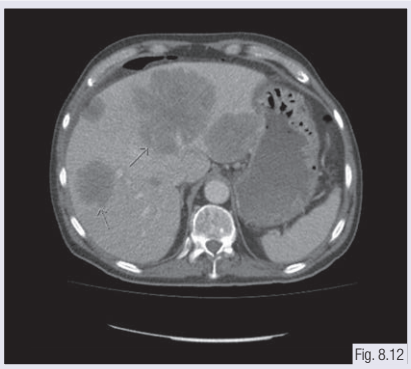


Fig. 8.12

REVISION QUESTIONS

1. How should surgical planes be defined in the surgical specimen after TME?
2. Which specific features should be reported by the pathologist in a rectal cancer specimen?
3. What are the main prognostic indicators for rectal cancer patients presenting with concomitant liver metastases?

Summary: Rectal cancer

- Rectal cancer diagnosis must be confirmed with an endoscopically guided biopsy
- All rectal cancer patients should have comprehensive local and systemic staging
- High-resolution pelvic MRI is the most accurate local staging tool to define involvement of the MRF, as well as other important prognostic features such as depth of mesorectal invasion, extramural vascular invasion, puborectal involvement and the presence of extramesorectal nodal metastases
- A qualified MDT should discuss all rectal cancer patient cases before making any therapeutic decision
- Patients with favourable local features may directly receive TME surgery
- SCRT (5 × 5 Gy) or LCRT (45-50.4 Gy over 5 weeks) with concurrent fluoropyrimidine-based ChT are considered equivalent in moderate-risk patients
- The use of concomitant LCRT is preferred in patients with more aggressive features, such as MRF involvement
- Neoadjuvant ChT has only been proven effective in terms of short-term endpoints, and should still be considered experimental
- The pathologist's report on the surgical specimen should describe the TNM status, but also the quality of the resection, as well as the distance from the tumour to the CRM
- A watch-and-wait strategy in lower-third rectal tumours can be an alternative to surgery in case of complete response after neoadjuvant treatment

Further Reading

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9 Pancreatic cancer

Epidemiology, diagnosis and staging

Pancreatic ductal adenocarcinoma (PDAC) is predicted to be the second leading cause of cancer death in the Western world by 2030.

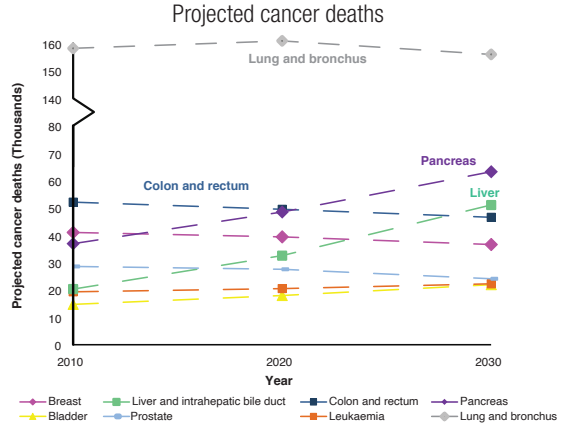


Fig. 9.1

PDAC is mainly diagnosed at a late stage: ~80% of patients are ineligible for curative surgery. Even after R0 resection, the 5-year overall survival (OS) is only 20%.

The standard of care for unresectable and locally advanced (LA) disease includes either chemotherapy (ChT) or combined chemoradiotherapy (CRT).

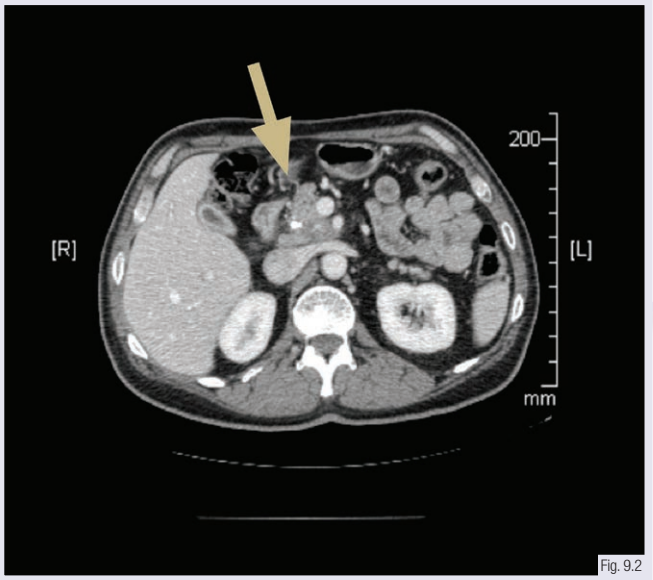


Fig. 9.2

Multidetector-row computed tomography (MDCT) and magnetic resonance imaging (MRI)/magnetic resonance cholangiopancreatography (MRCP) are the most sensitive means for PDAC diagnosis. Endoscopic ultrasound is comparable.

Contrast-enhanced, multi-phase MDCT is standard for staging. Arterial phase: allows assessment of tumour position to the coeliac trunk and superior mesenteric artery (SMA). Venous phase: allows determination of the tumour's spatial relation to the portal and splenic veins and identification of suspicious lymph nodes and distant metastases.

Borderline resectable and LA unresectable tumours are differentiated by the involvement of arterial vessels. Infiltration of the SMA of the coeliac trunk of >180 degrees is considered as LA unresectable disease.

The use of positron emission tomography-computed tomography (PET-CT) scan to exclude ineligible patients from surgery is not yet supported.

Tumour markers (e.g. CA19-9 protein) are not recommended for diagnosis.

In special cases, CA19-9 may be useful for differential diagnosis of a pancreatic lesion and to assess prognosis or response to treatment in the palliative setting.

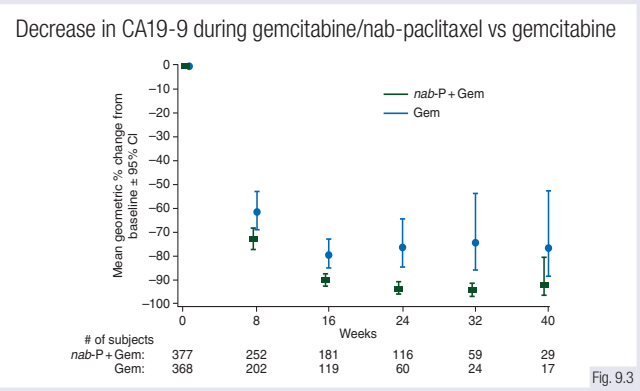


Fig. 9.3

CI, confidence interval; gem, gemcitabine; nab-P, nab-paclitaxel.

REVISION QUESTIONS

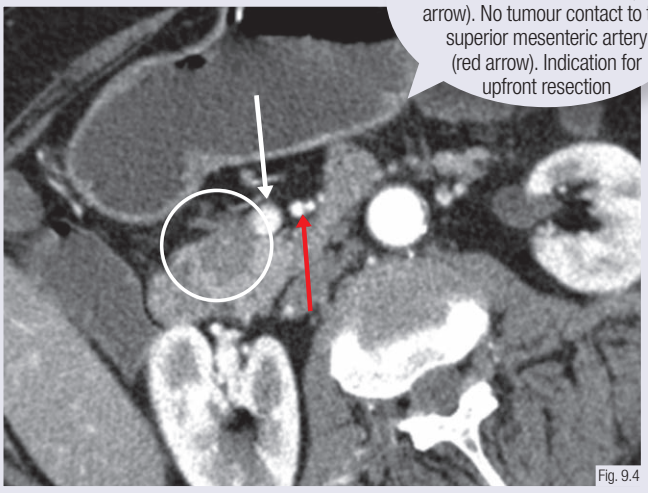
1. Which tumour type is predicted to be the second leading cause of cancer death by 2030?
2. How is borderline resectable PDAC differentiated from LA unresectable PDAC?
3. Can CA19-9 be used to screen and/or diagnose pancreatic cancer?

Surgery

Surgery is the only curative treatment. Goal: removal of tumour with tumour-free resection margins (R0). For PDACs in the pancreatic head, partial duodenopancreatectomy (DP) is used.

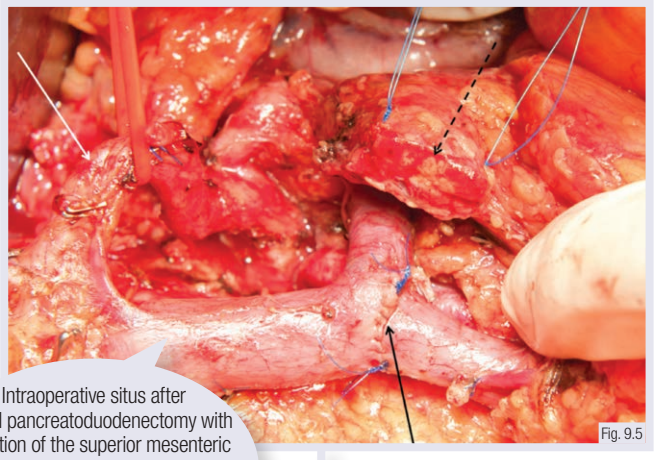
For carcinomas in the pancreatic body, either total DP or subtotal resection of the left pancreas is performed, based on tumour extension.

Carcinomas in the pancreatic tail are treated by a left-sided pancreatic resection. Resection margins should be inked to define the R-status at all resection planes.



Contrast-enhanced axial computed tomograph showing pancreatic cancer (white circle) with infiltration of the portal vein (white arrow). No tumour contact to the superior mesenteric artery (red arrow). Indication for upfront resection

Fig. 9.4



Intraoperative situs after partial pancreatoduodenectomy with resection of the superior mesenteric vein. Venous anastomosis (black arrow) below the confluens, pancreatic remnant (broken black arrow), hepatic artery (white arrow)

Fig. 9.5

There are no clear-cut criteria to define R0 resectability upfront, because imaging (CT or MRI) sensitivity and specificity are <100%. Tumour infiltration in vessels may not be clearly differentiated from involvement of vessels by peritumoural inflammation.

Various groups have proposed criteria to define resectability of PDAC by imaging.

If surgery with extensive arterial reconstruction is performed, there is an increased risk of peri- and/or post-operative morbidity and mortality. Curative surgery is not recommended with distant metastases, even in cases of limited metastases.

Infiltration of veins generally does not prevent curative surgery of PDACs.

At least 10 regional lymph nodes should be dissected. Extended lymphadenectomy is not recommended.

Pancreatic surgery should be performed in specialised high-volume centres. If a tumour is regarded as not resectable by a surgical team from a low-volume institution, a second opinion is recommended.

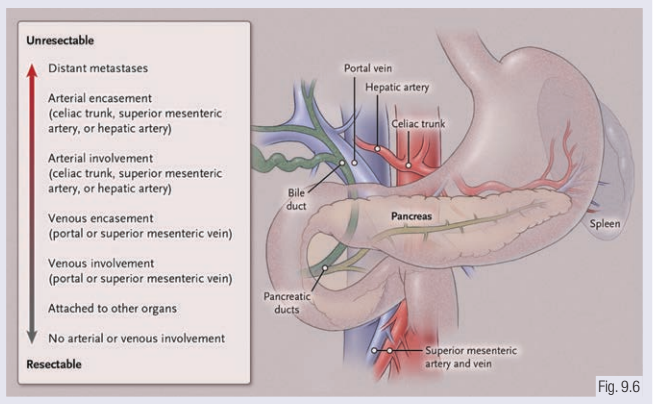


Fig. 9.6

REVISION QUESTIONS

1. Does MDCT or MRI always allow resectability of a pancreatic cancer to be defined?
2. Does involvement of veins always preclude resection of PDAC?
3. Is extended lymphadenectomy standard in pancreatic cancer surgery?

Radiotherapy and chemoradiotherapy

In resectable tumours, neoadjuvant CRT has been tested. This treatment may increase the R0 resectability rate for marginally resectable tumours.

After radical surgery, local CRT may positively affect patient outcome. The efficacy of adjuvant CRT has been tested in several clinical trials and results are controversial. Recent analysis suggests a better OS rate after adjuvant CRT, compared with radiotherapy (RT) alone.

Optimal therapy for patients with LA unresectable disease is still under debate. Currently, the standard of care includes either a combination of ChT and RT or ChT alone.

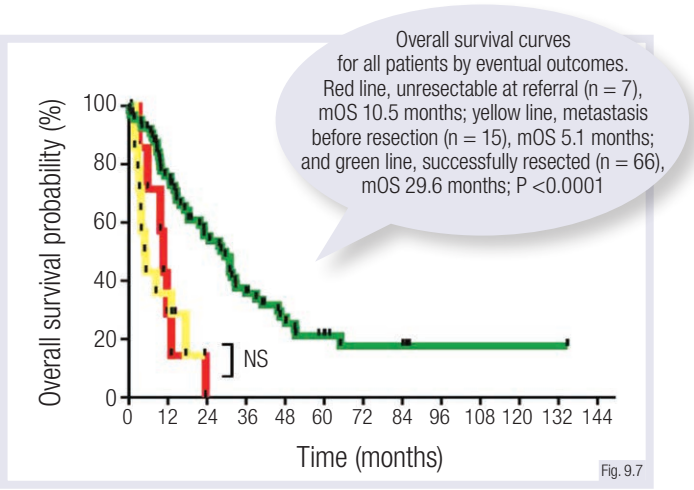


Fig. 9.7

mOS, median overall survival; NS, not significant.

Neoadjuvant treatment

Preoperative response to neoadjuvant treatment

	Total N=25	Unresected N=8	Resected N=17	R-PA N=9	BR-PA N=8
Tumour size cm, mean *(range)*					
Pre neoadjuvant	3.3 (1.8–5.5)	3.6 (1.9–5.5)	3.2 (1.8–5)	3.2 (1.8–5)	3.2 (2–5)
Post neoadjuvant	2.8 (1.4–5)	3.9 (1.9–5)	2.4 (1.4–4.5)	2.5 (1.5–4.5)	2.3 (1.5–4)
P	0.04	0.6	0.002	0.001	0.02
CA 19-9, U/mL *(range)*					
Pre neoadjuvant	1954.5 (0.7–36376)	5372.7 (3.25–36376)	345.8 (0.7–1457)	131.7 (0.7–321)	586.7 (46.16–1457)
Post neoadjuvant	923.5 (0.5–15199)	2515.5 (4.86–15199)	174.4 (0.5–1038)	59.1 (0.5–175)	304.2 (18.8–1038)
P	0.019	0.03	0.001	0.001	0.002
SUV, mean *(range)*					
Pre neoadjuvant	7.9 (1.7–13.4)	7.7	8.3	7.8	8.3
Post neoadjuvant	4.6	6.9	3.1	4.2	2.3
P	0.004	0.8	0.001	0.024	0.009
RECIST					
CR	0	0	0	0	0
SD	10	0	10	6	4
PaD	8	0	7	3	3
PrD	7	8[a]	0	0	0

BR-PA, borderline resectable pancreatic adenocarcinoma; CR, complete response; PaD, partial disease; PrD, progressive disease; RECIST, Response Evaluation Criteria in Solid Tumours; R-PA, resectable pancreatic adenocarcinoma; SD, stable disease; SUV, standard uptake value.
[a]One case found unresectable intraoperatively for peritoneal metastases.

Fig. 9.8

The role of neoadjuvant ChT or CRT in patients with resectable PDAC is under investigation. First results suggest a potential benefit of neoadjuvant treatment with respect to R0 resections and OS.

So far, neoadjuvant treatment of borderline resectable or LA tumours with intensified ChT regimens (e.g. FOLFIRINOX [leucovorin/5-fluorouracil (5-FU)/irinotecan/oxaliplatin] or gemcitabine/nab-paclitaxel) has shown a downsizing effect and improved OS in small prospective and larger retrospective analyses.

Data suggest that secondary resectability may be achieved in up to 25% of patients. Larger trials are under way.

CRT allows secondary resection in up to one third of initially unresectable patients.

However, results are limited by the fact that, while local treatment with CRT reduces local recurrence of the disease, the majority of patients die from distant metastases.

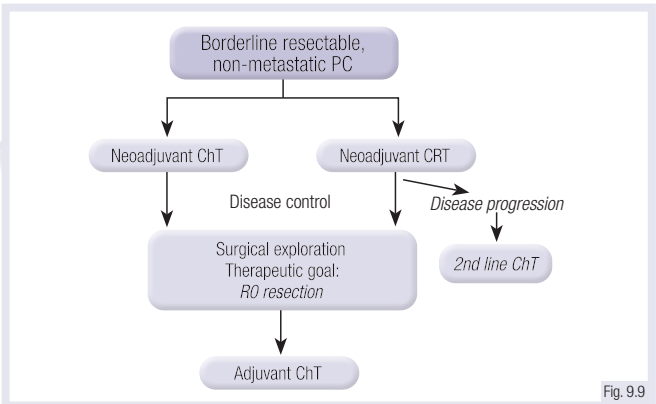


Fig. 9.9

ChT, chemotherapy; CRT, chemoradiotherapy; PC, pancreatic cancer.

REVISION QUESTIONS

1. Is CRT the standard approach for neoadjuvant treatment of PDAC?
2. Is there is an internationally accepted standard regimen for CRT of resectable PDAC?
3. Do large randomised clinical trials demonstrate the efficacy of FOLFIRINOX for downsizing of pancreatic cancer?

Adjuvant treatment

Every patient, regardless of age, should receive adjuvant treatment over 6 months after surgery with curative intent (R0 or R1). Adjuvant treatment improves disease-free survival (DFS) and OS compared with surgery alone, doubling the 5-year OS rate (ChT vs control: 20.7% vs 10.4%).

Gemcitabine and 5-FU are equally effective (ESPAC-3 trial median OS [mOS]: 23.0 months [5-FU] vs 23.6 months [gemcitabine], $p = 0.39$). In case of intolerance to either substance, the alternative compound should be used.

Modified FOLFIRINOX (mFOLFIRINOX) is a new standard for the adjuvant treatment of PDAC after resection. It substantially improved OS over gemcitabine, with OS of 63.4% at 3 years vs 48.6%. mFOLFIRINOX has a higher rate of grade 3/4 toxicity, particularly diarrhoea and sensory peripheral neuropathy. Patient selection mostly included Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-1 and ≤70 years of age.

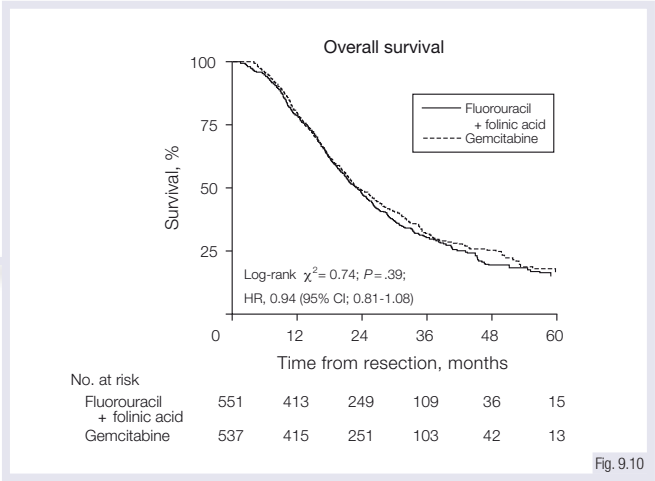


Fig. 9.10

CI, confidence interval; HR, hazard ratio.

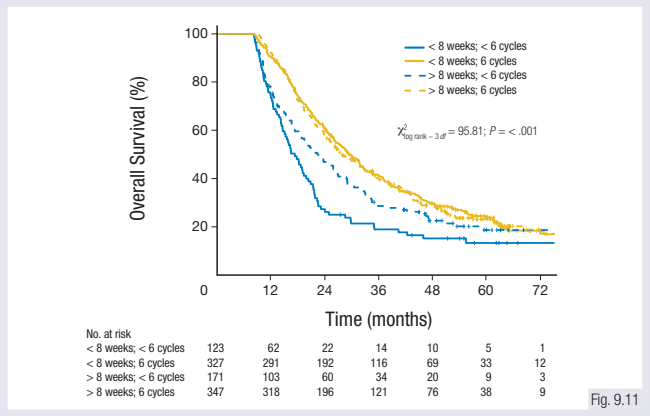


Fig. 9.11

The best time frame to start adjuvant treatment after PDAC resection is currently unclear. After pancreatic surgery, initiation of adjuvant treatment is often delayed due to postoperative morbidity or slow recovery of patients.

Retrospective subgroup analysis of the ESPAC-3 trial suggests that completing adjuvant treatment over 6 months, at appropriate dose intensity, is more important for survival than a very early start of adjuvant treatment after surgery.

Adjuvant treatment is not recommended if there are severe comorbidities or if the ECOG PS is >2.

CRT is still used in the USA as an adjuvant treatment, mainly due to data from the Gastrointestinal Tumor Study Group (GITSG), where RT was used in combination with 5-FU.

The ESPAC-1 trial showed that patients do not benefit from adjuvant CRT. This modality is currently not often used in Europe in the adjuvant setting.

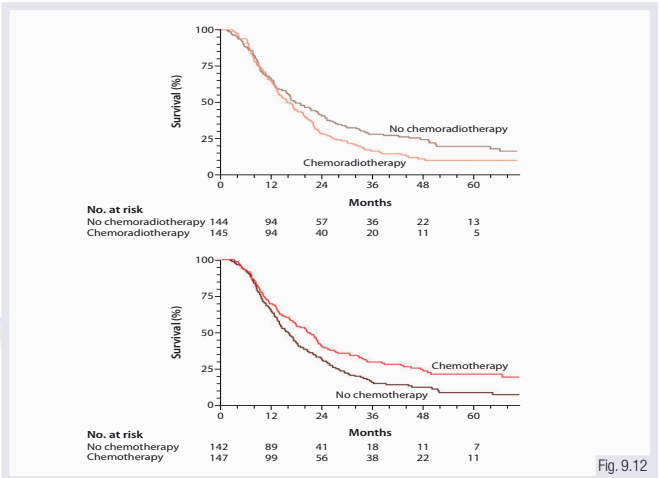


Fig. 9.12

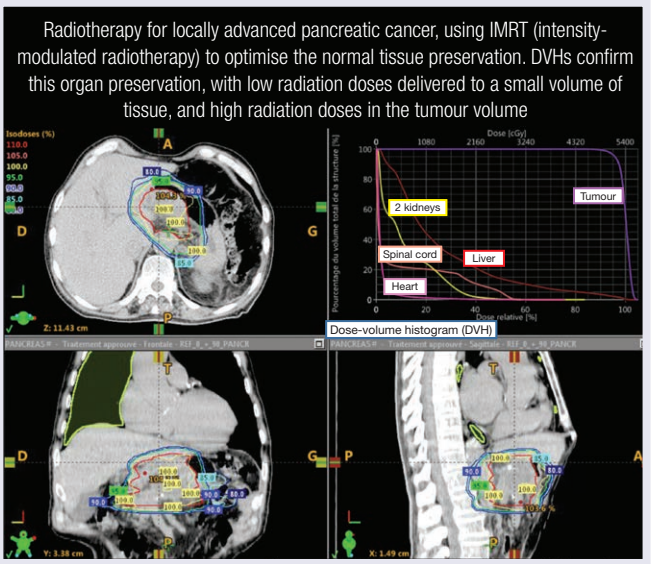
REVISION QUESTIONS

1. Is adjuvant ChT with gemcitabine or 5-FU the only standard treatment after R0 resection of PDAC?
2. Has the ESPAC-1 trial shown that adjuvant CRT is superior to adjuvant ChT after R1 resection of pancreatic cancer?
3. Is additive ChT the standard after R1 resection?

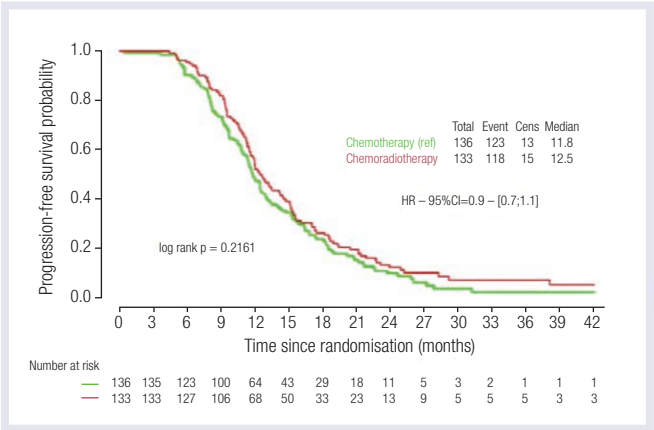
Treatment of unresectable patients

The optimal treatment for patients presenting with LA pancreatic adenocarcinoma remains unclear. Guidelines options include immediate CRT, single or multi-agent ChT alone, or ChT followed by CRT.

Uncertainties include: the optimal systemic regimen, whether RT should be added to systemic therapy (if so, immediately or after a period of induction ChT?), whether to use conventional RT or intensity-modulated RT (IMRT), which induces better tolerance and respect of normal tissues, or sterotactic body radiotherapy (SBRT), and deciding what systemic therapy should be delivered concurrently with RT.



DVHs, dose-volume histograms. Fig. 9.13



Cens, censored; CI, confidence interval; HR, hazard ratio. Fig. 9.14

Induction ChT followed by CRT was supported by a post-hoc analysis of GERCOR studies comparing survival of patients who received CRT vs patients continuing ChT alone.

However, a phase III trial, LAP07, failed to show the superiority of consolidation CRT over ChT alone. Thus, CRT cannot yet be recommended as a standard treatment of LA-PDAC.

There is increasing evidence that patients with LA-PDAC benefit from combination ChT such as FOLFIRINOX or gemcitabine/nab-paclitaxel.

Tumour necrosis and downstaging is often seen after neoadjuvant treatment.

In some cases, even in LA-PDAC, secondary resectability can be achieved.

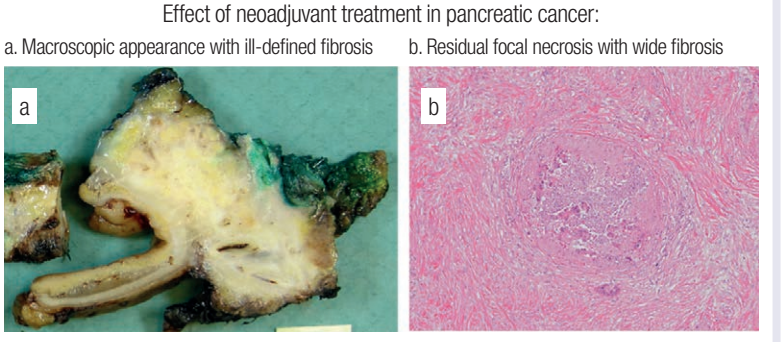


Fig. 9.15

REVISION QUESTIONS

1. Is CRT the established standard treatment for LA-PDAC?
2. Is there clear evidence from large trials that combination ChT prolongs OS in LA-PDAC?
3. Did a large clinical trial fail to show a significant difference in OS between ChT alone and ChT followed by CRT in LA-PDAC?

Palliative treatment

Patients with an ECOG PS of 0–2 should receive palliative ChT immediately after diagnosis of PDAC, as it improves OS and quality of life (QoL). If ECOG PS >2, the value of palliative ChT for PDAC treatment is questionable.

Gemcitabine used to be the standard treatment for LA-PDAC and metastatic PDAC (mPDAC).

The results published in 2007, by Moore et al, showed a statistically significant, but not clinically relevant, survival advantage for the combination of gemcitabine with the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) erlotinib.

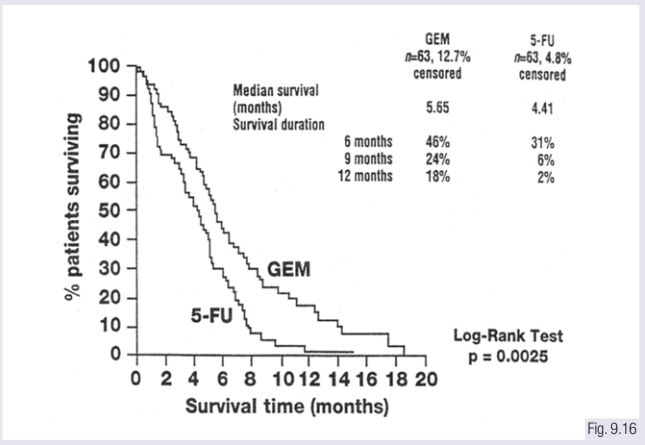


Fig. 9.16

5-FU, 5-fluorouracil; GEM, gemcitabine.

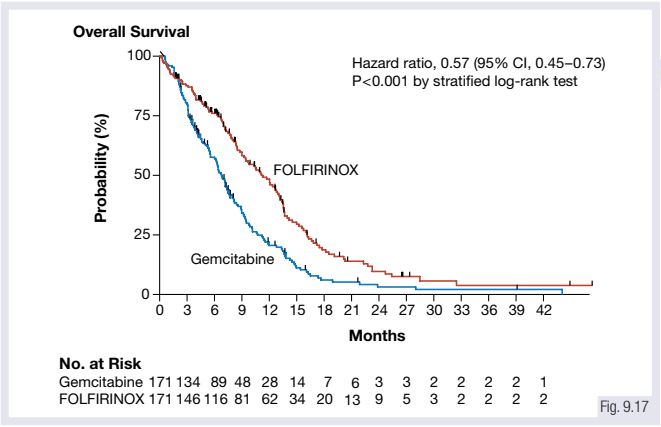


Fig. 9.17

CI, confidence interval; FOLFIRINOX, leucovorin/5-fluorouracil/irinotecan/oxaliplatin.

Compared with gemcitabine alone, FOLFIRINOX combination significantly improves mOS (6.8 vs 11.1 months) and overall response rate (ORR): 9.4% vs 31.6%.

The FOLFIRINOX regimen has a higher toxicity than gemcitabine (more grade 3/4 haematotoxicity, diarrhoea and ChT-associated neuropathy).

This treatment is suitable for patients with very good PS (ECOG 0–1), age <75 years and bilirubin level ≤1.5x upper limit of normal (ULN). Despite increased toxicity, FOLFIRINOX improves tumour-related QoL of patients.

Nab-paclitaxel led to a significant improvement in OS of patients with mPDAC in combination with gemcitabine, compared with gemcitabine alone.

Elderly patients (>65 years) as well as those with a Karnofsky PS (KPS) of 70–80 also benefited from the combination. Main treatment-associated toxicities were grade 3-4 haematotoxicity, fatigue and ChT-associated and sensory neuropathy.

In PDAC patients with *BRCA* germline mutations, olaparib maintenance improves PFS in patients harbouring mutations after induction treatment with platinum-based ChT.

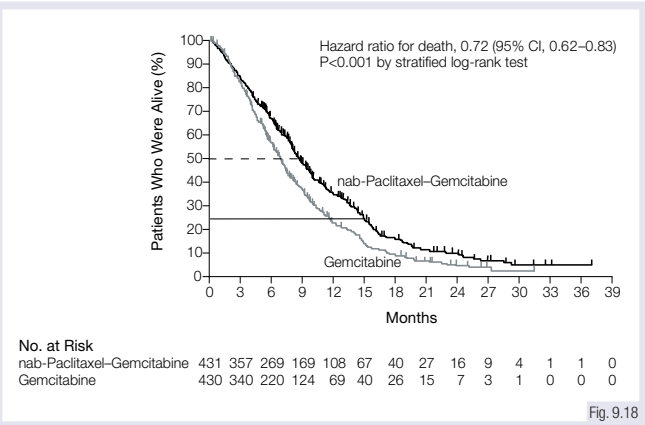


Fig. 9.18

CI, confidence interval.

REVISION QUESTIONS

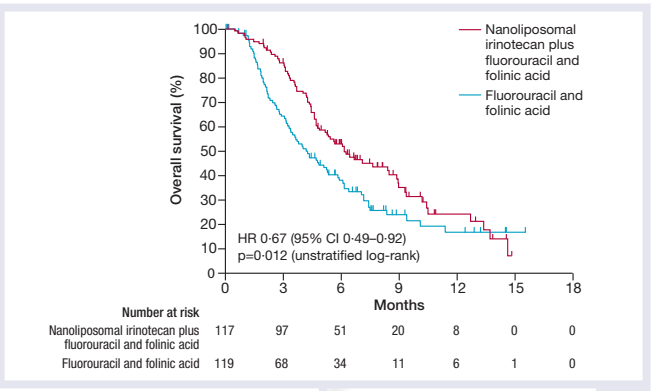
1. Does FOLFIRINOX significantly prolong OS of patients with mPDAC?
2. Can the combination gemcitabine/nab-paclitaxel be used in elderly patients with pancreatic cancer as well as in patients with a KPS of 70–80?
3. With more efficacious combination ChT regimens, are fewer patients with mPDAC receiving gemcitabine alone?

Second-line treatment

Patients with ECOG PS ≤2 progressing during first-line ChT should receive second-line treatment. If gemcitabine monotherapy is used in first line, the combination of 5-FU, leucovorin and oxaliplatin (OFF protocol) shows survival benefit over "best supportive care" (BSC).

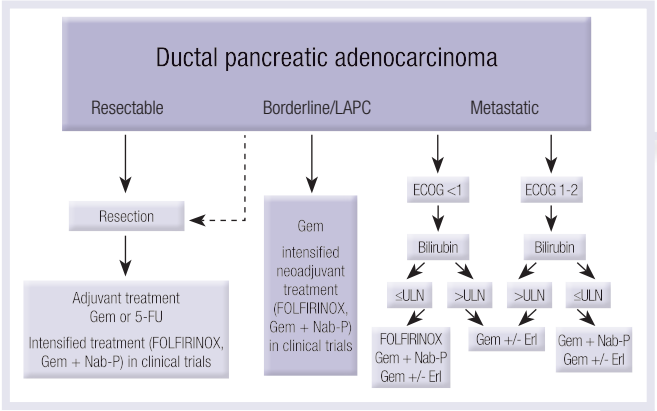
Patients progressing after FOLFIRINOX still benefit from gemcitabine treatment. Gemcitabine/nab-paclitaxel after FOLFIRINOX, or *vice versa*, appear to be treatment options.

Myelosuppression and neurotoxicity may be limiting for subsequent intensified treatments. Small trials are examining nab-paclitaxel as single agent in second line.



CI, confidence interval; HR, hazard ratio.

Fig. 9.19



5-FU, 5-fluorouracil; ECOG, Eastern Cooperative Oncology Group; Erl, erlotinib; FOLFIRINOX, leucovorin/5-fluorouracil/irinotecan/oxaliplatin; GEM, gemcitabine; LAPC, locally advanced pancreatic cancer; Nab-P, nab-paclitaxel; ULN, upper limit of normal.

Fig. 9.20

There are novel therapeutic strategies in the second- and even further-line settings. After failure of first-line gemcitabine, the combination of nanoliposomal (nal) irinotecan/5-FU/leucovorin achieved significant improvement in mOS vs BSC (6.1 vs 4.2 months; hazard ratio: 0.67). Frequent side effects were diarrhoea and fatigue.

Supportive care is key in pancreatic cancer. Adequate control of pain and nutrition as well as psycho-oncological support are essential components.

Radiotherapy as palliative treatment

Patients with LA disease often experience significant pain, and RT can provide durable palliation in 50%-85% of patients. Conventional irradiation and, more recently, IMRT and SBRT induced significantly reduced pain in most patients.

SBRT allows higher doses of radiation to be delivered and should result in improved and more durable pain relief.

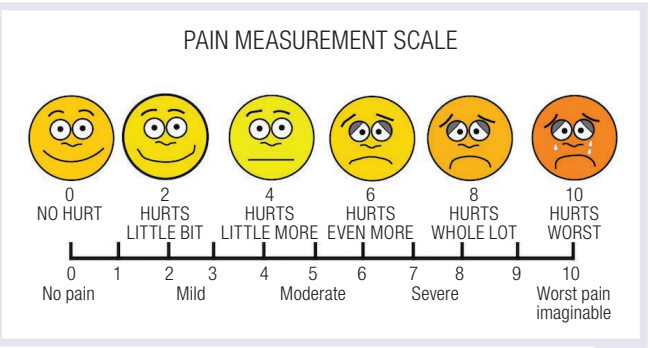


Fig. 9.21

REVISION QUESTIONS

1. Are there efficacious ChT regimens after failure of first-line treatments for patients with mPDAC?
2. Can the OFF regimen or the combination of 5-FU plus nal-irinotecan be used in the second-line setting for patients with mPDAC?
3. Apart from ChT, are supportive measures such as pain control and nutritional management paramount for patients with LA-PDAC?

Summary: Pancreatic cancer

- PDAC represents a serious clinical entity due to the anticipated increase of its incidence
- Surgery is still the only curative approach for localised pancreatic cancer
- All patients operated with a curative intent should be given adjuvant ChT for a 6-month period
- While neoadjuvant approaches are still under investigation, mFOLFIRINOX is the most efficacious option for adjuvant treatment of PDAC
- RT or CRT should be further examined in clinical trials to define the significance of these modalities for local tumour control
- Palliative treatment of mPDAC is based on ChT in patients with ECOG PS <2
- Palliative treatment has been substantially improved by the introduction of FOLFIRINOX and the combination of gemcitabine plus nab-paclitaxel. For the first time, a choice of efficient treatment strategies in the first-line setting is available
- Second-line therapies should be offered to patients with ECOG PS <2
- After a long period of therapeutic deadlock, there are now better treatments available and potentially more efficient strategies on the horizon
- Patients with germline mutations in *BRCA* genes may particularly benefit from PARP inhibition

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10 Hepatocellular carcinoma

Incidence of hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the fifth most common neoplasm and the third most frequent cause of cancer-related death worldwide.

In most cases HCC develops in patients with chronic liver diseases and cirrhosis, which can be either cryptogenic or due to viral hepatitis, autoimmune hepatitis, steatohepatitis or alcohol consumption.

Diagnosis of HCC can be made by contrast-enhanced imaging only in cirrhotic patients. Biopsy is mandatory in non-cirrhotic patients.

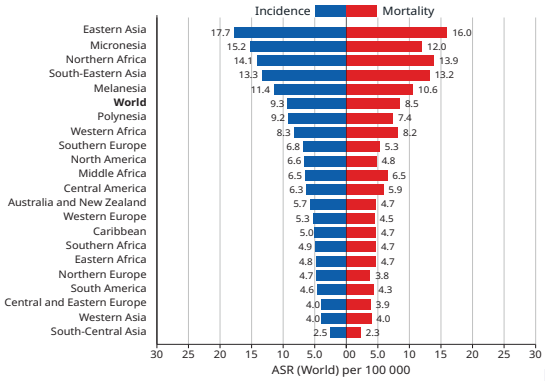


Fig. 10.1

ASR, age-standardised rate.

Screening and diagnosis in HCC

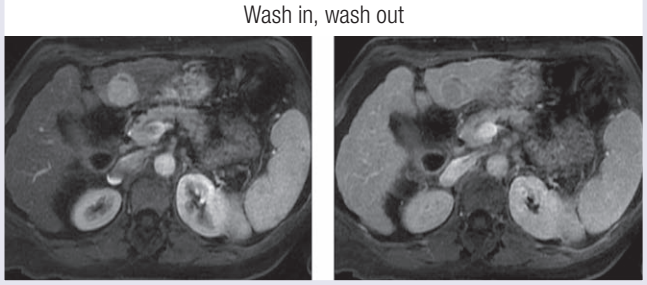


Fig. 10.2

In patients with liver cirrhosis, screening is recommended with abdominal ultrasound every 6 months. Additional determination of serum alpha foetoprotein (AFP) is of limited benefit.

Nodules ≥1 cm in a cirrhotic liver showing contrast uptake in the arterial phase, followed by contrast washout in the portal venous or delayed phases on computed tomography (CT) or magnetic resonance imaging (MRI) using gadolinium, are confidently diagnosed as HCC.

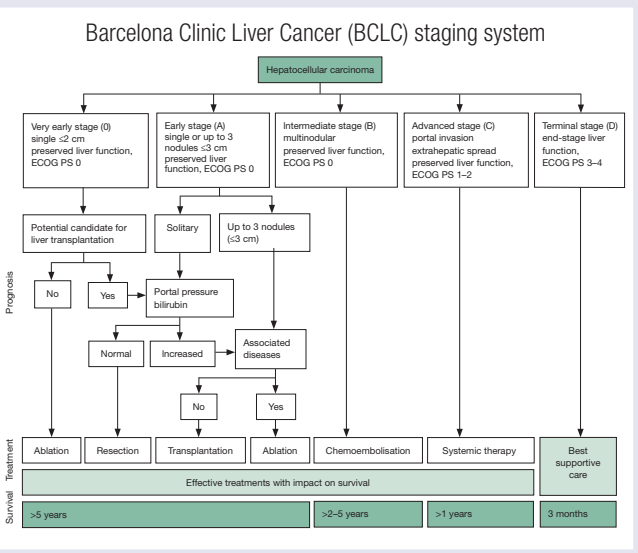
Increased tumour markers (such as AFP) should raise the suspicion of malignancy, but do not suffice to establish HCC diagnosis, as cholangiocarcinoma may also exhibit AFP increase.

Barcelona Clinic Liver Cancer classification

The Barcelona Clinic Liver Cancer (BCLC) classification accounts for all essential parameters: tumour stage, liver function impairment and presence of cancer-related symptoms.

It stratifies patients according to outcome and simultaneously links it with treatment indication for all stages of HCC. It has been endorsed by the European Society for Medical Oncology (ESMO), the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) guidelines.

Resection, liver transplantation (LT) and ablation are considered potentially curative treatments. Transarterial chemoembolisation (TACE) and systemic therapy (atezolizumab-bevacizumab, sorafenib, lenvatinib, regorafenib, cabozantinib, ramucirumab) are usually not curative but provide significant survival benefit.



ECOG, Eastern Cooperative Oncology Group; PS, performance status.
Fig. 10.3

REVISION QUESTIONS

1. Is screening in cirrhotic patients recommended every 6 or 12 months?
2. What are the non-invasive diagnostic criteria for HCC?
3. Which parameters does the BCLC classification consider?

Surgical treatments in HCC

LT allows treatment of the neoplasia and the underlying liver disease. The 'Milan criteria' (1 HCC ≤5 cm or up to 3 HCC ≤3 cm, without vascular invasion or extrahepatic spread) have become widely accepted. Expanded criteria are still not extensively validated.

Hepatocellular carcinoma in a cirrhotic liver

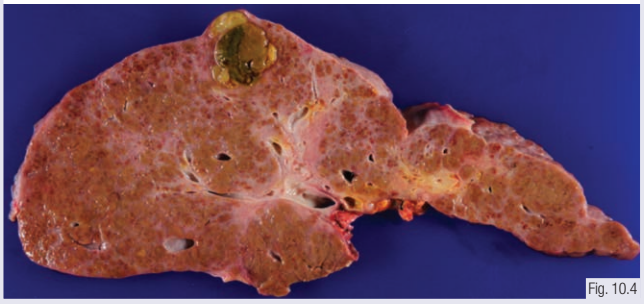


Fig. 10.4

Anatomical resection is the treatment of choice for patients with a single nodule, normal concentration of bilirubin and no clinically significant portal hypertension, with a 5-year survival rate >70%.

If histopathological examination of the resected explant shows risk factors for recurrence (microvascular invasion or satellite nodules), LT should be considered. Adjuvant therapy is not recommended for HCC patients after LT, resection or ablation.

Locoregional treatments

Prognosis of HCC suitable for ablation

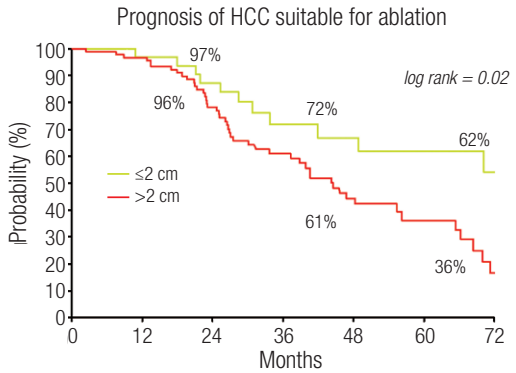


Fig. 10.5

HCC, hepatocellular carcinoma.

Ablation (usually percutaneous under image guidance) achieves complete necrosis of almost all HCCs ≤2 cm, while its efficacy is significantly reduced in HCCs >2 cm.

TACE combines injection of chemotherapy with obstruction of arterial blood supply, and significantly improves survival.

TACE benefits patients with preserved liver function (compensated cirrhosis) without portal thrombosis and/or extrahepatic spread (BCLC stage B).

TACE has limited efficacy in patients with multiple tumours (>4-5) not amenable for highly selective intervention, and in very large tumours.

No effective adjuvant or co-adjuvant option to TACE has been proven beneficial.

Options such as conformal high-dose rate radioablation, stereotactic body radiotherapy, radioembolisation and immunotherapy have been shown to bear some clinically significant activity, but positive prospective phase III studies are still awaited.

Transarterial chemoembolisation (TACE) procedure

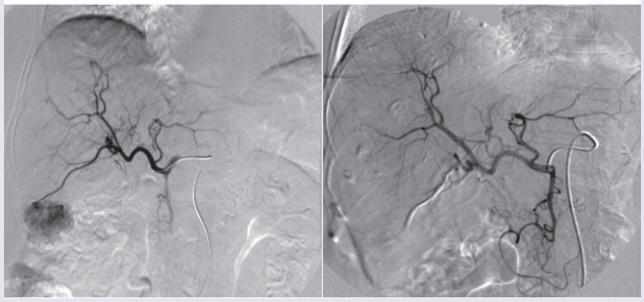


Fig. 10.6

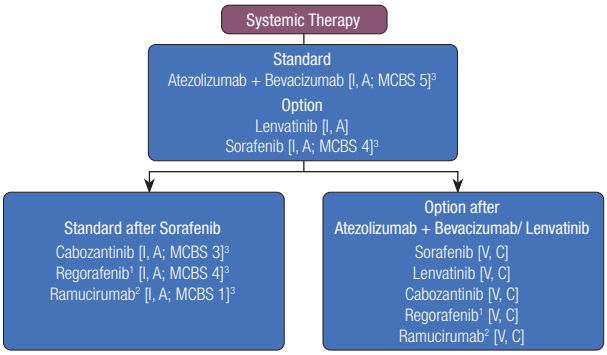
REVISION QUESTIONS

1. What are the accepted criteria for liver transplantation in HCC?
2. Is TACE a curative or palliative treatment?
3. Do you consider adjuvant or co-adjuvant options after TACE?

Systemic therapy

Systemic therapy should be initiated in patients with preserved liver function (usually fitting into Child-Pugh class A) in BCLC stage B, who are not candidates for TACE, have failed or are refractory to TACE (at least two TACE sessions without deep response) and in patients with advanced disease (BCLC stage C).

Systemic agents providing survival benefit are atezolizumab/bevacizumab, sorafenib and lenvatinib for first line, and regorafenib, cabozantinib and ramucirumab for second line.



AFP, alpha foetoprotein; EMA, European Medicines Agency; ESMO, European Society for Medical Oncology; MCBS, Magnitude of Clinical Benefit Scale; TKI, tyrosine kinase inhibitor.

Fig. 10.7

Overall survival of positive randomised controlled trials

	OS (months)		HR (95%CI)
First line			
Sorafenib vs placebo	10.7	7.9	0.69 (0.50-0.87)
Lenvatinib vs sorafenib	13.6	12.3	0.92 (0.79-1.06)*
Atezolizumab + bevacizumab vs sorafenib	Not estimable	13.2	0.58 (0.42-0.79)
Second line			
Regorafenib vs placebo	10.6	7.8	0.63 (0.50-0.79)
Cabozantinib vs placebo	10.2	8.0	0.76 (0.63-0.92)
Ramucirumab vs placebo	8.5	7.3	0.71 (0.53-0.94)

CI, confidence interval; HR, hazard ratio; OS, overall survival.
* designed for non-inferiority

Fig. 10.8

Sorafenib, lenvatinib, regorafenib and cabozantinib are inhibitors of several signalling pathways affecting proliferation, apoptosis, angiogenesis and immune and stromal status of the tumour.

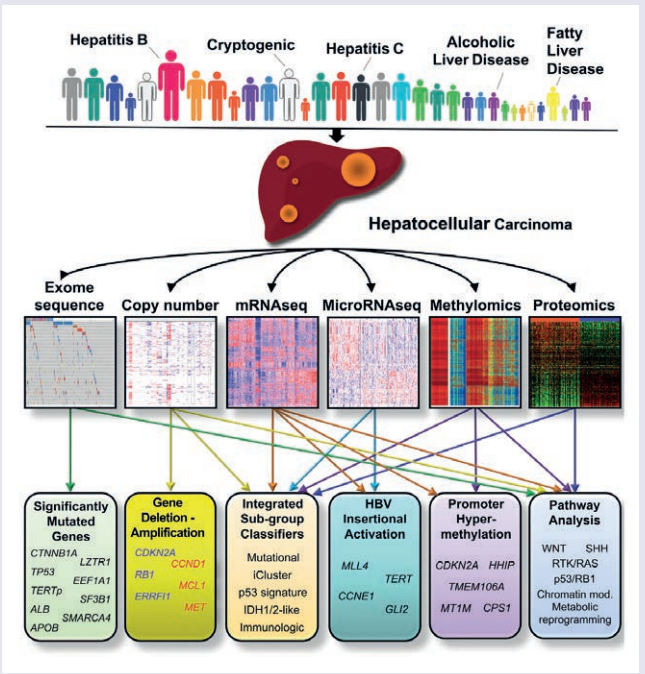
Molecular profiling of HCC

HCC is highly heterogeneous and displays somatic DNA mutations and aberrations. TERT activation is a very frequent abnormality (60% of cases). Other frequent mutations affect *TP53* (30% of cases), Wnt signalling (30%) or chromatin remodelling (ARID1A and ARID2).

Several molecular classifications according to gene profile and clinical characteristics have been proposed. However, none has been robustly proven useful for accurate outcome prediction or treatment selection. Currently, two major classes are used for stratification: proliferative class and non-proliferative class.

The proliferative class is more commonly seen in hepatitis-B virus (HBV)-positive cases and is associated with a more malignant profile (high AFP levels, poor differentiation, *TP53* mutations and active proliferation pathways). Such a profile is associated with poor outcomes, but there is no proof of a cause-effect relationship between molecular events and outcome.

Identification of new molecular biomarkers is urgently needed to guide patient stratification and treatment.



HBV, hepatitis-B virus; IDH 1/2, Isocitrate dehydrogenase 1/2; mRNAseq, messenger RNA sequencing; MicroRNAseq, micro RNA sequencing; SHH, Sonic Hedgehog.

Fig. 10.9

REVISION QUESTIONS

1. How can we define the best treatment sequence for systemic therapy in the absence of head-to-head or sequencing trails?
2. Have atezolizumab/bevacizumab, sorafenib and lenvatinib been tested in the same patient profiles in terms of inclusion/exclusion criteria?
3. Have immuno-oncology drugs as single agents shown survival benefit as compared with sorafenib in first line or versus placebo in second line?

Summary: Hepatocellular carcinoma

- Patients at high risk for developing HCC should be included in surveillance programmes: abdominal ultrasound every 6 months with and without determination of AFP
- Diagnosis of HCC in cirrhotic patients is based on non-invasive criteria (hypervascular in the arterial phase with washout in the portal venous or delayed phases in CT or MRI) or on pathology
- The BCLC staging system is recommended for prognostic prediction and treatment allocation
- Resection is the preferred treatment option for patients with solitary tumours and very well-preserved liver function: normal bilirubin with hepatic venous pressure gradient ≤10 mmHg
- LT is considered the best treatment option for patients with single tumours ≤5 cm or up to 3 nodules ≤3 cm (Milan criteria) not suitable for resection
- Local ablation is considered the standard of care for patients with BCLC stage 0-A tumours not suitable for surgery
- TACE is recommended for patients with BCLC stage B, with compensated liver disease, multinodular asymptomatic tumours without vascular invasion or extrahepatic spread
- Sorafenib and lenvatinib are effective first-line systemic therapies, while regorafenib, cabozantinib and ramucirumab are effective in second line. These agents should be considered for patients with well-preserved liver function and preserved performance status and with advanced tumours (BCLC stage C), or those with tumours progressing upon locoregional therapies (BCLC stage B)
- Several options such as conformal high-dose rate radioablation, stereotactic body radiotherapy or immunotherapy have shown activity, but their benefit in survival is awaited from phase III prospective investigations

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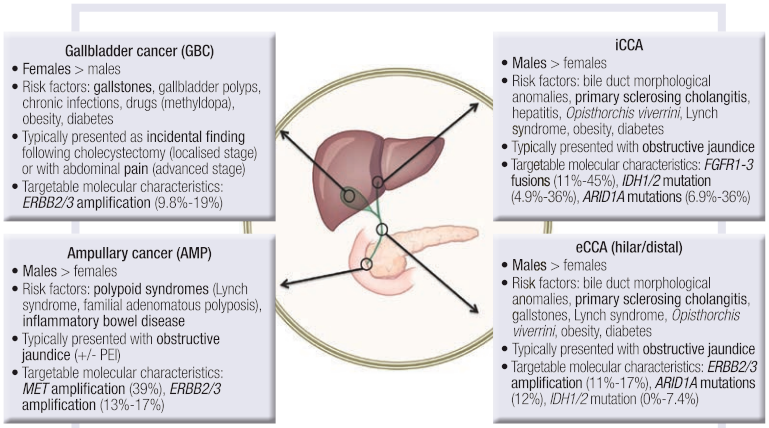
11 Biliary tract cancers

Epidemiology and clinical presentation

Biliary tract cancers (BTCs) include cholangiocarcinoma (CCA), gallbladder cancer (GBC) and ampullary (ampulla of Vater) cancers (AMP).

CCA can be subdivided into intrahepatic (iCCA) and extrahepatic (eCCA), which includes perihilar (hCCA) and distal (dCCA).

Epidemiology and clinical presentation vary between iCCA, eCCA, GBC and AMP.



eCCA, extrahepatic cholangiocarcinoma; iCCA, intrahepatic cholangiocarcinoma; IDH, isocitrate dehydrogenase; FGFR, fibroblast growth factor receptor; MET, mesenchymal epithelial transition; PEI, pancreatic exocrine insufficiency. Fig. 11.1

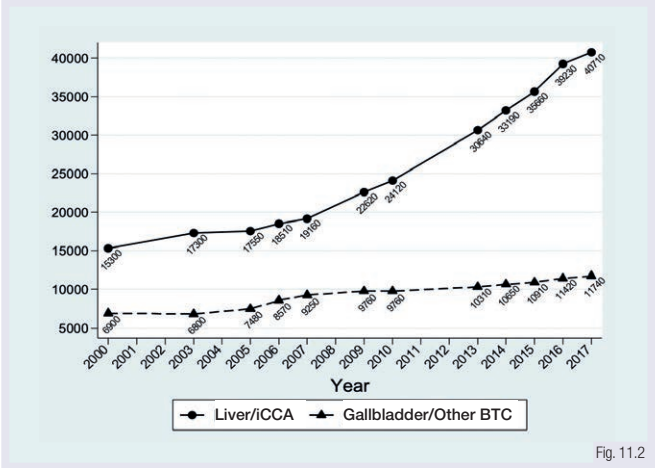


Fig. 11.2

BTC, biliary tract cancer; iCCA, intrahepatic cholangiocarcinoma.

BTCs have a poor prognosis with 5-year survival rates of 5%–15%. BTCs are rare, representing around 3% of all gastrointestinal cancers.

However, their incidence is slowly increasing. A more marked increase in incidence has been described for iCCA (vs other BTCs).

It is suggested that this increase is a reflection not only of recent changes in the International Classification of Diseases for Oncology (ICD-O) coding system but also of improved awareness and diagnosis.

There are no specific screening recommendations for early diagnosis of BTCs. Most iCCAs arise within healthy liver (vs cirrhotic liver in hepatocellular carcinoma [HCC]).

Primary sclerosing cholangitis (PSC) is a rare disorder characterised by multifocal bile duct strictures and progressive liver disease.

Patients with PSC are at a higher risk of developing CCA (mainly iCCA); these patients may benefit from screening programmes.

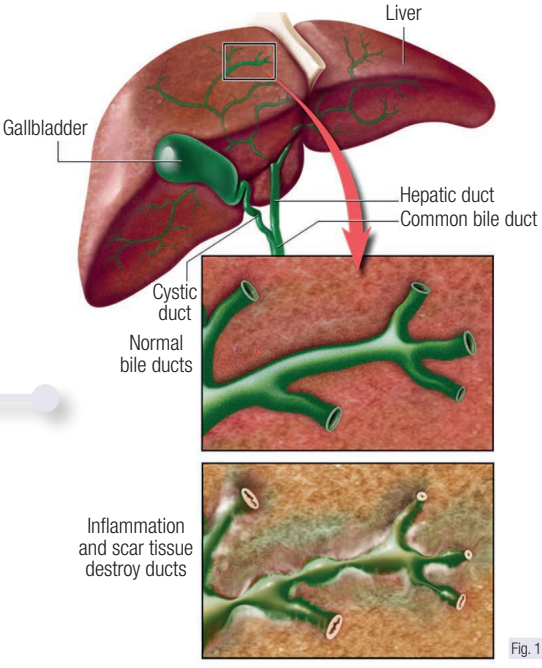


Fig. 11.3

REVISION QUESTIONS

1. Which tumours are included within the so-called 'BTCs'?
2. How are CCAs classified according to location?
3. Is cirrhosis the main risk factor for iCCA?

Diagnosis, staging and treatment planning

Diagnosis of BTCs always relies on pathological/cytological confirmation. Most BTCs (>90%) are of adenocarcinoma type, with few squamous or mixed CCA-HCC tumours.

Tumour staging relies on the Union for International Cancer Control (UICC) Tumour, Node, Metastasis (TNM) classification, last updated in 2018. The Bismuth–Corlette classification is used for hCCA.

Radiological investigations are the cornerstone for adequate assessment of site to biopsy, assess disease spread and tumour staging.

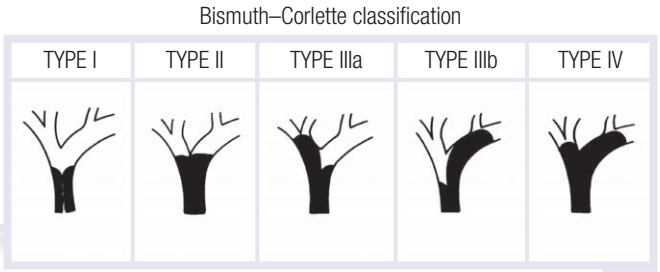


Fig. 11.4

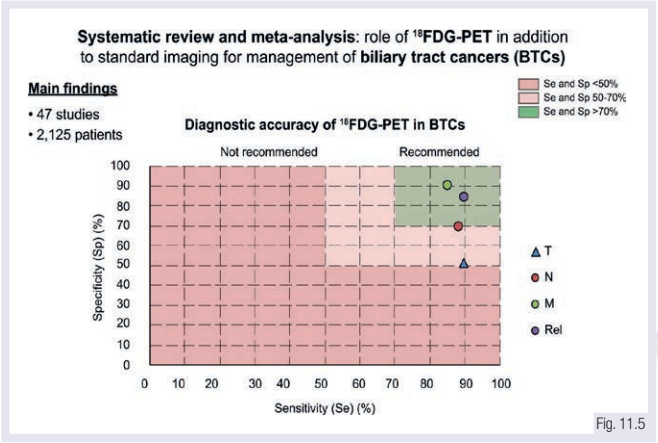


Fig. 11.5

[18]FDG-PET, [18]fluorodeoxyglucose-positron emission tomography.

For tissue acquisition, endoscopy (for biliary stenting/biopsy-cytology) and/or percutaneous biopsy (ultrasound or computed tomography [CT]-guided) are used.

Radiological investigations for staging include contrast-enhanced ultrasound, CT and magnetic resonance imaging (MRI).

[18]Fluorodeoxyglucose-positron emission tomography ([18]FDG-PET) can be used for identification of distant metastasis or nodal metastases when completing staging of potentially resectable disease.

Patient outcomes depend on stage and on whether the disease is amenable to curative resection (median overall survival [mOS] 51.1 months) or not (mOS 11.7 months).

Treatment of localised disease relies on potentially curative resection; long-term outcomes (overall survival [OS] and relapse-free survival [RFS]) depend on primary site and stage.

For locally advanced and metastatic disease, surgery would not be appropriate and palliative strategies are employed (mainly focused on systemic therapy).

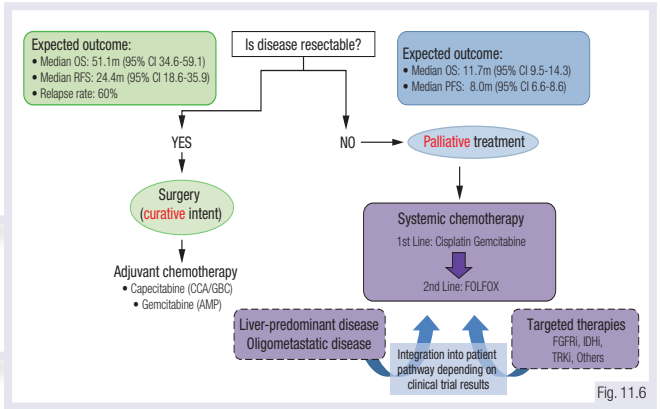


Fig. 11.6

AMP, ampullary cancer; CCA, cholangiocarcinoma; CI, confidence interval; FGFR, fibroblast growth factor receptor; FOLFOX, leucovorin/fluorouracil (5-FU)/oxaliplatin; GBC, gallbladder cancer; i, inhibitor; IDH, isocitrate dehydrogenase; MMR, mismatch repair; OS, overall survival; PFS, progression-free survival; RFS, recurrence-free survival; TRK, tropomyosin receptor kinase.

REVISION QUESTIONS

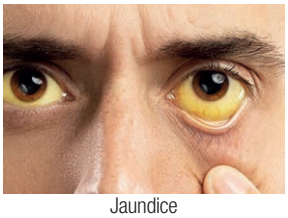
1. Is a histological or cytological diagnosis always required to confirm diagnosis of BTC?
2. Are there any circumstances when radiological diagnosis would suffice for planning therapy?
3. Which system is used for BTC tumour staging?

Obstructive jaundice: a medical emergency

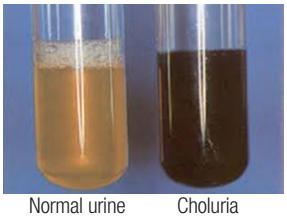
It is very common for patients diagnosed with BTC to present with biliary obstruction at initial presentation or during treatment.

Biliary obstruction is of special relevance in eCCA and AMP, but patients with GBC and iCCA may also be at risk of biliary obstruction, depending on site of disease.

Biliary obstruction is characterised by jaundice, itchy skin, dark urine (choluria), pale stools (acholia) and out of range liver function test.



Jaundice



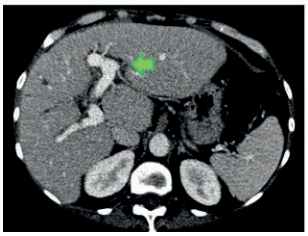
Normal urine Choluria

Itchy skin

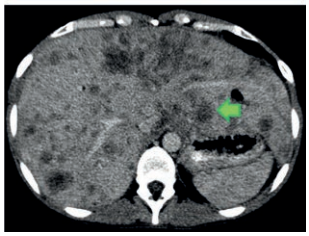
Normal stools

Acholia

Fig. 11.7



Computed tomography confirms presence of **biliary tract obstruction** that account for jaundice in this patient. **Urgent biliary stent is required**.



Computed tomography does not show significant presence of biliary tract obstruction; jaundice is likely to be related to **burden of liver metastases**. Biliary stent is not indicated in this scenario.

Fig. 11.8

When biliary obstruction is suspected, patients require urgent assessment and management as a medical emergency.

In the presence of suspected biliary obstruction, urgent imaging (ultrasound or CT) will confirm diagnosis.

If an underlying infection (cholangitis) is identified, antibiotics are urgently required to prevent clinical deterioration and biliary sepsis.

Once a diagnosis of biliary obstruction has been made, urgent plans for biliary stenting must be arranged; there is a preference for metal stent in the palliative setting.

Biliary stent insertion can be made endoscopically via endoscopic retrograde cholangiopancreatography (ERCP) for AMP and eCCA.

When ERCP is not feasible, percutaneous transhepatic cholangiography (PTC) is to be considered. Personalised case-by-case discussions with the interventional radiologist are encouraged.

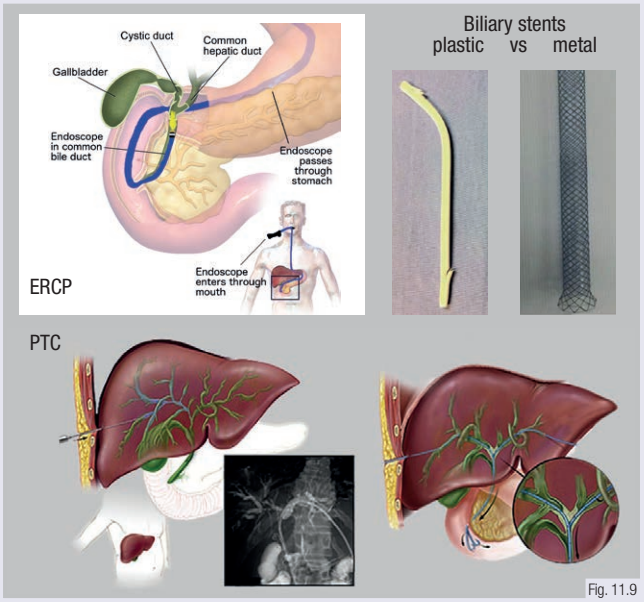


Fig. 11.9

ERCP, endoscopic retrograde cholangiopancreatography; PTC, percutaneous transhepatic cholangiography.

REVISION QUESTIONS

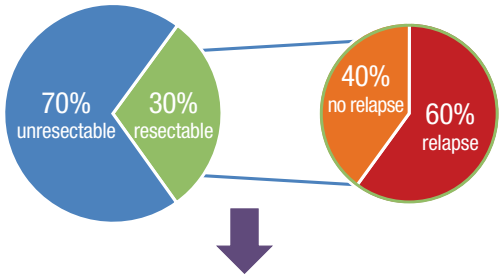
1. Is biliary obstruction considered a medical emergency in patients diagnosed with BTC?
2. Do all patients require radiological imaging for confirmation of diagnosis of biliary obstruction?
3. Once biliary obstruction is suspected, are patients required to start on antibiotic therapy?

Management of resectable disease

Approximately 30% of patients are diagnosed with resectable disease. Radical surgery (+ lymphadenectomy) is the only option for cure; however, post-surgical relapse rate remains high (~60%).

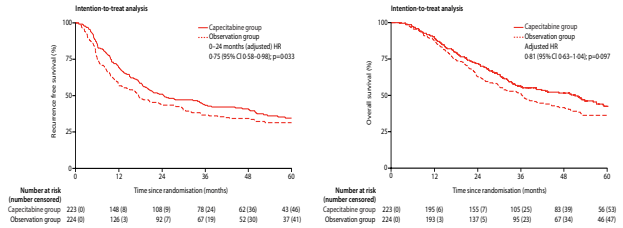
Surgical strategies vary depending on BTC subtype, location and T-stage and should be agreed at a specialist hepatobiliary multidisciplinary tumour board.

For patients with incidentally diagnosed GBC (post-cholecystectomy), completion surgery with radical intent should be considered for stage ≥T1b (± resection of port sites).



~12% of all patients diagnosed with biliary tract cancer will be resectable and will NOT relapse (cured)

Fig. 11.10



BILCAP trial	Recurrence-free survival	Overall survival		
	Median	Median	ITT (sensitivity anlysis)	Per-protocol analysis
Capecitabine	24.4 months	51.1 months	HR 0.71 (95% CI 0.55-0.92) P-value 0.010	HR 0.75 (95% CI 0.58-0.97) P-value 0.028
Observation alone	17.5 months	36.4 months		

CI, confidence interval; ITT, intention to treat; HR, hazard ratio.

Fig. 11.11

Three clinical trials (BILCAP, PRODIGE 12 and BCAT) exploring the role of adjuvant treatment after curative resection in CCA and GBC have been published with variable findings.

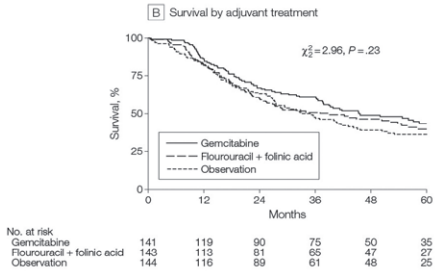
Based on the BILCAP clinical trial, capecitabine is the current standard of care for resected CCA/GBC. 447 patients were randomised to observation or capecitabine (6-month course).

Capecitabine did not reach OS statistical significance in the intention-to-treat (ITT) population; benefit from capecitabine was shown in sensitivity and per-protocol analyses.

Patients diagnosed with AMP were not included in the BILCAP clinical trial. Data regarding adjuvant treatment for AMP derives from the ESPAC-3 study.

428 patients with periampullary tumours (297 AMP) were randomised to observation, 5-fluorouracil (5-FU) or gemcitabine after curative surgery.

Multivariable analysis showed an improved OS with adjuvant chemotherapy (ChT) vs observation; there was also a benefit in favour of gemcitabine over 5-FU.



ESPAC-3 trial	Overall survival (all patients)			Overall survival (AMP patient)
	Median	Multivariable HR (95% CI)	HR (95% CI)	Median
Gemcitabine	45.7 months	0.75 (0.57-0.98); P-value 0.03	0.70 (0.51-0.97); P-value 0.03	70.8 months
5-FU	38.9 months		0.79 (0.58-18); P-value 0.13	57.8 months
Observation alone	35.2 months	1 (Ref)	1 (Ref)	40.6 months

AMP, ampullary cancer; CI, confidence interval; HR, hazard ratio; 5-FU, 5-fluorouracil.

Fig. 11.12

REVISION QUESTIONS

1. What is the only curative treatment for BTC?
2. What is the standard adjuvant ChT option for resected CCA and GBCs?
3. What is the standard adjuvant ChT option for resected AMPs?

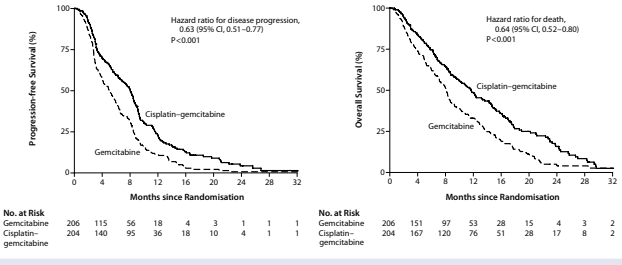
Management of advanced disease

Combination gemcitabine/cisplatin ChT is the first-line treatment of choice (ABC-02 trial). Gemcitabine can be considered if performance status = 2.

The ABC-02 clinical trial randomised 410 patients to gemcitabine/cisplatin or gemcitabine alone. An OS benefit was confirmed.

Ongoing clinical trials are exploring the role of other ChT agents and new combinations such as gemcitabine/cisplatin + nab-paclitaxel and FOLFIRINOX (leucovorin/5-FU/irinotecan/oxaliplatin).

ABC-02 trial	Complete response	Partial response	Disease control rate	Progression-free survival (median)	Overall survival (median)
Cisplatin/gemcitabine	0.6%	25.5%	81.4%	8 months	11.7 months
Gemcitabine	0.7%	14.8%	71.8%	5 months	8.2 months



CI, confidence interval.

Fig. 11.13

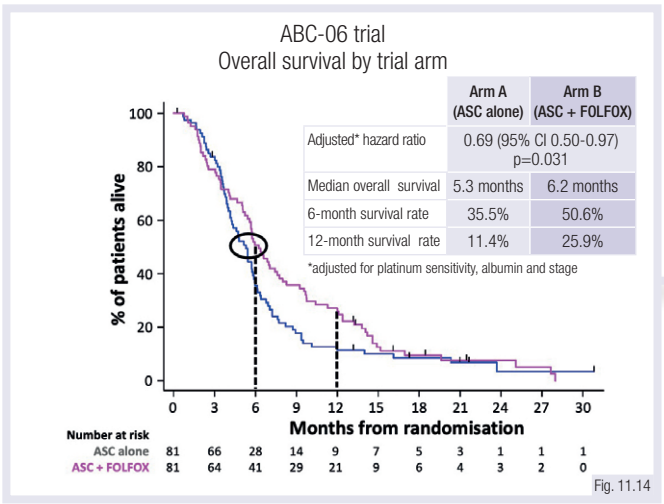


Fig. 11.14

ASC, active symptom control; CI, confidence interval; FOLFOX, leucovorin/5-fluorouracil/oxaliplatin.

For decades, quality evidence supporting second-line ChT was lacking; active symptom control (ASC) was considered standard second-line in many countries.

The ABC-06 trial randomised 162 patients to ASC or ASC + FOLFOX (leucovorin/5-FU/oxaliplatin) ChT, showing an OS benefit with meaningful differences in both 6- and 12-month survival rates.

FOLFOX is the current standard second-line ChT for BTCs after progression on gemcitabine/cisplatin. Other second-line alternatives are being explored in clinical trials.

Targeted therapies are likely to completely change treatment of advanced BTCs in the coming years, mainly for patients diagnosed with iCCA.

Around 20% of iCCAs harbour targetable *IDH1* mutations. In these patients, the ClarIDHy clinical trial showed a benefit in progression-free survival (PFS) from AG-120 (an IDH1 inhibitor).

An additional ~20% of iCCAs harbour targetable *FGFR2* (fibroblast growth factor receptor 2) fusions. Multiple FGFR inhibitors are being developed and tested in first- and second-line randomised trials; some are already approved by some regulatory authorities.

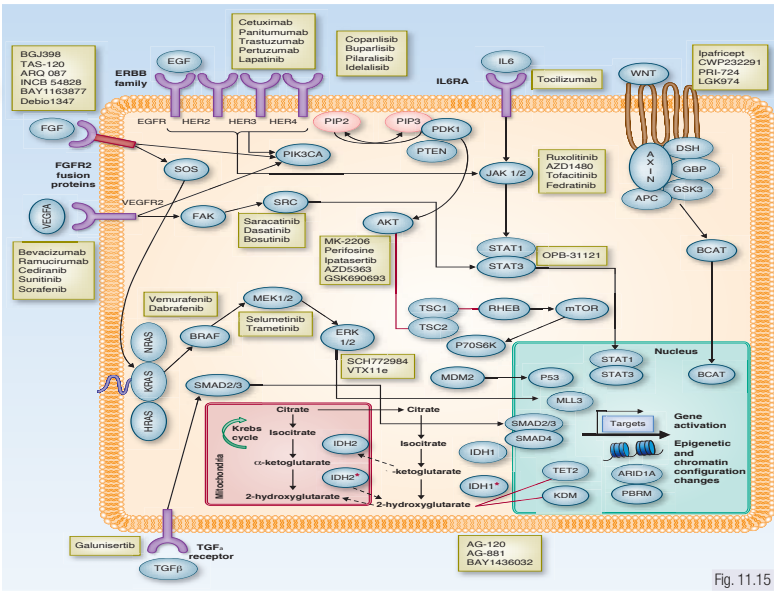


Fig. 11.15

REVISION QUESTIONS

1. What is the standard first-line ChT for fit patients with advanced disease?
2. What is the second-line ChT choice after progression on gemcitabine/cisplatin?
3. What targeted therapies are being developed in BTCs?

Summary: Biliary tract cancers

- BTCs are poor-prognosis tumours; their incidence is increasing
- Diagnosis requires pathological/cytological confirmation
- Staging relies on radiological imaging; ^{18}FDG-PET may have a role in selected scenarios
- Obstructive jaundice is a medical emergency that requires urgent action in patients diagnosed with BTCs
- Surgery is the only option of cure for resectable stages; unfortunately, relapse rates remain high
- Adjuvant capecitabine is recommended following surgery for CCA and GBC
- Adjuvant gemcitabine is recommended following surgery for AMP
- Gemcitabine/cisplatin is the standard-of-care first-line ChT for advanced stages
- There is evidence supporting second-line FOLFOX after progression on gemcitabine/cisplatin
- Targeted therapies focused on IDH and FGFR are being developed

Further Reading

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More advanced knowledge

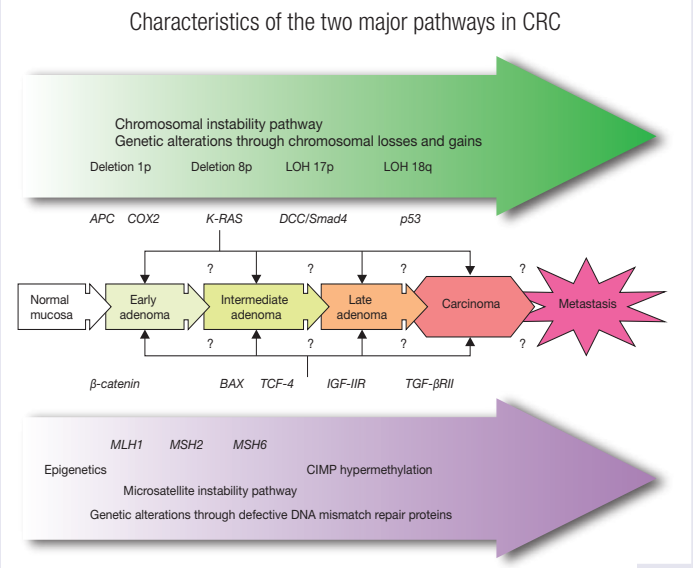
12 Biology of cancer development in the gastrointestinal tract

Genesis and progression of gastrointestinal (GI) cancers – a genetic disease

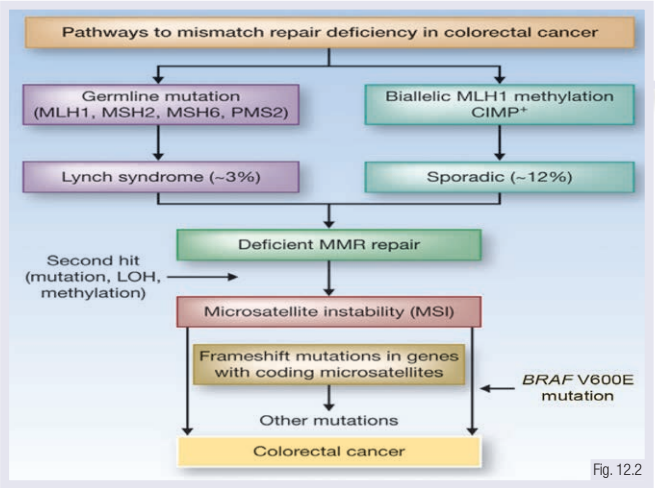
Colorectal cancer

Three different pathways are involved in the pathogenesis of colorectal cancer (CRC). 1. The chromosomal instability (CIN) pathway (85% of CRCs): often displays aneuploidy, is associated with mutation in adenomatous polyposis coli (APC) or loss of *5q*, mutation of *KRAS*, loss of *18q* and *17p*, which contains the *p53* gene.

2. The microsatellite instability (MSI) pathway (12%-15% of CRCs): mutation or inactivation of key proteins functioning in DNA mismatch repair (MMR), including MLH1, MLH3 and MSH2; high number of mutations/tumour.
3. The methylator pathway: extensive DNA hypermethylation at CpG islands; ~20%-25% of CRCs manifest the high frequency CpG island hypermethylation phenotype (CIMP-H).



APC, adenomatous polyposis coli; CIMP, CpG island methylation phenotype; CRC, colorectal cancer; IGF-IIR, insulin-like growth factor type II receptor; LOH, loss of heterozygosity; TGF, transforming growth factor.



CIMP, CpG island methylation phenotype; LOH, loss of heterozygosity; MMR, mismatch repair.

Several critical genes and pathways important in the initiation and progression of CRC have been identified so far.

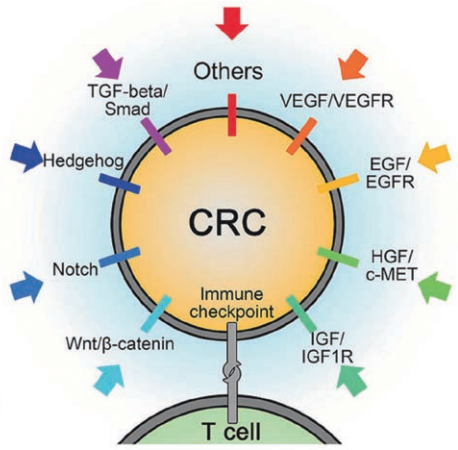
Wnt (predominantly in APC), RAS2, MAPK, PI3K, transforming growth factor beta (TGF-β), p53 and DNA MMR pathways are the most frequently detected genetic alterations.

These pathways represent potential targets for therapeutic intervention in CRC.

Two different pathways can lead to MSI.

Germline mutations of MMR genes (e.g. *MSH2*, *MSH6*, *MLH1* and *PMS2*) occur in patients with Lynch syndrome (~3% of CRCs).

MSI sporadic tumours (~12% of CRCs) frequently present a CIMP-H, leading to the repression of *MLH1*. These tumours frequently carry *BRAF* V600E mutations.



CRC, colorectal cancer; EGF(R), epidermal growth factor (receptor); HGF, hepatocyte growth factor; IGF, insulin-like growth factor; IGF1R, insulin-like growth factor 1 receptor; TGF-beta, transforming growth factor beta; VEGF(R), vascular endothelial growth factor (receptor).

REVISION QUESTIONS

1. Is the MSI pathway always related to hereditary colon cancer?
2. Can you comment on potential therapies for hypermutated colon cancer?
3. Name three genes involved in the CIN pathway.

Genesis and progression of GI cancers – a genetic disease (continued)

Gastric cancer

The vast majority of gastric cancers are adenocarcinomas, which can be further subdivided into intestinal and diffuse types according to the Lauren classification.

Most gastric cancers are associated with infectious agents, including the bacterium *Helicobacter pylori* and Epstein–Barr virus (EBV).

A minority are associated with germline mutation in epithelial (E)-cadherin (*CDH1*) or MMR genes, whereas sporadic MMR-deficient gastric cancers have epigenetic silencing of *MLH1* in the context of CIMP.

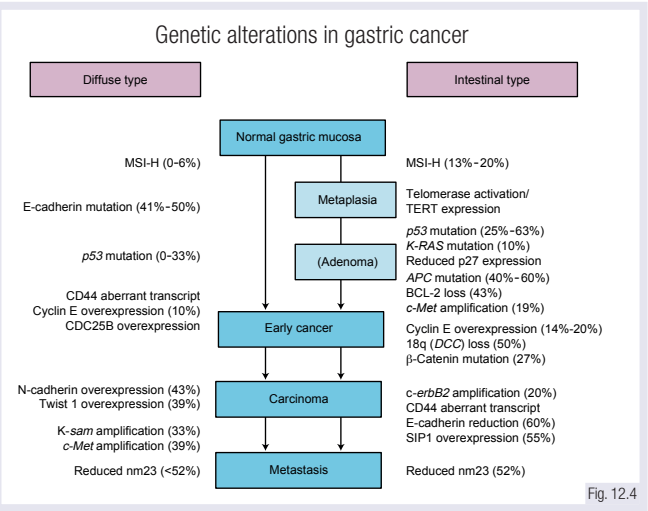


Fig. 12.4

APC, adenomatous polyposis coli, MSI-H, microsatellite instability-high.

Pancreatic cancer

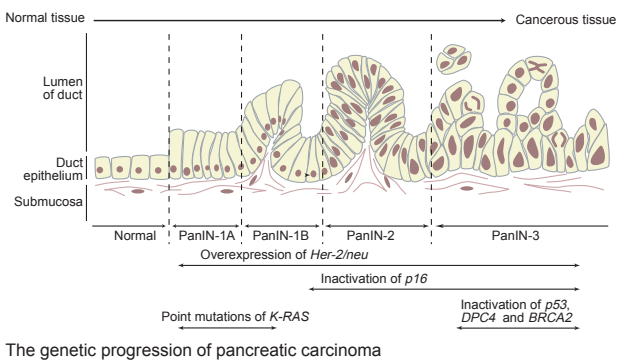


Fig. 12.5

HER2, human epidermal growth factor receptor 2; PanIN, pancreatic intraepithelial neoplasia.

Pancreatic adenocarcinoma presents a progression from distinct types of precursor lesions, with a propensity for both local invasion and distant metastasis.

The extensive stromal reaction (desmoplasia) results in a hypovascular and hypoxic microenvironment, reprogramming of cellular metabolism and evasion of tumour immunity.

There is a stepwise progression of pancreatic intraepithelial neoplasia (PanIN) from low to high grade in types 1, 2 and 3 with accumulating genetic alterations.

More than 90% of PanIN of all grades have *KRAS* mutations. Mutational inactivation of the *CDKN2A*, *p53* and *SMAD4* tumour suppressors occurs later in type 2 and type 3 lesions of PanIN.

In addition, 40%-80% have activating mutations in *GNAS* and ≥50% have inactivation of RNF43 (an antagonist of Wnt signalling).

The pancreatic adenocarcinoma genome is also characterised by diverse, large-scale chromosomal changes with frequent amplifications, deletions and rearrangements.

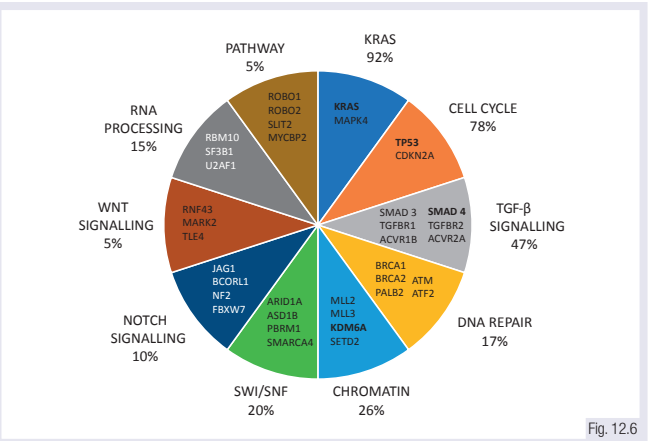


Fig. 12.6

TGF-β, transforming growth factor beta.

REVISION QUESTIONS

1. Are there any gastric cancers presenting with MSI?
2. How are diffuse-type gastric carcinomas molecularly defined?
3. What is the most common molecular alteration in pancreatic adenocarcinomas?

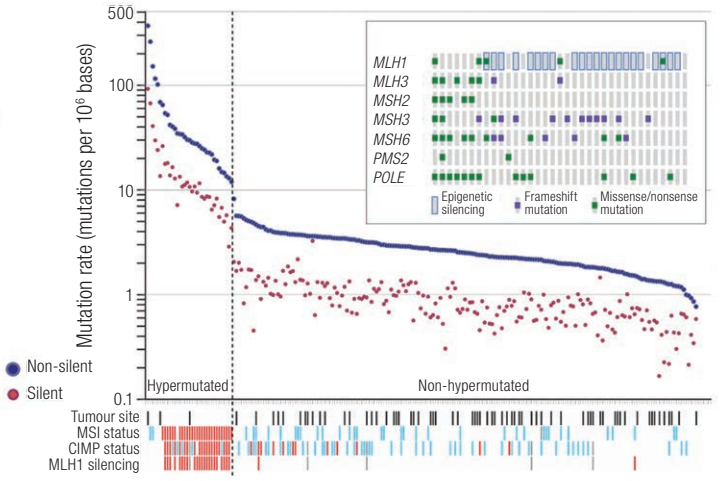
New molecular characterisation of GI tumours

Colorectal cancer

The Cancer Genome Atlas (TCGA) showed that among non-hypermutated tumours, patterns of changes in copy number, gene expression profile, DNA methylation and microRNA (miRNA) were indistinguishable between colon and rectal carcinomas.

Over 94% of tumours had a mutation in the Wnt signalling pathway. However, there were some differences between tumours from the right colon and all other sites.

Hypermethylation was more common in the right colon, and 75% of hypermutated samples came from the same site, although not all had MSI.



CIMP, CpG island methylation phenotype; MSI, microsatellite instability. Fig. 12.7

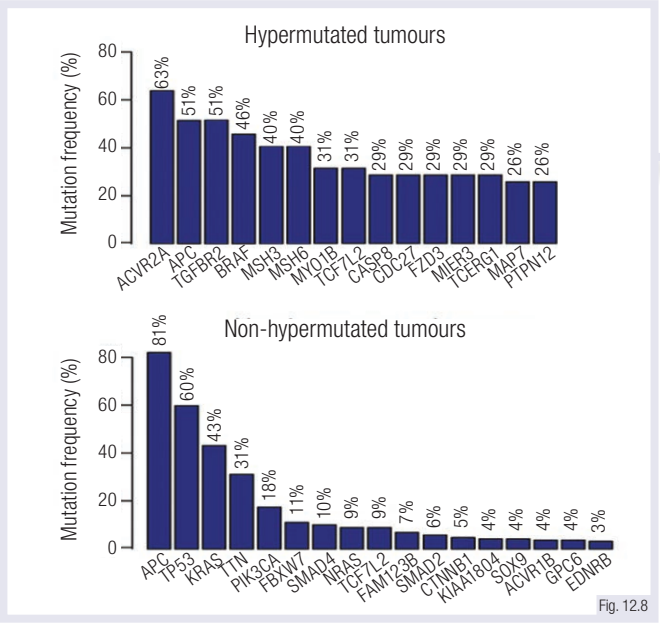


Fig. 12.8

APC, adenomatous polyposis coli; TGFBR2, transforming growth factor beta receptor 2.

TCGA findings included recurrent mutations in *FAM123B*, *ARID1A* and *SOX9* and very high levels of overexpression of the Wnt ligand receptor gene *FZD10*.

Activation of Wnt signalling and inactivation of the TGF-β signalling pathway result in activation of *MYC*. Integrated analysis revealed a set of changes in *TCF/LEF*-encoding genes.

Mutations in the ubiquitin ligases *RNF43* and *ZNRF3* or fusions of *RSPO2/3* genes activate Wnt/beta-catenin oncogenic signalling and represent a promising level for drug intervention.

In 2015, an international consortium proposed classification into four consensus molecular subtypes (CMSs): CMS1 (MSI immune, 14%), CMS2 (canonical, 37%), CMS3 (metabolic, 13%) and CMS4 (mesenchymal, 23%).

Currently, the molecular classification is one of the best proposed examples to describe the heterogeneity of CRC.

CMS1 MSI immune	CMS2 Canonical	CMS3 Metabolic	CMS4 Mesenchymal
14%	37%	13%	23%
MSI, CIMP high, hypermutation	SCNA high	Mixed MSI status, SCNA low, CIMP low	SCNA high
BRAF mutations		*KRAS* mutations	
Immune infiltration and activation	Wnt and MYC activation	Metabolic deregulation	Stromal infiltration. TGF-β activation, angiogenesis
Worse survival after relapse			Worse relapse-free and overall survival

CIMP, CpG island methylation phenotype; CMS, consensus molecular subtype; MSI, microsatellite instability; SCNA, somatic copy number alterations; TGF-β, transforming growth factor beta. Fig. 12.9

REVISION QUESTIONS

1. Which oncogenic pathway is the most frequently altered by mutations in CRC?
2. Is the TGF-β pathway activated or inactivated by mutations in CRC?
3. Which genes present fusions that activate oncogenic Wnt signalling?

New molecular characterisation of GI tumours (continued)

Gastric cancer

TCGA proposed a molecular classification of four subtypes based on gene mutations, somatic copy number alterations, and epigenetic and transcriptional changes:

1. EBV-positive tumours, which display recurrent *PIK3CA* mutations, extreme DNA hypermethylation and amplification of Janus kinase 2 (*JAK2*), programmed death-ligand 1 (PD-L1) and PD-L2.
2. MSI tumours, which show elevated mutation rates, including mutations of genes encoding targetable oncogenic signalling proteins.

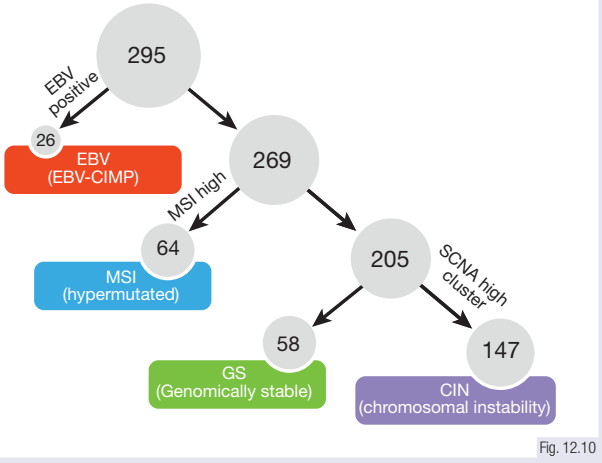
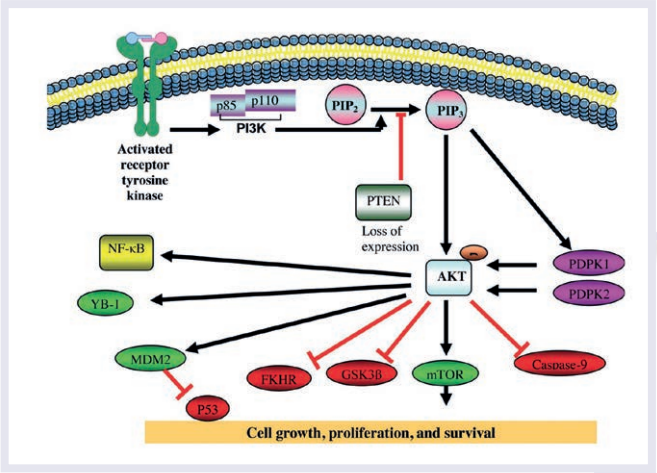


Fig. 12.10

CIMP, CpG island methylation phenotype; EBV, Epstein-Barr virus; MSI, microsatellite instability; SCNA, somatic copy number alteration.



mTOR, mammalian target of rapamycin.

Fig. 12.11

3. Genomically stable tumours, which are enriched for the diffuse histological variant and mutations of *RHOA* or fusions involving RAS-homologous (RHO)-family GTPase-activating proteins.
4. Tumours with CIN, which show marked aneuploidy and focal amplification of receptor tyrosine kinases.

Identification of these subtypes provides a roadmap for patient stratification and trials of targeted therapies.

CIN tumours show elevated frequency in the gastro-oesophageal junction/cardia, whereas EBV-positive tumours are prevalent in the gastric fundus or body.

Genomically stable tumours are diagnosed at an earlier age (median 59 years), whereas MSI tumours are diagnosed at relatively older ages (median 72 years).

MSI patients tend to be female; however, most EBV-positive cases are male.

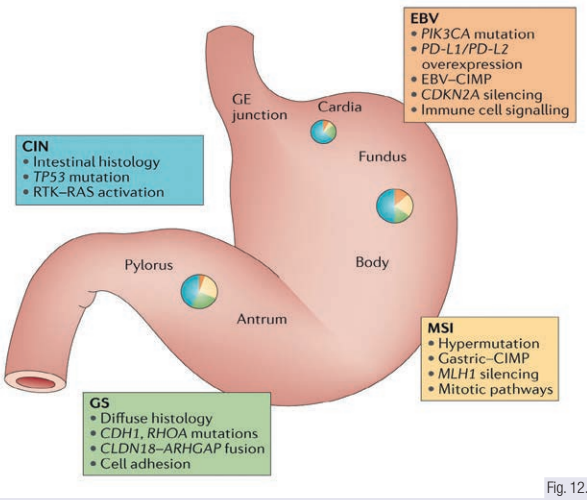


Fig. 12.12

CIMP, CpG island methylation phenotype; CIN, chromosomal instability; EBV, Epstein-Barr virus; GE, gastro-oesophageal; GS, genomically stable; MSI, microsatellite instability; PD-L1/2, programmed death-ligand 1/2.

REVISION QUESTIONS

1. Do CIN and mutations in tyrosine kinase receptors frequently co-occur in gastric cancer?
2. Are mutations in the PIK3CA gene frequent in MSI gastric tumours?
3. To which molecular subtype of gastric cancer is a diffuse histology related?

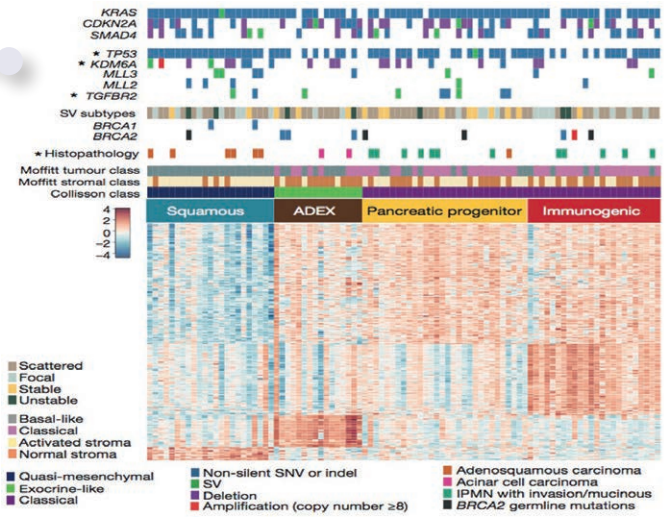
New molecular characterisation of GI tumours (continued)

Pancreatic cancer

In 2019 a study by the International Cancer Genome Consortium (ICGC) identified four molecular subtypes of pancreatic cancer.

Squamous tumours are characterised by alterations of genes involved in inflammation, hypoxia response, TGF-β signalling, MYC pathway activation and autophagy, and have a poor prognosis.

Pancreatic progenitor tumours express genes implicated in early pancreatic development (*FOXA2/3*, *PDX1* [pancreatic and duodenal homeobox 1] and *MNX1* [motor neurone and pancreas homeobox 1]).



ADEX, aberrantly differentiated endocrine exocrine; TGFBR2, transforming growth factor beta receptor 2; IPMN, intraductal papillary mucinous neoplasia; SNV, single-nucleotide variant; SV, structural variant. Fig. 12.13

The immunogenic subtype is associated with a significant immune infiltrate and displays an upregulation of cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1).

Aberrantly differentiated endocrine exocrine (ADEX) tumours display upregulation of genes that regulate networks involved in KRAS activation and both exocrine and endocrine differentiation.

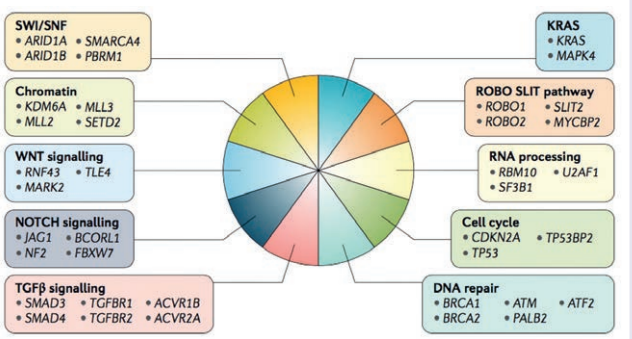


Fig. 12.14

ACVR1B/2A, activin A receptor type 1B/2A; ARID1A, AT-rich interaction domain 1A; ATF2, activating transcription factor 2; BCORL1, BCL6 corepressor like 1; CDKN2A, cyclin-dependent kinase inhibitor 2A; MAPK4, mitogen-activated protein kinase 4; MARK2, microtubule affinity regulating kinase 2; NF2, neurofibromin 2; PALB2, partner and localizer of BRCA2; PBRM1, polybromo 1; RNF43, Ring Finger Protein 43; SETD2, SET domain containing 2; SWI/SNF, SWItch/Sucrose Non-Fermentable; TGFβ, transforming growth factor beta.

The most common mutations in pancreatic cancer are *KRAS*, *SMAD4*, *TP53* and *CDKN2A*.

Defects of DNA damage repair (DDR) are present in 24% of pancreatic cancers and involve mutations in *BRCA1*, *BRCA2*, *ATM* and *PALB2*.

Alteration of DDR machinery determines genomic instability, which favours the progression of preneoplastic lesions in advanced pancreatic cancer.

The presence of a deficit in DDR renders cancer cells vulnerable to therapeutic interventions promoting DNA damage.

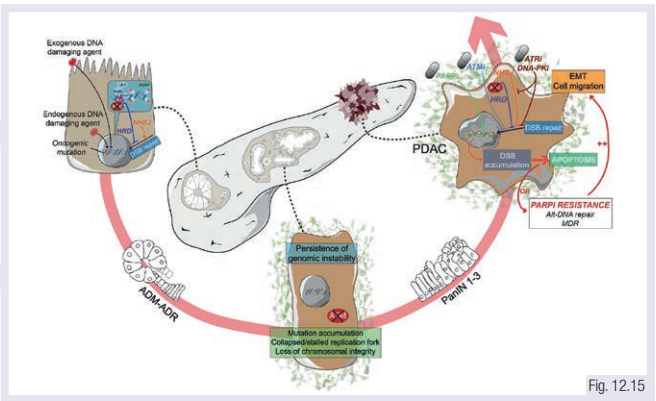


Fig. 12.15

ADM, acinar-to-ductal metaplasia; ADR, acinar-to-ductal reprogramming; DNA-PKi, DNA-dependent protein kinase inhibitor; DSB, double-strand break; EMT, epithelial-to-mesenchymal transition; HRD, homologous recombination-deficient; MDR, multidrug resistance; NHEJ, non-homologous end joining; PanIN, pancreatic intraepithelial neoplasia; PARPi, poly(ADP-ribose) polymerase inhibitor; PDAC, pancreatic ductal adenocarcinoma.

REVISION QUESTIONS

1. Which genes involved in chromatin remodelling are significantly mutated in pancreatic cancer?
2. Is *BRCA*-dependent DNA repair a cellular function altered by mutations in pancreatic cancer?
3. Which are the most frequent gene alterations in aberrantly differentiated exocrine endocrine tumours?

Summary: Biology of cancer development in the gastrointestinal tract

- CRC development is the consequence of a stepwise accumulation of mutations in tumour suppressor genes and oncogenes that promote cell proliferation and tumour progression
- The most frequent alteration observed in CRC is the activation of the Wnt/beta-catenin pathway, predominately APC
- Phylogenetically, CRCs can be divided into three molecular subtypes: those with CIN, those with MSI, and those with the methylator pathway
- In 2015, an international consortium proposed classification into four CMSs representing CRC heterogeneity
- Gastric cancers display a high number of genetic alterations contributing to tumour development, resulting in an aggressiveness phenotype
- Molecular classification of gastric cancer into four subtypes provides a roadmap for patient stratification and trials of targeted therapies
- Both CRC and gastric cancer present a major group of non-hypermutated tumours and a minor population of hypermutated/MSI tumours
- Pancreatic cancer progressively accumulates mutations in *KRAS*, *CDKN2A*, *p53* and *SMAD4*, but also presents alterations in genes involved in chromatin remodelling and axon guidance
- Less frequent gene alterations in pancreatic cancer include amplification of human epidermal growth factor receptor 2 (*HER2*), fibroblast growth factor receptor (*FGFR*) amplifications, neurotrophic tyrosine receptor kinase (*NTRK*) rearrangement and *BRAF* and mammalian target of rapamycin (mTOR) mutations
- DDR defects are present in about 24% of all pancreatic cancers and might be a potential therapeutic target

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13 Oligometastatic disease in gastrointestinal cancers

Oligometastatic disease: Definition and implications for clinical use

In 1995, Hellman and Weichselbaum postulated the existence of an interim stage between limited local disease (that can be cured by local treatment) and disseminated, generally incurable disease.

In this definition, oligometastatic state suggests a clinical situation in which local treatment is accompanied by an improved prognosis, ranging from (local) progression-free survival (PFS) to improved overall survival (OS).

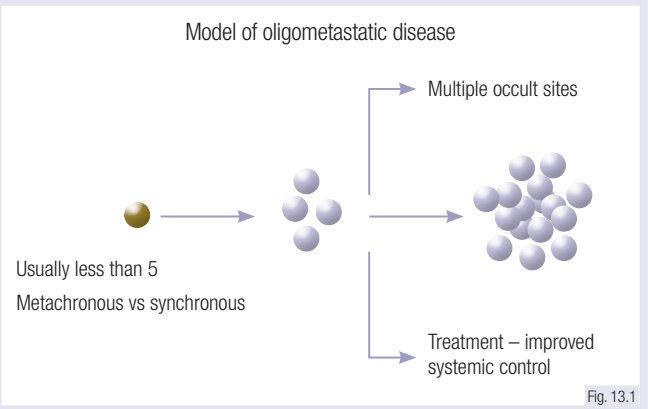

Fig. 13.1

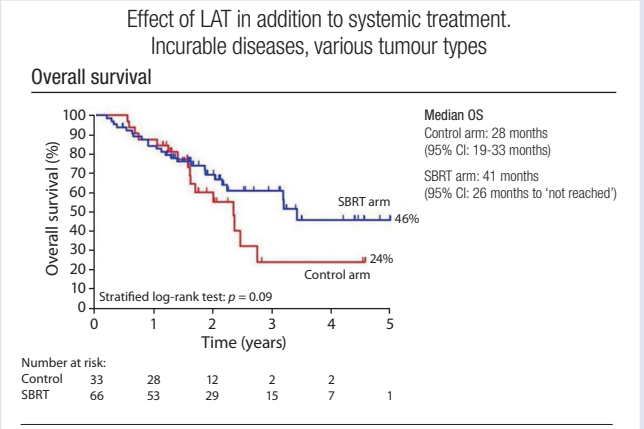

Fig. 13.2

CI, confidence interval; LAT, local ablative treatment; OS, overall survival; SBRT, stereotactic body radiotherapy.

In 2019, Palma et al showed that radical treatment of oligometastatic disease (OMD) leads to an improvement in both disease-free survival and OS.

This phase II trial in patients with a variety of solid tumour cancers demonstrated that radical treatment of OMD (here with stereotactic body radiotherapy [SBRT], N=66) resulted in an improved OS compared with standard treatment (palliative radiotherapy [RT]) and standard systemic treatment (median OS, 28-41 months: $p = 0.09$; hazard ratio [HR] 0.57).

Quality of life was not impaired by SBRT. A significant subset of patients had oligometastatic colorectal cancer (CRC).

The presence and treatment of OMD has been well recognised in CRC for the past 20 years. However, definitions of OMD status vary and are generally defined by consensus in expert groups. For example, OMD in metastatic CRC (mCRC) is characterised by numbers and sites of lesions.

Typically, primary lesions are visceral (occasionally lymphonodal). Possible involved sites in gastrointestinal (GI) cancers are liver, lung, peritoneum and ovaries. However, OMD must be amenable to a radical treatment strategy to fulfil the definition.

Standard investigations should include computed tomography (CT) or magnetic resonance imaging (MRI) where relevant, and, whenever available, a positron emission tomography (PET)-CT scan.

Definition of oligometastatic disease in colorectal cancer according to the ESMO Consensus Guidelines for the management of patients with metastatic colorectal cancer (Van Cutsem et al, Ann Oncol 2016)

- "...characterised by the localisation ... to a few sites and lesions and is associated with the option to use LAT ... with a view to improving disease control and therefore clinical outcome..."
- "...characterised by the existence of metastases at up to 2 or occasionally 3 sites and 5 or sometimes more lesions, predominantly visceral and occasionally lymphonodal."
- "...at other sites, such as multiple lesions in the bones and the brain, may also be treated using a local ablative approach, but as these patients are associated with an unfavourable prognosis, local ablative treatment strategies are only used to prevent immediate complications."

Fig. 13.3

ESMO, European Society for Medical Oncology; LAT, local ablative treatment.

REVISION QUESTIONS

1. What is the biological difference between widespread dissemination and localised occurrence of metastases?
2. How is OMD defined?
3. What is recommended in the diagnostic work-up?

Local ablative treatment: Prognostic implications and therapeutic strategies

The consideration whether a systemic or local treatment is preferred should include the clinical scenario and patient's characteristics as well as tumour-related factors, comprising clinical characteristics and biological factors.

However, most of those are not yet well defined.

There are several possible approaches to integrate local ablative treatment (LAT) in patients with OMD.

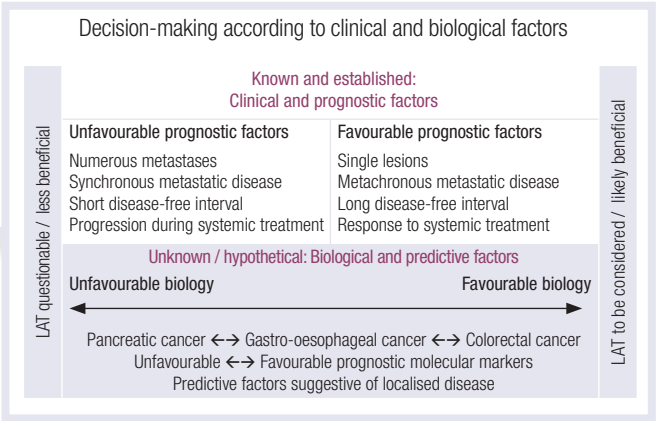

Fig. 13.4

LAT, local ablative treatment.

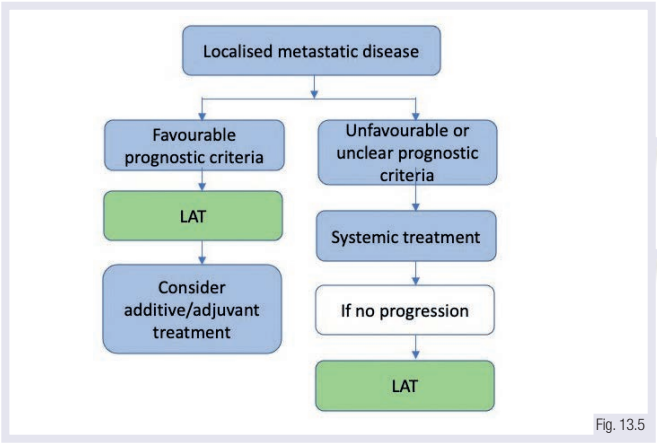

Fig. 13.5

LAT, local ablative treatment.

LAT can be used as a primary or metastasis-specific treatment to halt further dissemination. This could delay (or even eliminate) the need for systemic treatment.

LAT can be used following systemic therapy as a consolidative treatment, to delay or halt further treatment.

This can be done in place of surgery, especially in prognostically unclear situations or after response to systemic treatment in more widespread disease.

LAT may be considered in oligo-progressive disease (i.e. very limited recurrence / non-response in a patient receiving systemic treatment). Such OMD could be construed as a result of intratumoural heterogeneity.

The aim of LAT here is to eliminate the cell clones no longer responding to treatment to enable the otherwise still working systemic therapy.

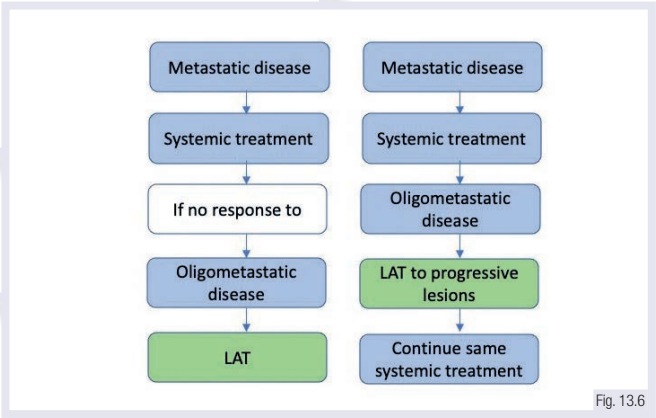

Fig. 13.6

LAT, local ablative treatment.

REVISION QUESTIONS

1. Which factors should be considered for use of LAT?
2. Where can LAT be ideally incorporated into a clinical sequence algorithm?
3. What is the role of LAT in progressive disease?

Treatment modalities: Surgery

Treatment strategies for patients with OMD should aim to achieve complete ablation of all tumour masses, using surgical resection and/or non-surgical interventions.

For patients with resectable OMD confined to a single organ (most frequently liver or lung), and/or a few organs and even localised peritoneal spread, surgery remains the standard and (potentially) best curative treatment approach.

Decisions about surgical resection of OMD have to be taken within the context of technical limitations, the overall specific disease-related prognosis and non-tumour related factors like patient morbidity.

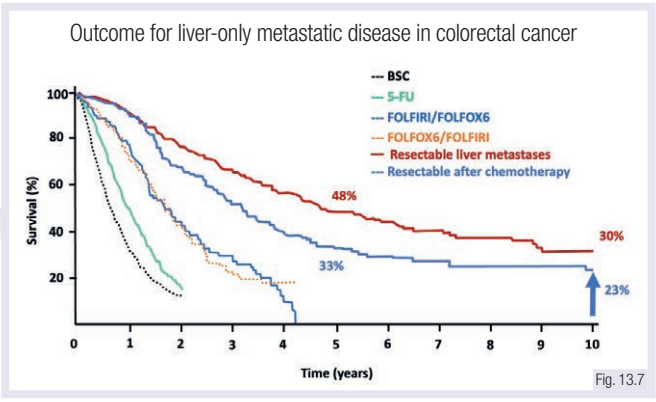

Fig. 13.7

BSC, best supportive care; 5-FU, 5-fluorouracil; FOLFIRI, leucovorin/5-FU/irinotecan; FOLFOX6, leucovorin/5-FU/oxaliplatin.

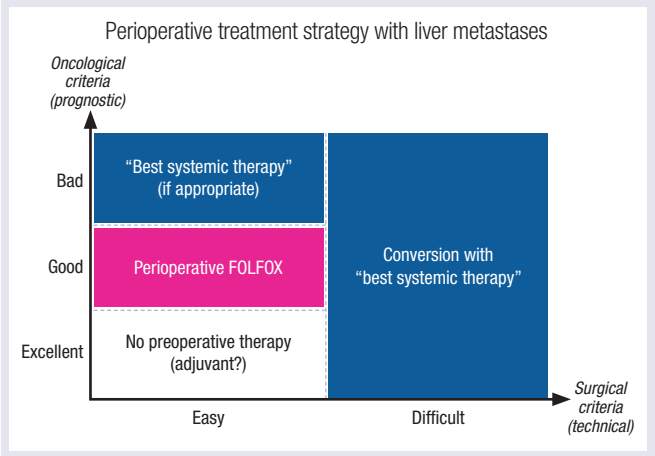

Fig. 13.8

FOLFOX, leucovorin/5-fluorouracil/oxaliplatin.

In a fit patient with favourable prognostic criteria and no technical issues surgically, perioperative systemic treatment may not be needed. On the contrary, appropriate systemic treatment will be required for those with adverse features when treating with curative intent.

Optimal systemic treatment may result in sufficient tumour shrinkage to allow consideration of localised treatments such as surgery. Frequent re-evaluation of disease burden in these circumstances is required to ensure optimal outcomes.

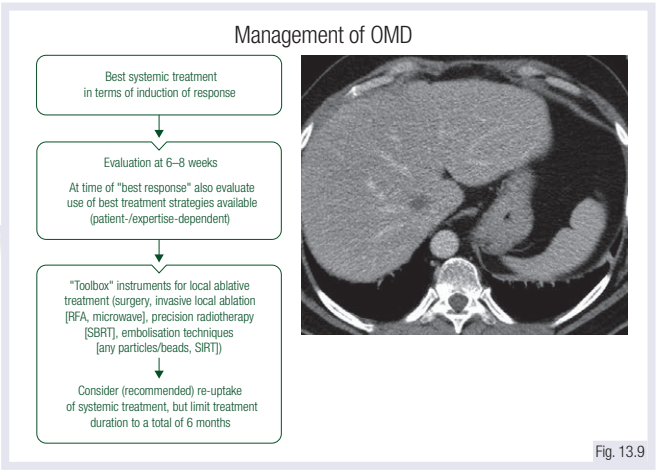

Fig. 13.9

OMD, oligometastatic disease; RFA, radiofrequency ablation; SBRT, stereotactic body radiotherapy; SIRT, selective internal radiotherapy.

REVISION QUESTIONS

1. Which organs with OMD are most frequently treated surgically?
2. Should definitive surgery for OMD be considered after downstaging chemotherapy?
3. Why should patients with metastatic disease be repetitively presented at multidisciplinary tumour boards?

Treatment modalities: Non-surgical LATs

Choice of treatment

Localised non-surgical LAT may become relevant in combination with systemic therapy, following a careful multidisciplinary team (MDT) discussion and assessment.

Liver-directed therapy and the 'toolbox of options' is an example of the variety of possible LAT interventions. The most important discriminator for the use of different toolbox instruments is tumour location and number.

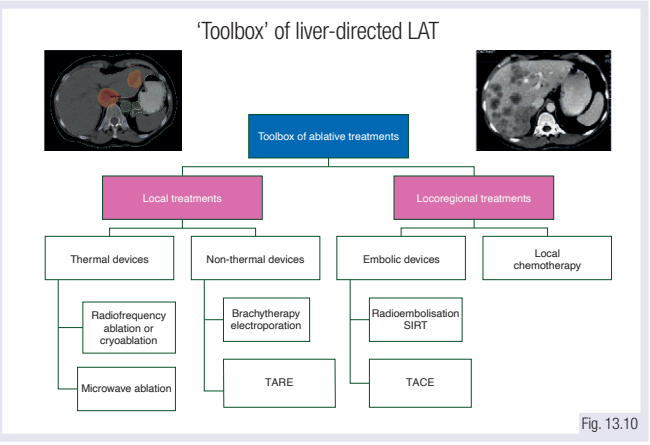

Fig. 13.10

LAT, local ablative treatment; RT, radiotherapy; SIRT, selective internal RT; TACE, transarterial chemoembolisation; TARE, transarterial radioembolisation.

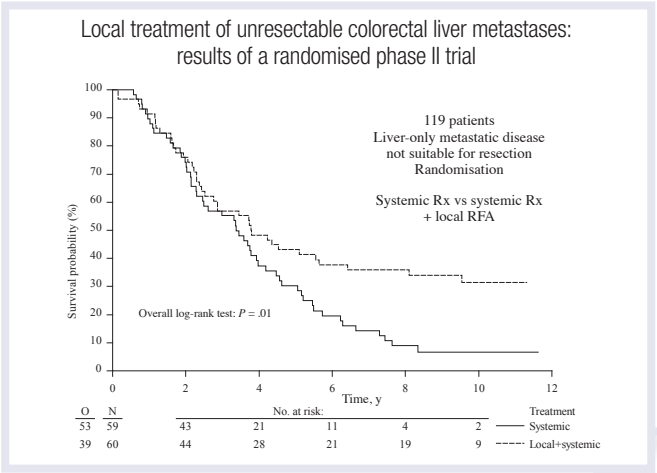

Fig. 13.11

RFA, radiofrequency ablation; Rx, treatment.

Radiofrequency ablation

Radiofrequency ablation (RFA) is an example of strictly local treatment, a commonly used alternative to surgery for liver lesions, and also an option for lung lesions.

The use of RFA is determined by the size of the lesion (generally <3 cm), its location (e.g. not too close to vascular structures) and the number of metastases.

The value of this approach has been examined in a prospective phase II study in patients with mCRC randomised to systemic chemotherapy (ChT) alone vs in combination with RFA to the liver lesions. It showed a survival advantage for patients treated with the combination.

SBRT

SBRT involves an ablative dose of radiation to an isolated site, leading to localised tumour necrosis and death. Developed in the early 1990s, ablative doses can now be delivered via standard linear accelerators as well as via more specialised machinery (e.g. Cyberknife).

It has been used in diverse sites with varying outcomes. The most important factor is probably the relative lack of severe acute side effects.

There have been multiple single-centre studies of this approach. The total radiation dose varies but the number of RT fractions is usually small, leading to a "high dose per fraction". In turn, this leads to a differing radiation effect, with doses ≥7 Gy per fraction associated with cell death due to necrosis, rather than mitotic arrest and consequential apoptosis.

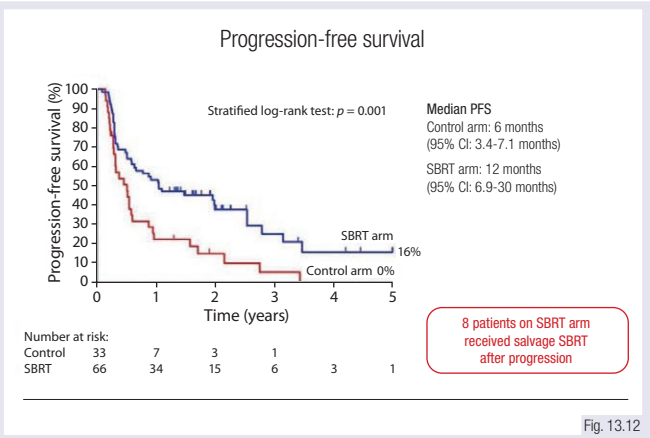

Fig. 13.12

CI, confidence interval; PFS, progression-free survival; SBRT, stereotactic body radiotherapy.

REVISION QUESTIONS

1. Which factors define the optimal selection of treatment modality from a "toolbox" of options?
2. What is the difference between a strictly local treatment and a locoregional treatment?
3. Can SBRT be integrated with systemic ChT?

Treatment modalities: Non-surgical LATs (continued)

SBRT (continued)

Most studies in GI malignancies have been single-centred and focused on CRC. A 2018 review by Petrelli et al examined the role of SBRT in liver metastases. Results suggest a local disease control rate of 67% and 59.3% at 1 and 2 years, and an OS of 31.5 months. Nodal metastases seem to respond well, with a high local control rate.

Depending upon the site of metastasis, there is some initial evidence of a differing effect in terms of disease control (O'Cathail SM et al, Radiother Oncol 2020). Evidence for treatment of OMD due to other GI malignancies remains vague. If this approach, still experimental at the time of publication, is considered, then a careful review of potential benefits vs acute morbidity should be made.

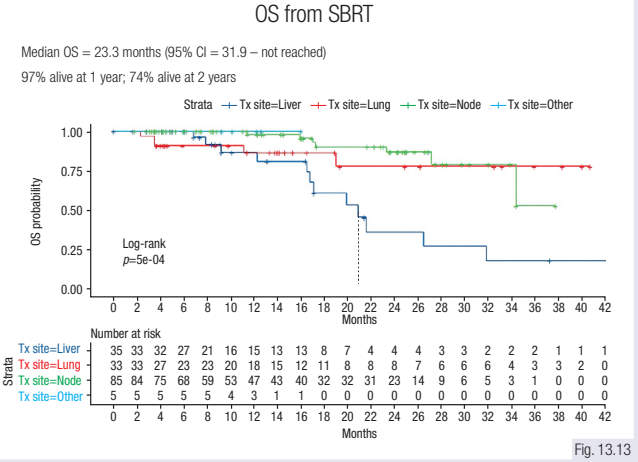

Fig. 13.13

CI, confidence interval; OS, overall survival; SBRT, stereotactic body radiotherapy.

Locoregional treatments: Transarterial chemoembolisation (TACE) or radioembolisation (TARE)

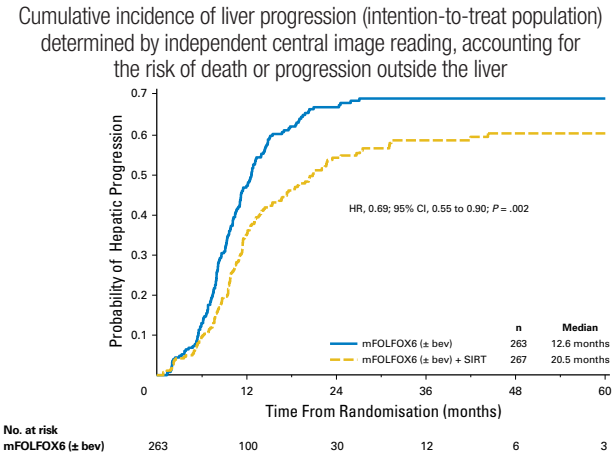

Fig. 13.14

bev, bevacizumab; CI, confidence interval; HR, hazard ratio; mFOLFOX6, modified leucovorin/5-fluorouracil/oxaliplatin; SIRT, selective internal radiotherapy.

TACE and TARE are a combination of a regional treatment, with administration of an active drug (e.g. a fluoropyrimidine, or irinotecan) via the hepatic artery, with a local destructive treatment by embolisation or RT, respectively.

TACE uses particles such as microspheres or chemo-loaded beads, whereas TARE incorporates the delivery of yttrium-90 connected to either resin or glass particles into the hepatic artery.

In mCRC, large registries demonstrated the potential benefit of these treatments, although phase III trials failed to show a significant benefit in early treatment lines.

REVISION QUESTIONS

1. Which sites of OMD respond best to SBRT?
2. Do other GI malignancies have an oligometastatic phenotype? If so, which ones?
3. How are TARE and TACE administered?

Summary: Oligometastatic disease in gastrointestinal cancers

- OMD was initially postulated as an interim stage between local and disseminated disease
- Localised treatment may lead to improvements in local and systemic disease control with the possibility of an improved OS
- OMD is defined as usually less than 5 sites of metastatic disease within 2 organs
- CRC offers an excellent example of a malignancy that has an oligometastatic interim stage
- OMD may be synchronous or metachronous. For synchronous disease, systemic treatment prior to management of the oligometastases would seem sensible since the PFS is unknown
- Surgical resection of colorectal liver metastases has been shown to improve OS
- Site of disease determines the likely outcome with liver-only disease appearing to have the best results
- There are multiple forms of ablative treatment including RFA and SBRT. Both appear to integrate safely with systemic ChT
- SBRT has been shown to improve OS when integrated with ChT
- Combining ablative therapy with immunotherapy will be the next stage in developing these techniques

Further Reading

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14 Uncommon gastrointestinal tumours: small intestine and anal cancer

Small bowel adenocarcinoma: Epidemiology, pathology and treatment

Only 3% of all gastrointestinal (GI) adenocarcinomas arise in the small intestine, although this organ covers over 90% of the mucosal surface of the GI tract. The incidence is 2.3/100 000 people.

This low incidence is attributed to the high transit of food and low bacterial content. Risk factors for small bowel cancer (SBC) are coeliac and Crohn's disease, as well as advanced age. However, while this is a rare cancer, the incidence of small bowel adenocarcinoma (SBA) is increasing while the incidence of colorectal cancer (CRC) is decreasing.

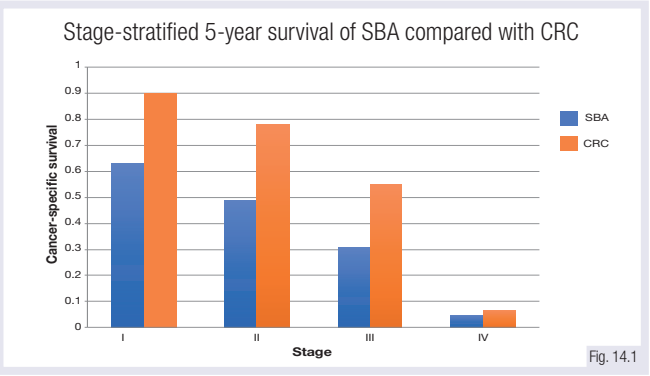

Fig. 14.1

CRC, colorectal cancer; SBA, small bowel adenocarcinoma.

The molecular profile of SBA is distinct from colorectal and gastric adenocarcinomas. Of the top 20 most commonly altered genes, 12 were statistically different between SBA and colorectal adenocarcinoma. One of the fundamental molecular differences between SBA and colorectal adenocarcinoma is the low alteration rate of adenomatous polyposis coli (APC): 26.8% vs 75.9%. For the comparison between SBA and gastric adenocarcinoma, 12 genes were statistically different.

Endoscopic (top left) and PET images (axial view bottom left, coronal view right) of small bowel adenocarcinoma of second part of duodenum

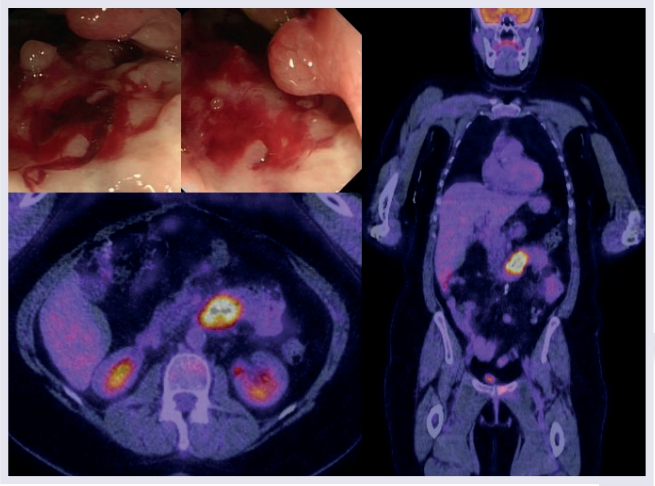
Fig. 14.2

PET, positron emission tomography.

Due to non-specific symptoms, SBC is often diagnosed at an advanced stage and, when compared across the corresponding stages with CRC, the survival rate is worse.

Symptoms are: dysphagia, weight loss, abdominal pain, nausea, vomiting, fatigue, gastric outlet syndrome and bleeding.

The histological diagnosis is made by endoscopic biopsy. A computed tomography (CT) scan or positron emission tomography (PET)/CT scan should be made to rule out more advanced disease. However, some patients present with intestinal obstruction, and diagnosis is made following surgical intervention.

CT imaging at diagnosis (left) showing an obstructing small bowel tumour (arrowed). CT image on right shows treatment response with no small bowel seen and no dilation of the bowel loops. Of note, this patient's tumour was mismatch repair-deficient and was treated with immune checkpoint inhibition.

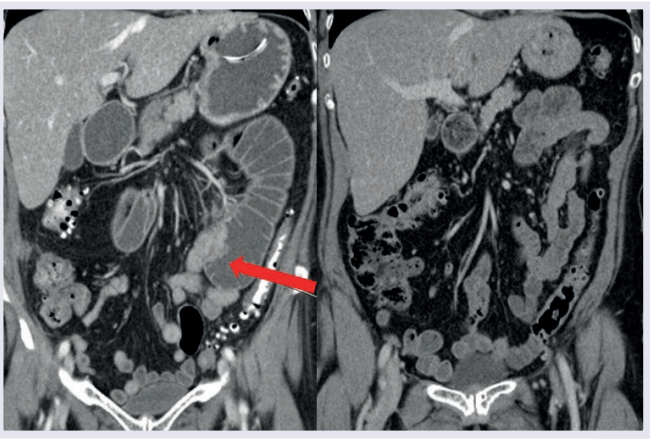
Fig. 14.3

CT, computed tomography.

In case of localised disease, the type of operation depends on the tumour location. Duodenal adenocarcinomas require a pancreaticoduodenectomy. Jejunal or ileal adenocarcinomas require a wide excision.

Neoadjuvant (downsizing) and adjuvant chemotherapy (ChT) (node-positive disease) can be advocated, but phase III evidence for clinical benefit is lacking. ChT schedules usually consist of a pyrimidine analogue (5-fluorouracil [5-FU] or capecitabine) +/- oxaliplatin.

Small bowel adenocarcinoma (continued)

In case of advanced SBC, palliative ChT can be useful.

5-FU or capecitabine in combination with oxaliplatin or irinotecan is usually preferred, based on retrospective and limited phase II data.

For patients whose tumour is deficient in mismatch repair (dMMR), immune checkpoint inhibitors may be an option. Pembrolizumab, a programmed cell death protein 1 (PD-1) checkpoint inhibitor, has Food and Drug Administration (FDA) approval for the treatment of dMMR SBA that had progressed on prior treatment.

x10 magnification of small bowel tumour on lower left and normal small bowel mucosa on upper right. Absence of staining of mismatch repair protein MLH1 on tumour indicates this tumour is mismatch repair-deficient and may benefit from immunotherapy

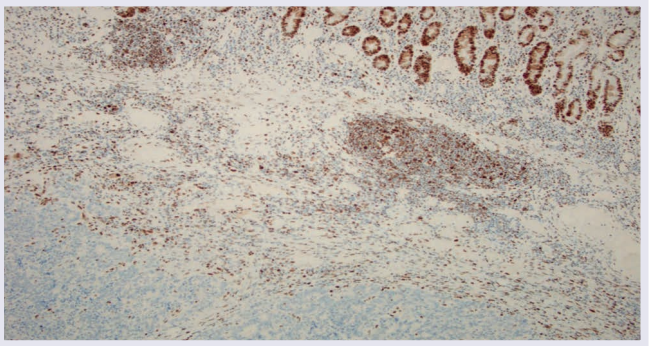

Fig. 14.4

REVISION QUESTIONS

1. What are the risk factors associated with SBA?
2. What are the survival outcomes for SBA in stage I, II, III and IV disease?
3. Which first-line palliative ChT would you choose for a fit patient with SBA?

Anal carcinoma: Anatomy, staging and prognosis

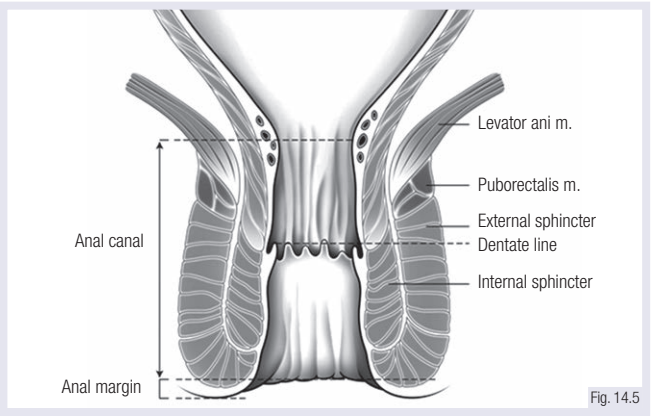

Fig. 14.5

The anal region extends from the anorectal junction to the anal margin. Tumours localised above the linea dentata drain to the perirectal and iliac nodes; distal tumours spread to the superficial inguinal and femoral nodes.

Staging procedures include the following:

- Physical examination (including the groin)
- Histological biopsy
- Pelvic magnetic resonance imaging (MRI)
- CT scan of the thorax
- In selected cases, PET/CT could be indicated.

Epidemiology: The incidence of anal squamous cell carcinoma (ASCC) is 1-2/100 000 but rising in the Western world by 2.2% per year. Mean age at diagnosis is 60-70 years.

Risk factors: Infection with human papillomavirus (HPV) (mainly types 16-18), immunosuppression – human immunodeficiency virus (HIV), organ transplants, corticosteroids/azathioprine, autoimmune disorders, smoking, inflammatory bowel disease (Crohn's disease). There is no recognised hereditary component.

Symptoms: Diagnosis is often delayed because symptoms (bleeding, itching, mucous discharge, discomfort) are non-specific and attributed to benign conditions (haemorrhoids or anal fissures).

Stage	5-year survival rate
I (T1N0)	71%
II (T2-T3, N0)	64%
IIIA (T1-3, N1; T4N0)	48%
IIIB (T4N1; T1-4, N2-3)	43%
IV (metastases)	21%

Fig. 14.6

REVISION QUESTIONS

1. What are the risk factors for developing anal cancer?
2. What is the pattern of lymphatic spread in anal cancer?
3. How does anal cancer need to be staged?

Anal carcinoma: Treatment

Small ASCC (<2 cm) in the anal margin with intermediate or good differentiation grade may be treated with excision, if clear margins can be accomplished. This strategy should be approved by a multidisciplinary team (MDT).

Mitomycin C plus fluoropyrimidines (5-FU or capecitabine) with concomitant radiation is the current standard of care for ASCC.

Radiotherapy (RT) doses of at least 45–50 Gy are recommended. Higher doses and additional boosts are under investigation for more advanced tumours, and lower doses for earlier stages.

DFS/PFS in the large randomised trials by clinical stage

TNM stage	RTOG 9811 DFS (%)	ACT-1 LRFFS (%)	ACT-2 PFS (%)
T2N0	72%**	No data	81%*
T3N0	61%**	No data	No data
T4N0	50%**	No data	No data
T2N+	57%**	No data	No data
T3N+	38%**	No data	No data
T4N+	31%**	No data	No data
T3-4N+	38%*, 36%**	No data	No data
T3-4any	53%*	67%#	63%*
* **3-year** DFS ** **5-year** DFS # **2-year** LRF	Gunderson L, et al. J Clin Oncol 2012	UKCCR. Lancet 1996	James R, et al. Lancet Oncol 2013

DFS, disease-free survival; LRF, locoregional failure; LRFFS, locoregional failure-free survival; PFS, progression-free survival; TNM, Tumour, Node, Metastasis. Fig. 14.7

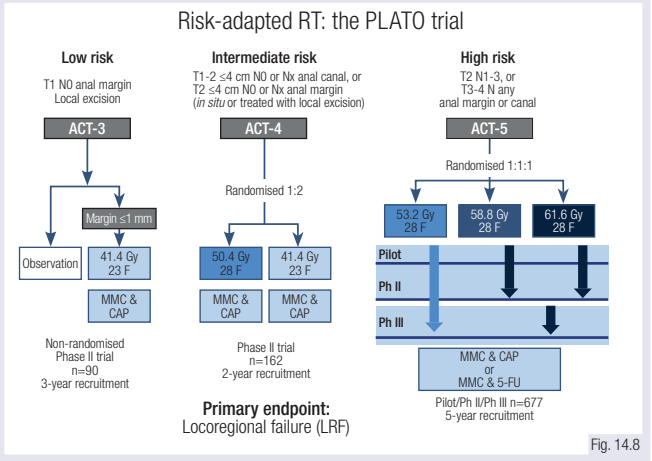

Fig. 14.8

CAP, capecitabine; 5-FU, 5-fluorouracil; MMC, mitomycin C; RT, radiotherapy.

The addition of induction ChT using 5-FU/cisplatin before chemoradiotherapy (CRT) or consolidation with 5-FU/cisplatin after CRT have not improved outcomes.

Response evaluation after CRT includes digital rectal examination and radiological imaging (MRI and CT). Routine biopsy of normal appearances is discouraged.

In the absence of progression, patients can be followed with careful surveillance for 6 months after CRT, as it may take 26 weeks to achieve complete response (CR).

In case of recurrent or persistent disease, salvage surgery may be needed. Abdominoperineal resection (APR) still offers the potential for a long recurrence-free interval and long-term survival.

In advanced and metastatic disease, a randomised phase II trial (InterAACT) showed no difference in overall response rate (ORR) between carboplatin/paclitaxel and cisplatin/5-FU, but with less toxicity for the first combination, hence carboplatin/paclitaxel should be a new standard of care.

Immunotherapy with checkpoint inhibition will have an important role in treatment, but currently robust biomarkers able to predict benefit are lacking.

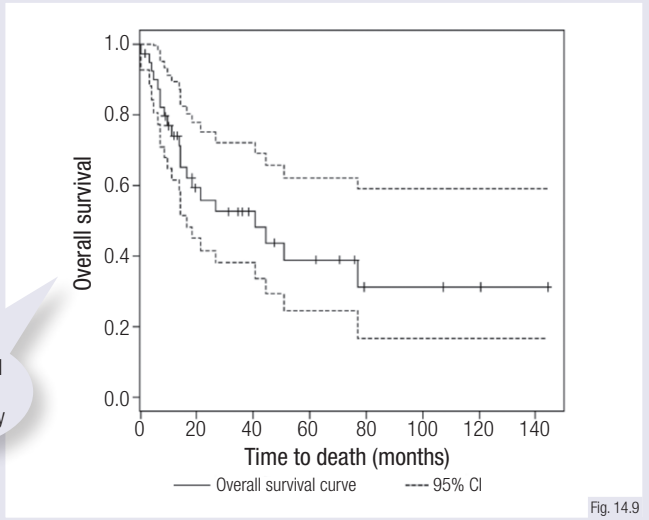

Fig. 14.9

CI, confidence interval.

REVISION QUESTIONS

1. Is primary surgery a good option in anal cancer?
2. Why is CRT used to treat most anal cancers?
3. Which regimen is the preferred standard for CRT?

Summary: Uncommon gastrointestinal tumours: small intestine and anal cancer

- Small bowel adenocarcinoma:
  - SBA has its own genetic alterations that make it distinct from colorectal and gastric adenocarcinomas
  - The type of surgery depends on tumour localisation
  - Due to the low incidence, there are no phase III data regarding neoadjuvant, adjuvant and palliative systemic therapies
  - All patients who have progressed after palliative ChT and are suitable for more treatment should have their tumour tested for MSI (microsatellite instability)/dMMR as they may benefit from immunotherapy
- Anal carcinoma:
  - ASCC is a rare tumour that arises near the squamocolumnar junction
  - Anal cancer is often linked to HPV and a known risk factor is immunosuppression, which is often associated with HIV infection
  - HPV vaccination may reduce the incidence of anal cancer
  - Gold-standard treatment for localised disease is CRT with concurrent 5-FU and mitomycin C. This combined modality approach has led to an increase in sphincter preservation
  - Survival of patients with localised anal cancer is excellent and many patients are spared colostomy
  - In some cases, salvage surgery (APR) is needed, keeping in mind that anal cancers tend to regress slowly after completion of CRT
  - ChT commonly used for metastatic disease is a combination of carboplatin and paclitaxel

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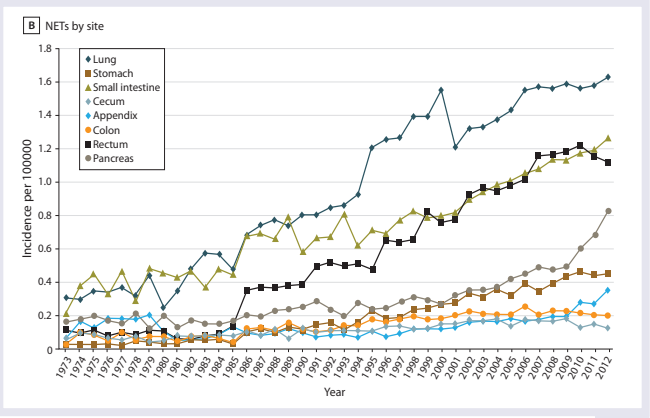
15 Neuroendocrine gastrointestinal tract tumours

Epidemiology, histopathology and tumour biology

Low/intermediate-grade gastroenteropancreatic (GEP) neuroendocrine tumours (NETs) are the most common among all NETs.

Their incidence has been increasing over recent decades at all gastrointestinal (GI) primary sites.

The reason for this increase in incidence is not precisely known, but improved diagnostic and treatment procedures together with greater awareness among physicians have contributed to this.



NET, neuroendocrine tumour. Fig. 15.1

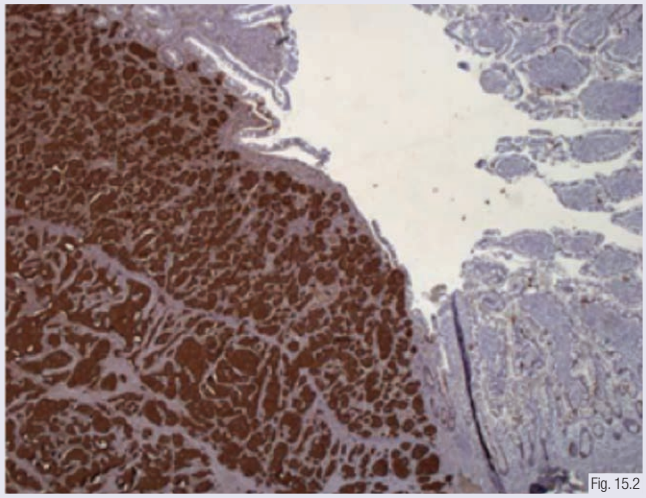


Fig. 15.2

NETs contain neurosecretory granules with hormones and amines that can be detected with immunohistochemistry using specific antibodies.

Every tumour specimen taken, either by biopsy or surgery, should be investigated with these markers to confirm neuroendocrine differentiation.

These markers are chromogranin A (CgA) and synaptophysin, which are positive for NETs in the majority of the cases.

Neuroendocrine neoplasms (NENs) comprise well-differentiated neoplasms, called NETs, and poorly-differentiated neoplasms, named neuroendocrine carcinomas (NECs).

NETs are much more frequent and have a better prognosis than NECs.

The World Health Organization (WHO) classifies GEP-NENs based on their tumour morphology and proliferation index.

Classification and grading criteria for neuroendocrine neoplasms (NENS) of the GI tract and hepatopancreatobiliary organs

Terminology	Differentiation	Grade	Mitotic rate (mitoses/2 mm²)	Ki-67 index
NET, G1	Well differentiated	Low	<2	<3%
NET, G2		Intermediate	2-20	3%-20%
NET, G3		High	>20	>20%
NEC, small cell type (SCNEC)	Poorly differentiated	High	>20	>20%
NEC, large cell type (LCNEC)			>20	>20%
MiNEN	Well or poorly differentiated	Variable	Variable	Variable

Fig. 15.3

GI, gastrointestinal; LCNEC, large cell NEC; MiNEN, mixed neuroendocrine-non-neuroendocrine neoplasm; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumour; SCNEC, small cell NEC.

REVISION QUESTIONS

1. Why has the incidence of NETs increased?
2. Which antibodies should be used for immunohistochemistry?
3. How are GEP-NETs classified?

Clinical and inherited syndromes associated with GEP-NETs

GEP-NETs can be functioning or, more commonly, non-functioning, depending on the presence or absence of clinical symptoms related to tumour-induced hormone hypersecretion.

The most common clinical symptoms are known as carcinoid syndrome, and usually relate to primary small intestinal NETs. Symptoms mainly include flushing and diarrhoea and, more rarely, can cause right-sided valvular-related heart disease. Pancreatic NETs may cause hypersecretion of other hormones, such as insulin, glucagon and most commonly gastrin, resulting in a variety of clinical symptoms/syndromes.

Rarely, GEP-NETs, especially pancreatic, can be seen in some inherited syndromes, most commonly multiple endocrine neoplasia type 1 (MEN-1) or von Hippel-Lindau (VHL) syndrome.

Clinical syndromes associated with endocrine pancreatic tumours

Functioning (50%-70%)	
insulinoma	1–3 per million (17%)
gastrinoma	0.5–3 per million (15%)
VIP-oma	0.05–0.2 per million (2%)
glucagonoma	0.01–0.1 per million (1%)
somatostatinoma ACTH-oma, GRF-oma calcitonin-, serotonin PTH-rp producing	<10%
Non-functioning (30%–50%)	0.2–2 per million

ACTH, adrenocorticotropic hormone; GRF, growth hormone-releasing factor; PTH-rp, parathyroid hormone-related protein; VIP, vasoactive intestinal peptide.

Fig. 15.4

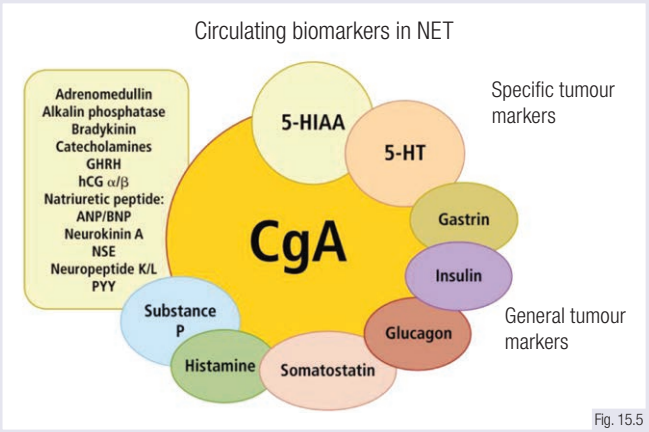


Fig. 15.5

5-HIAA, 5-Hydroxy-3-indoleacetic acid; 5-HT, serotonin; ANP/BNP, atrial natriuretic peptide and brain/ventricular natriuretic peptide; CgA, chromogranin A; GHRH, growth hormone releasing hormone; hCG, human chorionic gonadotropin; NET, neuroendocrine tumour; NSE, neurone-specific enolase; PYY, peptide YY.

A functional NET is defined as such when hormonal hypersecretion causes a clinical syndrome; a NET with immunohistochemical expression or elevated blood levels of hormones/markers without a clinical syndrome is not defined as 'functional'.

Monitoring urinary 24h level of hydroxy-indoleacetic acid (HIAA) can be a useful aid to control carcinoid symptoms.

CgA, the most widely known circulating NET biomarker, is not specific and has more of a prognostic value rather than a diagnostic one.

Many physiological and pathological situations can interfere with CgA blood level.

Drugs such as proton pump inhibitors (PPIs) cause serum CgA levels to rise through elevations in gastrin promoted by acid suppression.

Most common false-positive elevations of CgA blood levels

Pathological situations	Drugs
• Impaired renal function • Hypertension • Chronic atrophic gastritis • Cardiovascular diseases • Inflammatory diseases	• Proton pump inhibitors (PPIs) • Steroids

Fig. 15.6

CgA, chromogranin A.

REVISION QUESTIONS

1. What is the most common NET-related clinical syndrome?
2. What is the most common circulating marker of NETs?
3. Why do PPIs increase the CgA concentration?

Imaging of neuroendocrine GEP-NETs

Different imaging techniques are used to characterise a GEP-NEN. Morphology can be explored with standard radiology techniques, but tracers are required for functional evaluation.

Chest and abdomen contrast-enhanced computed tomography (CT) is recommended for staging. Additional magnetic resonance imaging (MRI) and endoscopic ultrasound (EUS) are often specifically indicated in suspected pancreatic NETs.

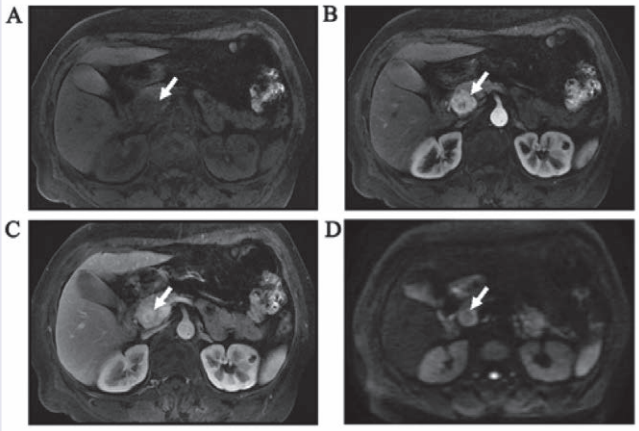
^{68}Ga-DOTA-peptide positron emission tomography (PET)/CT is currently the best tool for evaluation of somatostatin receptor expression in GEP-NETs, although ^{18}F-fluorodeoxyglucose (^{18}FDG)-PET/CT is preferred for poorly-differentiated GEP-NECs.

Imaging of neuroendocrine tumours: techniques

Morphological	Functional
Ultrasound Computed tomography (CT) Magnetic resonance imaging Endoscopic ultrasound	Diffusion-weighted magnetic resonance Somatostatin receptor scintigraphy ^{68}Ga-DOTA-TATE/TOC/CT ^{11}C-5-HTP, ^{18}F-DOPA/CT ^{18}F-FDG/CT
At diagnosis, CT abdomen and thorax, including a dynamic contrast enhancement of pancreas and liver + somatostatin receptor imaging	

DOPA, dihydroxyphenylalanine; DOTA, tetraxetan; DOTA-TATE, DOTA-octreotate; DOTA-TOC, DOTA-ocreotide; FDG, fluorodeoxyglucose; HTP, hydroxytryptophan.

Fig. 15.7



Representative case of a 65-year-old female with a pathologically proven G1 neuroendocrine tumour in the pancreatic head. (A) T1-weighted unenhanced and gadolinium-enhanced images; (B) arterial phase and (C) portal phase; (D) diffusion-weighted imaging (DWI) image (b=1000 sec/mm^2).

Fig. 15.8

Diffusion-weighted imaging (DWI) MRI is a very sensitive tool for pancreatic NETs.

Opposite, somatostatin receptor scintigraphy, using ^{111}Indium (octreoscan), of two cases with small intestinal NETs. White arrows indicate metastases.

Somatostatin receptor scintigraphy, with ^{111}Indium and gamma camera imaging, was the standard of care for many years to stage NETs. However, ^{68}Ga-PET/CT-DOTA-peptide is superior and now used in many centres.

In patients with intermediate-grade GEP-NETs, dual tracer, ^{68}Ga-PET/CT-DOTA-peptide and ^{18}FDG-PET/CT, are used to determine disease burden and the best therapeutic options.

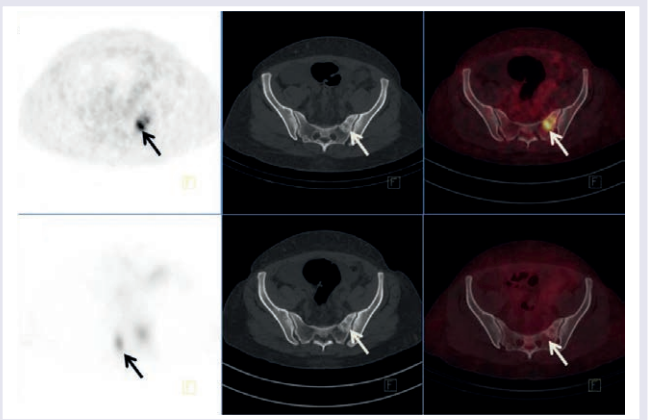


Fig. 15.9

REVISION QUESTIONS

1. Which standard imaging techniques are used for diagnosis/staging/characterisation of GEP-NETs?
2. Which is the best molecular imaging technique for somatostatin receptor functional detection?
3. Which is the most adequate tracer to use with PET/CT for poorly-differentiated GEP-NECs?

Treatment of GEP-NETs

Surgical resection is the best treatment for radically resectable locally advanced or oligometastatic GEP-NETs.

Over 50% of patients have unresectable metastatic disease at diagnosis. In these cases, systemic therapies and/or liver-directed non-surgical treatments should be considered.

Everolimus and sunitinib are approved for advanced/progressive well-differentiated pancreatic NETs. Everolimus is also approved for advanced non-functioning progressive GI-NETs.

Therapeutic options: neuroendocrine tumours

Surgery
- Curative (rarely), ablative (very often)

Debulking
- Radiofrequency ablation (RFA)
- Embolisation / chemoembolisation / radioembolisation (SIRT)

Irradiation
- External (bone, brain metastases)
- Tumour targeted, radioactive therapy (MIBG, ^{90}Y-DOTATOC, ^{177}Lu-DOTATATE)

Medical therapy
- Chemotherapy
- Biological treatment
  - Somatostatin analogues
  - Interferon alpha
  - mTOR inhibitors
  - Vascular endothelial growth factor receptor inhibitors
  - Other tyrosine kinase inhibitors

Fig. 15.10

DOTA, tetraxetan; DOTATATE, DOTA-octreotate; DOTATOC, DOTA-ocreotide; mTOR, mammalian target of rapamycin; SIRT, selective internal radiation therapy.

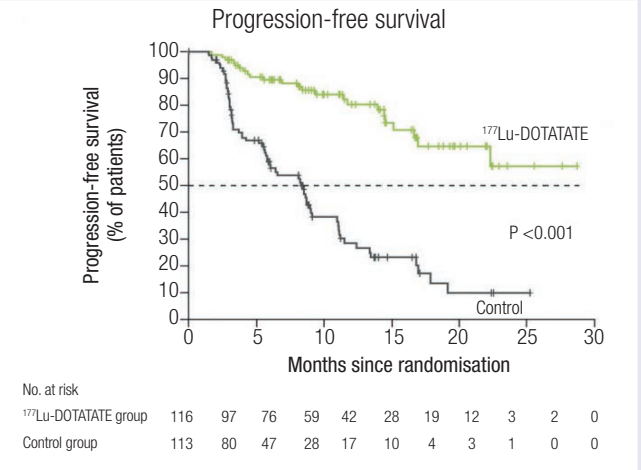


Fig. 15.11

Somatostatin analogues have been used for symptom control, particularly for carcinoid syndrome. Antitumour efficacy in advanced <10% Ki-67 GEP-NETs was demonstrated in two phase III trials comparing octreotide long-acting release (LAR) and lanreotide depot with placebo, the PROMID and CLARINET trials, respectively.

Peptide receptor radionuclide therapy (PRRT) with ^{177}Lu-DOTATATE has been recently approved for treatment of progressive advanced, somatostatin receptor-positive, G1-G2, GEP-NETs.

PRRT is indicated in highly and homogeneously uptaking ^{68}Ga-PET/CT GEP-NETs.

Telotristat ethyl is a recently approved drug for carcinoid syndrome-related diarrhoea resistant to somatostatin analogues. It reduces serotonin production by inhibiting tryptophan hydroxylase.

Strict cardiological monitoring should be performed in patients with carcinoid syndrome.

Unfortunately, no validated predictive biomarkers of response/efficacy of therapy exist so far.

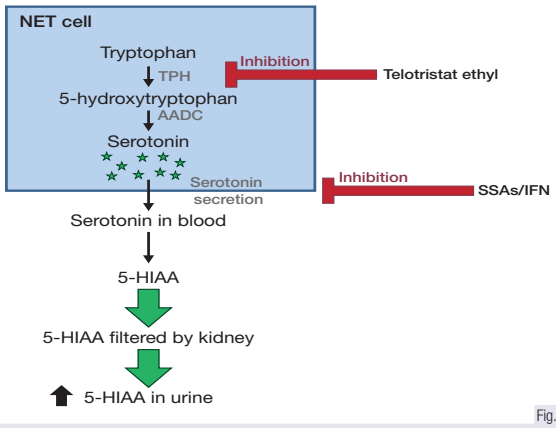


Fig. 15.12

5-HIAA, 5-hydroxy-3-indoleacetic acid; AADC, aromatic L-amino acid decarboxylase; IFN, interferon; NET, neuroendocrine tumour; SAA, somatostatin analogue; TPH, tryptophan hydroxylase.

REVISION QUESTIONS

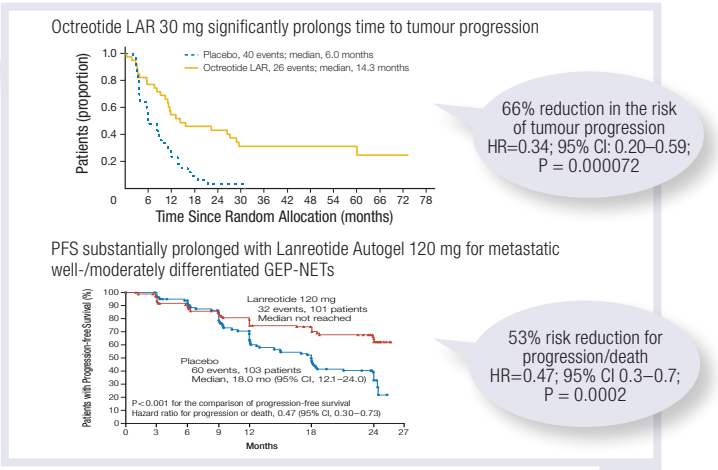
1. What is the optimal treatment for locally advanced resectable GEP-NETs?
2. For which GEP-NENs is PRRT indicated?
3. Which mTOR (mammalian target of rapamycin) inhibitor could be given in patients with an advanced GEP-NET?

Treatment of GEP-NETs (continued)

Today somatostatin analogues are considered to be the first-line treatment for low-proliferating GEP-NETs with a proliferation index of Ki-67 up to 10%.

Interferon alpha, introduced in the early 1980s for treatment of small intestinal NETs, controls symptoms in up to 60% but results in RECIST (Response Evaluation Criteria in Solid Tumours) response in only ~10% of patients.

Alkylating agents are commonly used in advanced pancreatic NETs. Temozolomide is the latest compound in this category, and is often used as a single agent in GEP-NETs, sometimes in combination with capecitabine.



CI, confidence interval; GEP-NET, gastroenteropancreatic neuroendocrine tumour; HR, hazard ratio; LAR, long-acting release; PFS, progression-free survival.

Fig. 15.13

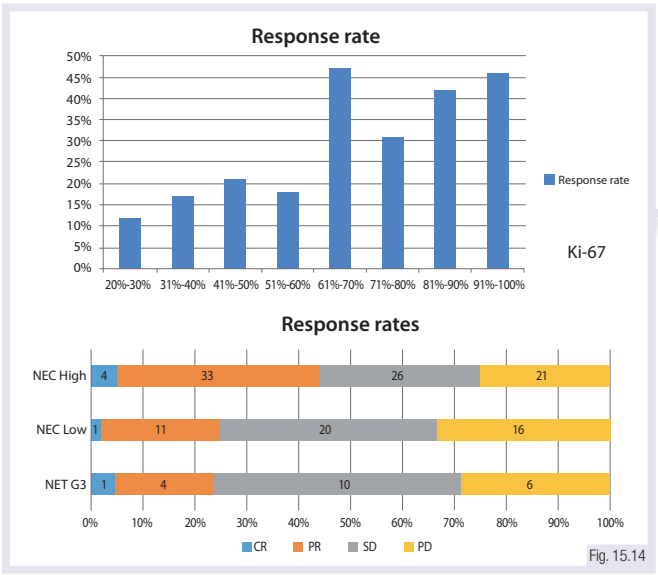


Fig. 15.14

CR, complete response; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumour; PD, progressive disease; PR, partial response; SD, stable disease.

Poorly-differentiated advanced GEP-NECs are usually treated with cisplatin or carboplatin/etoposide. Response rates to platinum/etoposide are higher for those with highly proliferative (>55% Ki-67) GEP-NECs compared with patients with GEP-NETs, which have lower proliferation rates (≤55% Ki-67).

The first studies with immune checkpoint inhibitors have not been shown to be effective in patients with GEP-NETs. Clinical trials remain very important in these rare conditions and should be considered at any time for these patients.

Over the last few decades, several new therapies have been developed, some approved by both the FDA/EMA (Food and Drug Administration/European Medicines Agency).

There is no validated sequence of treatments for patients with GEP-NETs. Personalised therapeutic strategies should be defined.

GEP-NET patients should be managed within NEN-dedicated multidisciplinary teams.

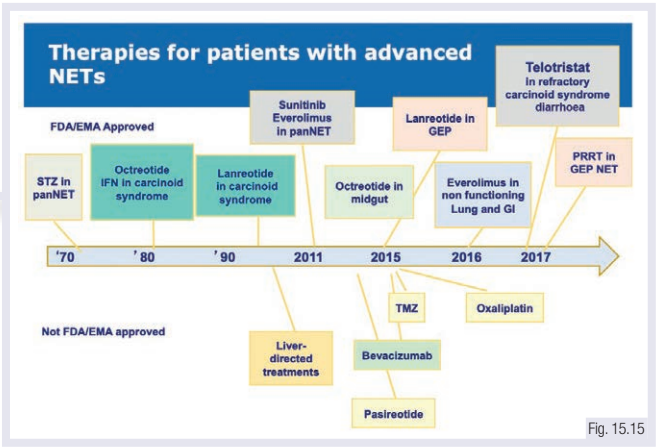


Fig. 15.15

EMA, European Medicines Agency; FDA, Food and Drug Administration; GEP, gastroenteropancreatic; GI, gastrointestinal; IFN, interferon; NET, neuroendocrine tumour; panNET, pancreatic NET; PRRT, peptide receptor radionuclide therapy; STZ, streptozotocin; TMZ, temozolomide.

REVISION QUESTIONS

1. For which type of NETs should somatostatin analogues be considered?
2. What is the latest alkylating agent used in GEP-NETs?
3. What is the tumour response rate to platinum/etoposide chemotherapy in the different subtypes of high-grade GEP-NENs?

Summary: Neuroendocrine gastrointestinal tract tumours

- GEP-NET patients should be treated within dedicated NEN multidisciplinary teams
- The incidence of GEP-NETs has increased over the last few decades
- The WHO 2019 classification of GEP-NETs is based on morphology and proliferation indices: mitotic rate and Ki-67
- CgA is the most common circulating marker of GEP-NETs; it is not sufficiently specific for diagnosis
- Molecular imaging, with tracers, is becoming increasingly important for diagnosis/management
- Somatostatin analogues are the first-line therapy for low-proliferating advanced GEP-NETs (Ki-67 <10%)
- Everolimus is approved for the treatment of well-differentiated progressive pancreatic NETs and for non-functioning GI-NETs
- Sunitinib is approved for well-differentiated progressive pancreatic NETs
- PRRT is approved for progressive somatostatin receptor-positive G1-G2 GEP-NETs

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16 Emerging treatment strategies and new drugs for gastrointestinal cancers

Emerging targets in colorectal cancer

Immune checkpoint inhibitors (ICIs) have shown efficacy only in microsatellite unstable (MSI) metastatic colorectal cancers (mCRCs) (5%). The KEYNOTE-177 (pembrolizumab) and CheckMate 142 (nivolumab, alone or combined with ipilimumab) trials reported outstanding results.

In microsatellite stable (MSS) tumours, several combinatorial strategies have been carried out to overcome the immunosuppressant biology of CRC (Wnt, transforming growth factor beta [TGF-β], MEK).

Anti-CEA-TCB (carcinoembryonic antigen T-cell bispecific) is a bispecific antibody that simultaneously binds CD3 on T cells and CEA on tumour cells. Two phase I trials using anti-CEA-TCB as single agent or in combination with atezolizumab demonstrated promising results.

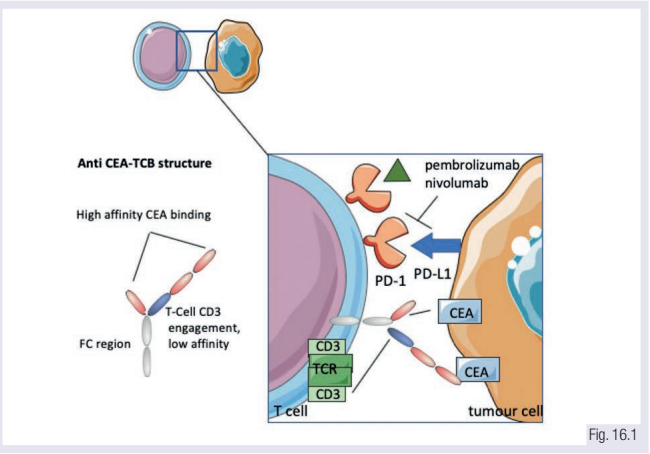


Fig. 16.1

CEA, carcinoembryonic antigen; FC, fragment crystallizable; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TCB, T-cell bispecific; TCR, T cell receptor.

The current strategy for mCRC treatment should be a personalised approach based on genomic alterations such as *RAS* and *BRAF* mutations, human epidermal growth factor receptor 2 (*HER2*) and *MET* amplifications as well as kinase fusions.

HER2 amplification/overexpression (2%-6% of CRCs) is associated with resistance to anti-epidermal growth factor receptor (EGFR) drugs. The phase II HERACLES trial cohort A (trastuzumab+lapatinib) and MyPathway trial (trastuzumab+pertuzumab) showed anti-tumour efficacy in patients with pretreated *HER2*-amplified mCRCs.

Recently, the MOUNTAINEER trial (tucatinib+trastuzumab) and the DESTINY-CRC01 trial (trastuzumab+deruxtecan) also showed very promising preliminary efficacy results.

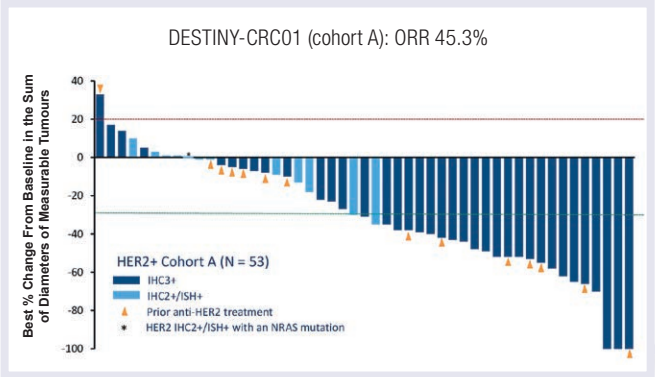


Fig. 16.2

HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, *in situ* hybridisation; ORR, overall response rate.

Anaplastic lymphoma kinase (*ALK*), *ROS1*, neurotrophic tyrosine receptor kinase (*NTRK*) and *RET* kinase genes are found in 1% of CRCs. Case reports with exceptional responses have been described in fusion-positive mCRC with ALK and tyrosine receptor kinase (TRK) inhibitors larotrectinib and entrectinib (approved by the Food and Drug Administration [FDA] in 2018/2019, respectively).

RAS mutations occur in 67% of CRCs, most commonly in *KRAS* gene (*KRAS*^{G12D} 12%, *KRAS*^{G12V} 8%, *KRAS*^{G13D} 7%, *KRAS*^{G12C} 4%) and represent an elusive target. AMG 510 *KRAS*^{G12C} inhibitor has shown promising preliminary results in terms of efficacy and safety in an ongoing phase I clinical trial, in patients with *KRAS*^{G12C} mutation.

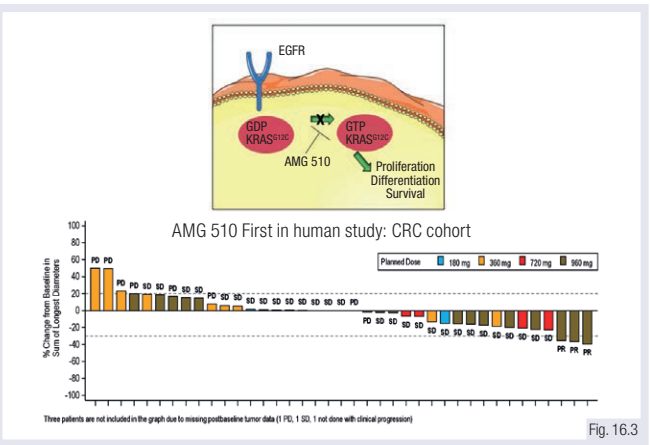


Fig. 16.3

CRC, colorectal cancer; EGFR, epidermal growth factor receptor; PD, progressive disease; SD, stable disease.

REVISION QUESTIONS

1. What is the current status of immunotherapy in CRC?
2. Which is the best therapeutic approach for patients with *HER2*-amplified mCRC?
3. Do *RAS* mutations represent a targetable driver in mCRC?

Oesophageal and gastric cancers

ICIs have shown efficacy in oesophageal cancer (OC), gastric cancer (GC) and oesophagogastric junction cancer (OGJC).

Adjuvant treatment with nivolumab following chemoradiotherapy and surgery in patients with OC and OGJC demonstrated a 31% reduction in the risk of recurrence or death (CheckMate 577).

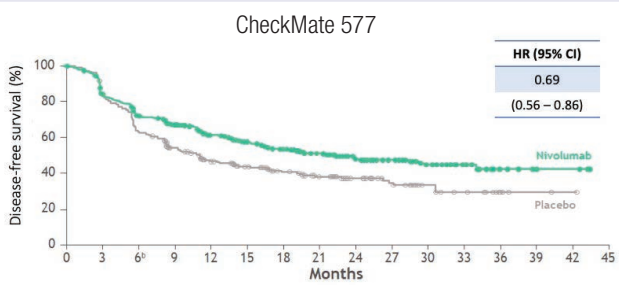


Fig. 16.4

CI, confidence interval; HR, hazard ratio; OS, overall survival.

Pembrolizumab demonstrated better survival outcomes when added to the first-line chemotherapy (ChT) in OC (KEYNOTE-590).

Pembrolizumab also demonstrated efficacy when compared with second-line ChT in OC with PD-L1 (programmed death-ligand 1) CPS (combined positive score) ≥10, especially in SCC (squamous cell carcinoma, KEYNOTE-181). Nivolumab was superior to second-line ChT in squamous cell OC in Asia (ATTRACTION-3).

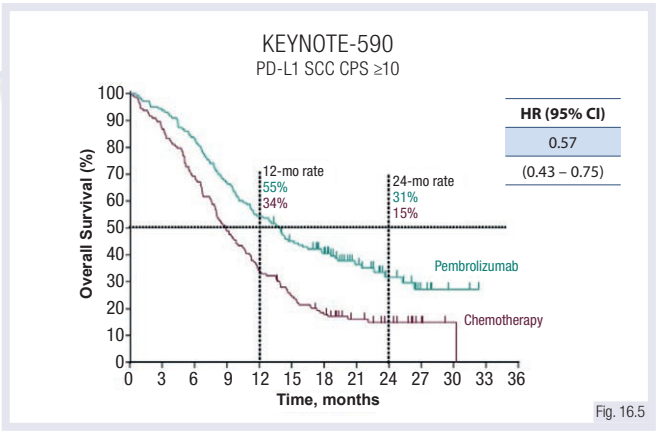


Fig. 16.5

CI, confidence interval; CPS, combined positive score; HR, hazard ratio; PD-L1, programmed death-ligand 1; SCC, squamous cell carcinoma.

In GC and OGJC, avelumab was not superior to ChT in maintenance after first-line treatment (JAVELIN-100), nor in third-line when compared with ChT (JAVELIN-300).

Nivolumab showed better survival when compared with placebo in the refractory setting in an Asian population (ATTRACTION-2). Pembrolizumab behaved similarly in the global population (phase II KEYNOTE-059).

In the second-line setting, pembrolizumab was not statistically superior to weekly paclitaxel (PD-L1 CPS ≥1). The results were contradictory, as survival curves crossed before the year, thus violating the proportional hazards assumption (KEYNOTE-061).

Pembrolizumab monotherapy showed a clinically meaningful benefit in first-line GC/OGJC with PD-L1 CPS ≥1 (KEYNOTE-062). When combined with first-line FOLFOX (leucovorin/5-fluorouracil/oxaliplatin), nivolumab showed a 29% reduction in the risk of death in GC and OGJC with PD-L1 CPS ≥5 (CheckMate 649).

MSI should be considered a new biomarker for immunotherapy, irrespective of the treatment line (KEYNOTE-062, KEYNOTE-061, KEYNOTE-059). Other immune biomarkers are needed to identify MSS patients for immunotherapy.

HER2-targeted antibody-drug conjugate trastuzumab deruxtecan or the Claudin 18.2-IgG1 antibody zolbetuximab add to the armamentarium of molecularly-driven treatments.

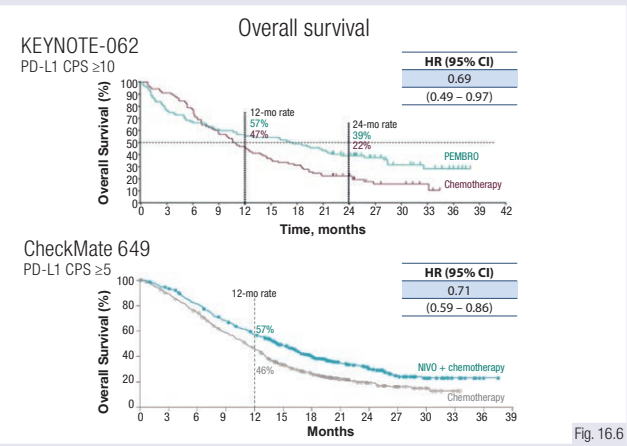


Fig. 16.6

CI, confidence interval; CPS, combined positive score; HR, hazard ratio; NIVO, nivolumab; PD-L1, programmed death-ligand 1; PEMBRO, pembrolizumab.

REVISION QUESTIONS

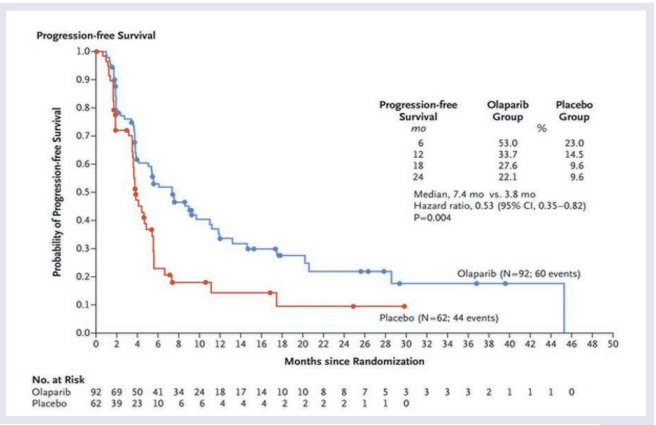
1. Which immunotherapies have shown efficacy in OC?
2. Which immunotherapies should be considered in gastric and GEJ cancers?
3. What should be considered as a new biomarker in gastric and GEJ cancers?

Emerging targets in pancreatic-biliary tract cancers

Many homologous recombination-deficient tumours, such as those with *BRCA* mutations, will be sensitive to poly (adenosine diphosphate–ribose) polymerase (PARP) inhibition.

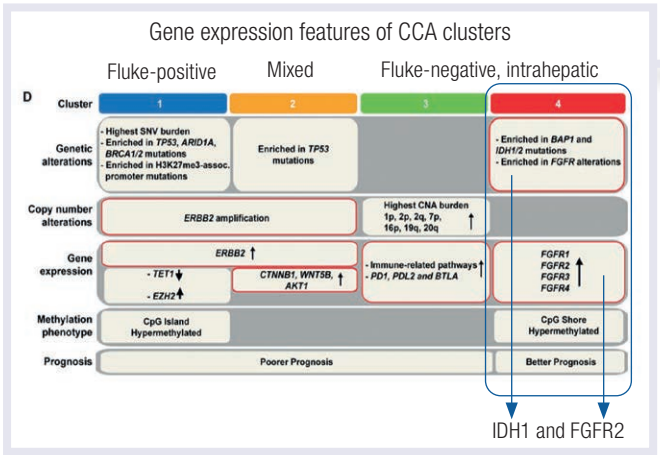
Four to seven percent of pancreatic cancers harbour a germline *BRCA1/BRCA2* mutation (gBRCAm). A phase II study of olaparib showed clinical activity in 23 patients with refractory metastatic gBRCAm pancreatic tumours.

The phase III POLO trial demonstrated the efficacy of maintenance olaparib in those gBRCAm patients treated with a first platinum-based line without progression.



CI, confidence interval.

Fig. 16.7



CCA, cholangiocarcinoma; CNA, copy number alteration; FGFR, fibroblast growth factor receptor; IDH, isocitrate dehydrogenase; PD-1, programmed cell death protein 1; PD-L2, programmed death-ligand 2; SNV, single-nucleotide variant.

Fig. 16.8

Several actionable oncogenic alterations have been identified in advanced cholangiocarcinoma (CCA), including fibroblast growth factor receptor 2 (*FGFR2*) and isocitrate dehydrogenase 1 (*IDH1*) genes.

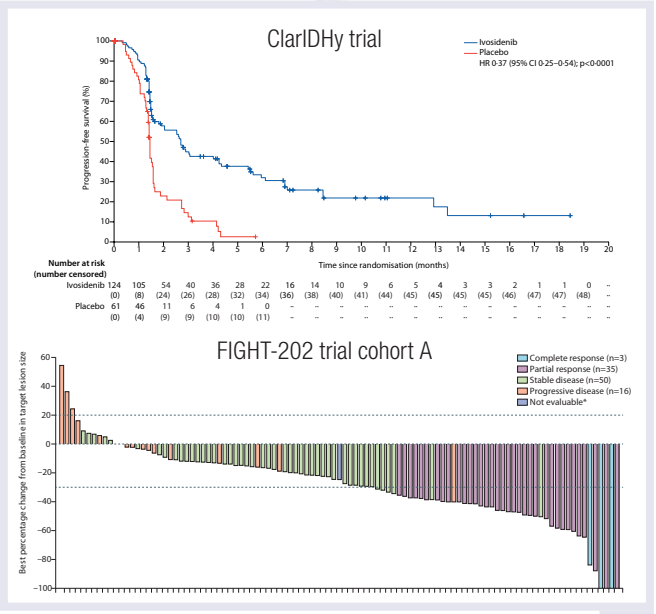
IDH1 mutations occur in up to ~20% of intrahepatic CCA.

The ClarIDHy randomised phase III trial demonstrated significantly better survival outcomes with ivosidenib (AG-120), a first-in-class, oral, small-molecule inhibitor of the mutant IDH1 (mIDH1) protein, vs placebo in patients with *IDH1*-mutated refractory advanced CCA.

FGFR2 fusions occur predominantly in intrahepatic CCA, with a prevalence of 10%-16%. Pan-FGFR inhibitors showed durable partial responses and prolonged progression-free survival (PFS) in target-positive populations.

Pemigatinib and BGJ398, orally bioavailable, selective pan-FGFR inhibitors, demonstrated widespread responses in patients with advanced pretreated CCAs harbouring *FGFR2* rearrangements (phase II FIGHT-202 and BGJ398 trials).

Finally, the combination of dabrafenib and trametinib demonstrated promising activity in biliary tract cancer (BTC) patients harbouring *BRAF* V600E mutations (ROAR basket trial).



CI, confidence interval; HR, hazard ratio.

Fig. 16.9

REVISION QUESTIONS

1. For which subset of patients with metastatic pancreatic cancer is olaparib active?
2. Which cluster of CCAs has the best prognosis?
3. Which target genes (other than *BRCA*, *FGFR2* and *IDH1*) have been tested in BTC?

Summary: Emerging treatment strategies and new drugs for gastrointestinal cancers

- GI cancers are complex diseases with multiple levels of intra- and inter-tumour heterogeneity
- MSI CRCs and GEJ cancers merit treatment with ICIs
- MSS CRCs present with an innate immunosuppressive biology that confers resistance to ICIs
- While *HER2* overexpression/amplification is a well-established target in GC, it may also represent a therapeutic target in CRC; different drug combinations are currently under clinical investigation
- PD-L1 CPS-high gastric cancers benefit from ICIs
- ICIs represent a new treatment option for OC
- Germline *BRCA1/2*-mutated pancreatic tumours benefit from maintenance treatment with PARP inhibitors (e.g. olaparib)
- *FGFR2* rearrangements and *IDH1* mutations constitute new actionable targets for patients with advanced CCA
- The comprehensive understanding of the molecular characterisation of GI cancers should be the basis for future tailored treatments
- Next goals include the discovery of new biomarkers of response and the implementation of innovative techniques, such as liquid biopsy, to optimise the increasingly successful personalised therapeutic approach

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Image sources

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