Surgical Oncology Course

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Foreword

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Contribution: Critical review and structural contributions to the manuscript

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This course was not born in an office. It was born at Memorial Sloan Kettering Cancer Center in New York — one of the most

demanding and prestigious surgical oncology fellowship programmes in the world — while I was operating on retroperitoneal sarcomas and peritoneal malignant disease alongside surgeons who had made those pathologies their sole surgical purpose.

At MSKCC I understood something that no manual had written: the surgical oncologist who does not understand the biology of what he is operating on is not a safer surgeon — he is a more dangerous one. And that the distance between knowing the TNM stage of a tumour and knowing exactly why, how much, and how far to operate is the distance that separates a well-trained resident from a surgical oncologist.

Back at the Hospital General Universitario Gregorio Marañón — where I was shaped by surgeons of the calibre of Prof. García Sabrido and Prof. González Bayón, who taught me that technical precision and scientific rigour are not options but obligations — I found that the gap between the oncology textbook and the surgical atlas remained as wide as ever in residency training. This course is my answer to that gap.

It presupposes that you already know anatomy. It does not presuppose that you know why you are operating, when you should stop, or what the evidence says about the operation you are about to perform. That is precisely what this material addresses.

The structure follows a rigorous but readable format adapted from the First Aid model to surgical oncology: epidemiology, TNM classification (AJCC 8th Edition throughout), clinical presentation, surgical treatment as the core, systemic therapy — only what the surgeon needs to know — follow-up, board pearls, and common pitfalls. Landmark trials are presented in structured format. Controversies are not hidden; they are front and centre, because that is where surgical judgement lives.

Use this course as a companion in the clinic and before the tumour board. Argue with it. Check the references. The day you stop questioning what you read is the day you stop learning surgery.

— Pablo Lozano Lominchar

Madrid, 2025

📌 **COURSE OBJECTIVE**

Directed to: General surgery residents (year 3–5), surgical oncology fellows, and surgeons preparing for EBSQ board examinations.

Prior knowledge assumed: Surgical anatomy, basic oncology principles, AJCC staging framework.

Upon completion you will be able to:

(1) Apply AJCC 8th Edition TNM staging to all major solid tumours in surgical oncology practice.

(2) Define the surgical strategy, resection margins, and lymphadenectomy extent for each tumour type.

(3) Integrate landmark trial evidence into perioperative and multidisciplinary decision-making.

This course does not replace: Direct surgical training, institutional protocols, or individual tumour board discussion.

Acknowledgements

This work would not have been possible without the example and intellectual generosity of three surgeons at the Hospital General Universitario Gregorio Marañón in whom I have seen, throughout my training, an academic mirror:

Dr. González Bayón, for teaching me that technical precision and scientific rigour are not options but obligations of the surgical oncologist.

Dr. José Luis García Sabrido, master of radical surgery and of reasoned clinical courage, whose vision of the oncological patient continues to guide my practice.

Dr. José Manuel Asencio, for demonstrating that surgical excellence and academic humility are not incompatible — they are inseparable.

All three have been, and remain, inevitable references.

The editorial contribution of **Dr. Juan Carbonell**, resident in General Surgery at the HGUGM, was decisive in the pedagogical structuring of this material during his training.

His critical reading shaped the course in ways that will not appear in any single footnote.

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Module 1

Surgical Oncology

Principles

Section I — General Principles

1.1. R-Classification: The Language of Margins

AJCC 8th Edition | UICC TNM 8th | CAP Reporting Protocols

The R-classification system describes the status of residual tumour after surgical treatment and is the single most important predictor of long-term oncological outcome across virtually all solid tumours. R0 indicates no residual tumour with microscopically negative margins, R1 denotes microscopic residual disease at the resection margin, R2 means gross residual disease was left behind, and RX indicates that residual tumour status cannot be assessed. The fundamental goal of curative surgical oncology is to achieve an R0 resection, because an R1 or R2 margin is consistently associated with dramatically reduced disease-free and overall survival.

Intraoperative frozen section analysis is the surgeon's primary tool for achieving R0 resection in real time. When there is any doubt about margin adequacy, fresh tissue from the resection bed or the specimen margin should be sent for frozen section before closing. This is particularly important in breast-conserving surgery, pancreatic head resections (where the retroperitoneal and superior mesenteric artery margins are

critical), and soft tissue sarcoma surgery where re-excision is challenging. The surgeon must orient the specimen carefully and communicate with the pathologist about which margins are of concern.

Margin adequacy varies by tumour type and anatomical site. In breast cancer, the current consensus (SSO-ASTRO 2014) accepts "no tumour on ink" as an adequate margin for invasive carcinoma after whole-breast radiation. In soft tissue sarcoma, a 1 cm margin or an intact fascial plane is considered adequate. In rectal cancer, a circumferential resection margin (CRM) of ≥1 mm is required for an R0 resection. Understanding these site-specific definitions is essential for the surgical oncologist.

Classification	Definition	Clinical Implication
R0	No residual tumour (negative margins)	Goal of curative surgery. Best prognosis.
R1	Microscopic residual at margin	Consider re-excision or adjuvant RT. Reduced DFS/OS.
R2	Gross residual tumour left	Palliative intent. Systemic therapy.
RX	Cannot be assessed	Inadequate pathological evaluation. Repeat if possible.

> 🎯 **CLINICAL PEARL**
>
> Always orient specimens with sutures or clips and communicate margin concerns to pathology BEFORE resection. An R0 result is a team effort between surgeon and pathologist.
>
> "No tumour on ink" is the current breast margin standard (SSO-ASTRO 2014). Wider margins do NOT reduce local recurrence after whole-breast radiation.

Wittekind C. UICC TNM 8th Ed 2017 | Moran MS. Ann Surg Oncol 2014 (SSO-ASTRO) | AJCC Cancer Staging Manual 8th Ed 2017

1.2. Biopsy Techniques in Surgical Oncology

NCCN Soft Tissue Sarcoma v2.2024 | ESMO Breast 2024

The choice of biopsy technique is a critical decision that can determine the success or failure of subsequent definitive treatment. In surgical oncology, the biopsy must achieve two goals simultaneously: obtain sufficient tissue for histological diagnosis and molecular profiling, while avoiding contamination of uninvolved tissue planes that could compromise future resection. A poorly planned biopsy can turn a curable cancer into a complex reconstructive challenge or even render it unresectable.

Core needle biopsy (CNB) is the preferred initial diagnostic technique for most solid tumours, including breast masses, soft tissue sarcomas, and lymph nodes. It provides tissue architecture for histological subtyping and sufficient material for immunohistochemistry and molecular testing. In breast cancer, CNB has replaced excisional biopsy as the standard diagnostic method because it allows preoperative planning including sentinel lymph node biopsy, neoadjuvant therapy decisions, and oncoplastic surgical planning. Fine needle aspiration cytology (FNAC) remains useful for thyroid nodules (Bethesda classification) and for confirming metastatic disease in lymph nodes, but provides insufficient tissue architecture for primary diagnosis of most solid tumours.

For soft tissue sarcomas, biopsy technique is especially critical. The biopsy tract must be placed in line with the planned definitive resection incision so that it can be excised en bloc with the tumour. A transverse or poorly placed biopsy tract in an extremity sarcoma may contaminate additional compartments and require a wider, more morbid resection — or even amputation. Incisional biopsy should only be performed when CNB fails to provide a diagnosis, and must be done by or in direct consultation with the surgeon who will perform the definitive resection.

Technique	Indication	Key Rule
CNB (Core Needle)	Breast, soft tissue, lymph node, liver	Preferred first-line. Provides architecture + molecular.
FNAC	Thyroid (Bethesda), LN confirmation	Cytology only. Insufficient for primary STS/breast dx.
Incisional	Failed CNB, large deep masses	Align with definitive incision. Sarcoma rule.
Excisional	Small superficial lesions (<3 cm)	Only if won't compromise definitive surgery.

> ⚠ **WARNING: THE SARCOMA RULE**
>
> NEVER biopsy a suspected soft tissue sarcoma with a transverse incision or through an uninvolved compartment. The biopsy tract MUST align with the planned definitive resection. Violation of this rule can convert a limb-sparing surgery into an amputation.

Mankin HJ. JBJS 1996 | NCCN Soft Tissue Sarcoma v2.2024 | Morrow M. Ann Surg Oncol 2011 | Cibas ES. Thyroid 2017 (Bethesda III)

1.3. Lymphadenectomy in Surgical Oncology

NCCN Guidelines 2024 | ACOSOG Z0011 | MSLT-II | Dutch TME Trial

Lymphadenectomy serves two fundamental purposes in surgical oncology: staging and therapeutic disease control. Accurate nodal staging determines prognosis and guides adjuvant therapy decisions. In many cancers, the extent of lymph node dissection directly influences overall survival. The sentinel lymph node biopsy (SLNB) concept, pioneered by Morton for melanoma and Krag for breast cancer, revolutionised the management of clinically node-negative disease by identifying the first draining node(s) and sparing patients the morbidity of complete lymph node dissection when those sentinel nodes are tumour-free.

The ACOSOG Z0011 trial (Giuliano, JAMA 2011, updated Lancet Oncol 2017) was a paradigm-shifting study demonstrating that in breast cancer patients with T1-T2 tumours, 1-2 positive sentinel nodes, and planned whole-breast radiation, completion axillary dissection (ALND) provides no survival benefit compared with SLNB alone. Ten-year overall survival was equivalent between groups (83.6% vs 86.3%). This trial fundamentally changed practice: the majority of sentinel node-positive breast cancer patients no longer require ALND, avoiding the significant morbidity of lymphoedema, shoulder dysfunction, and numbness.

For melanoma, the MSLT-II trial (Faries, NEJM 2017) demonstrated that completion lymph node dissection (CLND) after a positive sentinel node does not

improve melanoma-specific survival compared with nodal observation by ultrasonography. Three-year melanoma-specific survival was 86% in both groups. However, CLND did improve regional disease control. Current NCCN guidelines recommend CLND as an option but no longer mandate it for all SLN-positive melanoma patients, allowing shared decision-making based on tumour burden in the sentinel node.

Complete mesocolic excision (CME) with central vascular ligation for colon cancer and total mesorectal excision (TME) for rectal cancer represent the gold standard of surgical technique for colorectal malignancies. TME, introduced by Heald in 1982, reduced local recurrence rates from 30-40% to less than 5% by removing the entire mesorectal envelope along anatomical planes. D2 lymphadenectomy remains the standard for gastric cancer as discussed in Module 2. Minimum lymph node counts are essential for adequate staging: 12 nodes for colorectal cancer (AJCC 8th), 16 for gastric cancer, and 15 for oesophageal cancer.

Cancer Type	Procedure	Minimum Nodes	Key Trial / Reference
Breast (cN0, 1-2 SLN+)	SLNB alone (no ALND)	N/A	Z0011 (Giuliano 2011/2017)
Melanoma (SLN+)	Observation vs CLND	N/A	MSLT-II (Faries 2017)
Colon	CME + CVL	12	AJCC 8th / Hohenberger 2009
Rectum	TME	12	Heald 1982 / Dutch TME Trial
Gastric	D2 lymphadenectomy	16 (25+ optimal)	Dutch D2 / AJCC 8th
Oesophageal	En bloc + 2-field LND	15	AJCC 8th / NCCN 2024

> 💡 **EVIDENCE SPOTLIGHT**
>
> Z0011: No ALND needed for T1-T2 breast cancer with 1-2 positive SLNs and planned whole-breast RT. 10-yr OS equivalent.
>
> MSLT-II: CLND does not improve melanoma-specific survival after positive SLNB. Observation with ultrasound is an option.
>
> TME (Heald 1982): reduced rectal cancer local recurrence from 30-40% to <5%. The most impactful technical advance in colorectal surgery.

Giuliano AE. JAMA 2011 / Lancet Oncol 2017 | Faries MB. NEJM 2017 | Heald RJ. Br J Surg 1982 | Hohenberger W. Col Dis 2009 | AJCC 8th Ed 2017

1.4. Enhanced Recovery After Surgery (ERAS)

ERAS Society Guidelines 2024 | Kehlet H. Lancet 1997

Enhanced Recovery After Surgery (ERAS) is a multimodal, evidence-based perioperative care framework designed to reduce the surgical stress response, maintain physiological function, and accelerate postoperative recovery. The concept was introduced by Henrik Kehlet in 1997, who demonstrated

that a coordinated approach to perioperative care could dramatically reduce hospital stay and complications after colorectal surgery. The core philosophy is simple: everything we do to a patient before, during, and after surgery either helps or hinders recovery, and evidence should guide every decision.

ERAS protocols typically encompass 20-25 individual elements across preoperative, intraoperative, and postoperative phases. Preoperatively, key elements include patient education and counselling, carbohydrate loading (clear fluids with maltodextrin up to 2 hours before anaesthesia), avoidance of prolonged fasting, and thromboprophylaxis. Intraoperatively, the protocol emphasises goal-directed fluid therapy (avoiding both hypovolaemia and fluid overload), multimodal analgesia avoiding excessive opioids, maintenance of normothermia, and minimally invasive surgical approaches when feasible. Postoperatively, early oral feeding (within 4-6 hours), early mobilisation (out of bed on the day of surgery), early removal of drains and catheters, and multimodal nausea prophylaxis are prioritised.

The evidence supporting ERAS is robust. Meta-analyses consistently demonstrate a 30-50% reduction in length of hospital stay, 40% reduction in overall complications, and significant reductions in readmission rates without increasing mortality. Critically, compliance matters: the benefits of ERAS

are dose-dependent, with significant improvements observed only when overall protocol compliance exceeds 70%. This means that implementing two or three elements in isolation is insufficient — the power lies in the cumulative effect of the entire pathway. Audit and feedback systems are essential for maintaining compliance over time.

> 💡 **KEY ERAS COMPONENTS**
>
> Preoperative: Patient education · Carbohydrate loading · No prolonged fasting · No bowel prep (colorectal) · Thromboprophylaxis
>
> Intraoperative: Goal-directed fluids · Multimodal analgesia (TAP/epidural) · Normothermia · MIS when feasible · Avoid drains/NGT
>
> Postoperative: Early oral feeding (4-6h) · Mobilisation day 0 · Remove catheter day 1 · Multimodal antiemesis · Audit compliance >70%

Kehlet H. Lancet 1997 | Ljungqvist O. Lancet 2019 | ERAS Society Guidelines 2024 | Gustafsson UO. World J Surg 2019

1.5. TNM Staging — AJCC 8th Edition

AJCC Cancer Staging Manual 8th Edition 2017 | UICC TNM 8th

The TNM classification system is the universal language of cancer staging, providing a standardised framework for describing anatomical disease extent that determines prognosis and guides treatment. T describes the size and local extent of the primary tumour, N indicates the presence and extent of regional lymph node metastases, and M denotes distant metastatic disease. The AJCC 8th edition (effective January 2018) introduced several important changes that the surgical oncologist must understand to correctly stage patients and make treatment decisions.

Staging prefixes provide critical context. The "c" prefix (cTNM) indicates clinical staging based on imaging and physical examination before treatment. The "p" prefix (pTNM) indicates pathological staging after surgical resection. The "yc" and "yp" prefixes indicate staging after neoadjuvant therapy (clinical and pathological, respectively). These distinctions are essential because they define different patient populations with different prognoses — a ypT0N0 after neoadjuvant chemotherapy has a fundamentally different prognosis than a pT0N0 without prior treatment.

Key changes in the AJCC 8th edition that are high-yield for board examinations include: differentiated thyroid cancer raised the age cut-off from 45 to 55 years for stage grouping, dramatically downstaging many patients and reflecting the excellent prognosis of younger patients even with advanced

disease. Melanoma staging now includes M1d for central nervous system metastases as a separate category. Oropharyngeal cancer received a separate staging system for HPV-positive (p16+) tumours, reflecting their fundamentally different biology and superior prognosis compared with HPV-negative disease. Pancreatic cancer redefined resectability criteria with emphasis on vascular involvement.

Change	AJCC 7th	AJCC 8th	Clinical Impact
Thyroid age cut-off	45 years	55 years	Many patients downstaged; reflects better prognosis in young
Melanoma M1 subcategory	M1a-M1c	M1a-M1d (CNS)	Separate CNS category recognises worse prognosis
HPV oropharynx	Single system	Separate p16+ staging	HPV+ downstaged; reflects superior biology/outcomes
Pancreas resectability	Anatomic only	Vascular contact criteria	Standardised borderline resectable definition

> ⚠ **WARNING: COMMON STAGING ERRORS**
>
> Confusing clinical (cTNM) and pathological (pTNM) staging when reporting to tumour boards — these are different systems with different stage groupings.
>
> Forgetting "yp" prefix after neoadjuvant therapy: a ypT0 is NOT the same as pT0. The neoadjuvant context completely changes prognosis.
>
> Using the old 45-year cut-off for thyroid cancer staging instead of the current 55-year threshold.

AJCC Cancer Staging Manual 8th Ed 2017 | Amin MB. CA Cancer J Clin 2017 | Brierley JD. UICC TNM 8th Ed 2017

1.6. General Surgical Oncology Workup

NCCN Framework | Multidisciplinary Tumour Board Principles

The systematic approach to a new cancer diagnosis follows a structured pathway from initial presentation through definitive treatment. Every patient should be discussed in a multidisciplinary tumour board (MDT) where surgeons, medical oncologists, radiation oncologists, pathologists, and radiologists collaboratively determine the optimal treatment strategy. The following algorithm outlines the general workup

applicable across tumour types, adapted to NCCN staging and treatment frameworks.

💡 **NCCN GENERAL SURGICAL ONCOLOGY WORKUP**

Presentation → History, physical exam, imaging (CT/MRI/PET as indicated). Identify primary tumour site.

Tissue Diagnosis → CNB preferred (architecture + molecular). FNAC for thyroid/LN only. Align biopsy with definitive incision (sarcoma rule).

Staging → Complete TNM (AJCC 8th). Appropriate prefixes (c/p/yp). Site-specific imaging and biomarkers.

MDT Discussion → Multidisciplinary tumour board review. Define intent (curative vs palliative). Assess resectability.

Neoadjuvant? → If indicated: CRT (oesophageal/rectal), FLOT (gastric), chemo (breast/sarcoma). Restage after completion.

Surgery → R0 resection goal. ERAS protocol. Adequate lymphadenectomy. Specimen orientation for pathology.

Pathology → Definitive pTNM. Margin status (R-classification). Molecular profiling. Node count adequacy.

Adjuvant Therapy → Based on final pathology: chemotherapy, RT, immunotherapy, targeted therapy as

> indicated per NCCN.
>
> **Surveillance** → Site-specific follow-up schedule. Imaging, labs, clinical exam per NCCN guidelines.

NCCN Clinical Practice Guidelines 2024 | ESMO Clinical Practice Guidelines 2024

Board Review: High-Yield Pearls

💡 **MUST-KNOW FACTS**

R0 is the goal of curative surgery. Frozen section is the intraoperative tool to achieve it.

Breast margins: "no tumour on ink" is sufficient after whole-breast RT (SSO-ASTRO 2014).

Sarcoma biopsy rule: biopsy tract MUST align with planned definitive resection incision.

Z0011: No ALND for T1-T2 breast cancer with 1-2 positive SLNs and planned whole-breast RT.

MSLT-II: CLND does not improve melanoma-specific survival after positive SLNB.

TME reduced rectal cancer local recurrence from 30-40% to <5%.

ERAS benefits are dose-dependent: compliance must exceed 70% for meaningful improvement.

AJCC 8th: Thyroid age cut-off now 55yr. Melanoma M1d = CNS. HPV+ oropharynx has separate staging.

⚠ ERRORS TO AVOID

Transverse biopsy in extremity sarcoma → compartment contamination → potential amputation.

ALND for all SLN-positive breast cancer patients without considering Z0011 criteria.

Confusing cTNM with pTNM when reporting staging. Forgetting "yp" prefix after neoadjuvant therapy.

Implementing isolated ERAS elements without protocol-level compliance tracking.

Not sending frozen sections when margin adequacy is uncertain during oncological resection.

Module 2

Surgical Oncology

Esophagogastric

Section II — Upper Gastrointestinal Tumours

2.1. Oesophageal Cancer

NCCN Esophageal v4.2024 | ESMO 2023

Oesophageal cancer presents as two distinct entities with different epidemiology, biology, and treatment implications. Squamous cell carcinoma (SCC) predominates in the upper and middle thirds of the oesophagus and is strongly associated with alcohol consumption and tobacco use. Adenocarcinoma, by contrast, arises in the lower third and gastro-oesophageal junction (GOJ), typically in the setting of chronic gastro-oesophageal reflux disease (GORD) and Barrett oesophagus. This distinction matters because SCC shows higher pathological complete response rates to chemoradiotherapy (49% in the CROSS trial) compared with adenocarcinoma (23%).

Staging is critical and must include endoscopic ultrasound (EUS) for T and N assessment, and PET-CT for detection of distant metastases. EUS is mandatory: it provides the most accurate locoregional staging and directly influences the decision between upfront surgery and neoadjuvant therapy. PET-CT changes management in 10-20% of patients by detecting occult distant disease not seen on CT alone.

2.1.1. NCCN Algorithm by Stage

> 💡 **NCCN OESOPHAGEAL CANCER**
>
> **Tis / T1a N0** → Endoscopic mucosal resection (EMR). Surveillance.
>
> **T1b N0** → Oesophagectomy. No neoadjuvant needed.
>
> **T2 N0** → Oesophagectomy (preferred) OR neoadjuvant CRT then surgery.
>
> **T3-T4a / N+** → Neoadjuvant CRT (CROSS protocol) then oesophagectomy.
>
> **T4b / M1** → Palliative systemic therapy. Stenting for dysphagia.

2.1.2. The CROSS Protocol and Beyond

The CROSS trial (van Hagen, NEJM 2012) established neoadjuvant chemoradiotherapy as the standard of care for locally advanced oesophageal cancer (cT3+ or N+). The regimen consists of weekly carboplatin and paclitaxel with concurrent 41.4 Gy radiation over 5 weeks, followed by surgery. Median overall survival was 49 months in the CRT arm versus 24 months with surgery alone, a landmark result that transformed clinical practice worldwide.

More recently, CheckMate-577 (Kelly, NEJM 2021) addressed the question of adjuvant therapy after neoadjuvant CRT plus surgery in patients with residual disease (non-pCR). Adjuvant nivolumab for one year doubled disease-free

survival (22.4 vs 11.0 months, HR 0.69), establishing a new standard for patients who do not achieve complete pathological response after CROSS.

> 💡 **EVIDENCE SPOTLIGHT**
>
> CROSS: OS 49 vs 24 months. pCR 29% overall (SCC 49%, adenoca 23%).
>
> CheckMate-577: DFS 22.4 vs 11.0 months (HR 0.69). Adjuvant nivo x1yr if residual disease.
>
> KEYNOTE-590: pembro + chemo 1L advanced. OS HR 0.73. Especially SCC.

2.1.3. Surgical Approaches

The choice of surgical approach depends primarily on tumour location. For middle and lower third adenocarcinomas, the Ivor Lewis procedure (laparotomy plus right thoracotomy with intrathoracic anastomosis) is the most commonly performed. For upper and middle third SCC, the McKeown three-field approach with cervical anastomosis provides better proximal margins. The transhiatal approach avoids thoracotomy and is preferred for GOJ tumours in patients with significant pulmonary comorbidity. Minimally invasive oesophagectomy (MIE) has equivalent oncological outcomes with reduced short-term morbidity.

> ⚠️ **PITFALL**
>
> Omitting EUS in staging: understages T and N. EUS is MANDATORY before treatment planning.
>
> Operating without PET-CT: misses 10-20% of occult distant metastases.

van Hagen P. NEJM 2012 | Kelly RJ. NEJM 2021 | Sun JM. Lancet 2021 | NCCN Esophageal v4.2024

2.2. Gastric Cancer

NCCN Gastric v3.2024 | ESMO Gastric 2022 | JGCA 6th Ed.

Gastric cancer remains one of the most common and lethal malignancies worldwide, with marked geographic variation. The Lauren classification divides gastric cancer into two main histological types with distinct clinical implications. The intestinal type is well-differentiated with glandular architecture, tends to be associated with Helicobacter pylori infection and intestinal metaplasia, and carries a relatively better prognosis. The diffuse type, characterised by signet ring cells and poor cohesion, tends to present as linitis plastica with peritoneal dissemination and carries a significantly worse prognosis.

For tumours at the gastro-oesophageal junction (GOJ), the Siewert classification guides the surgical approach: Type I (epicentre 1-5 cm above GOJ) is treated as oesophageal cancer, Type III (epicentre 2-5 cm below GOJ) is treated as gastric cancer, and Type II (epicentre within 1 cm above to 2 cm below) can be approached either way depending on the extent of oesophageal involvement.

2.2.1. NCCN Algorithm by Stage

> 💡 **NCCN GASTRIC CANCER**
>
> **T1a N0** → ESD if: well-differentiated, <2 cm, no ulceration, no LVI. Otherwise surgery.
>
> **T1b-T2 N0** → Gastrectomy (subtotal preferred) + D2 lymphadenectomy. No neoadjuvant.
>
> **T2 N+ / T3-T4** → Diagnostic laparoscopy FIRST. Then perioperative FLOT (4 pre + 4 post) + D2 gastrectomy.
>
> **Metastatic HER2+** → Trastuzumab + chemotherapy (based on ToGA). Test PD-L1 CPS.
>
> **Metastatic HER2-** → FOLFOX/CAPOX + nivolumab if CPS >= 5 (CheckMate-649). MSI-H: pembrolizumab.

2.2.2. Perioperative Chemotherapy: The FLOT Standard

The FLOT4 trial (Al-Batran, Lancet 2019) definitively established perioperative FLOT (5-fluorouracil, leucovorin, oxaliplatin, and docetaxel) as the new standard for resectable locally advanced gastric cancer, replacing the older ECF/ECX regimens. The regimen consists of 4 cycles before and 4 cycles after surgery. FLOT4 demonstrated superior overall survival (50 vs 35 months) and a higher pathological complete response rate (16% vs 6%) compared with ECF/ECX. This trial changed global practice and FLOT is now recommended by both ESMO and NCCN.

2.2.3. Mandatory Molecular Testing

Three biomarkers must be tested in every patient with gastric or GOJ adenocarcinoma before initiating treatment. This is not optional: each test directly determines treatment eligibility for targeted or immune therapies that significantly improve outcomes.

> 💡 **TEST BEFORE TREATMENT**
>
> HER2 (IHC + FISH if 2+): mandatory ALL gastric/GOJ adenocarcinoma. HER2+ = trastuzumab eligible (ToGA: OS 13.8 vs 11.1 months).
>
> MSI / dMMR: mandatory ALL gastric cancers. MSI-H = better prognosis, excellent immunotherapy response. May avoid chemotherapy in some settings.
>
> PD-L1 CPS: determines nivolumab eligibility in first-line metastatic (CheckMate-649: benefit if CPS >= 5, OS HR 0.71).

2.2.4. D2 Lymphadenectomy

D2 lymphadenectomy is the standard of care for curative gastric cancer surgery. It encompasses the perigastric nodes (stations 1-6, which constitute a D1 dissection) plus nodes along the named arterial trunks: left gastric artery, common hepatic artery, coeliac trunk, splenic hilum, and splenic artery (stations 7-12). The Dutch D2 trial (Songun, Lancet Oncol 2010), with 15-year follow-up, demonstrated that D2 significantly reduces cancer-related mortality compared with D1 (HR 0.75). The AJCC 8th edition requires a minimum of 16 nodes for adequate staging, though 25 or more are recommended for optimal prognostic accuracy.

2.2.5. Diagnostic Laparoscopy

Diagnostic laparoscopy is mandatory in all patients with locally advanced gastric cancer (cT3-T4 or N+) before initiating neoadjuvant chemotherapy. Occult peritoneal carcinomatosis, invisible on cross-sectional imaging, is found in 20-30% of these patients. Without laparoscopy, these patients undergo weeks of futile neoadjuvant chemotherapy followed by an unnecessary laparotomy. A simple 30-minute laparoscopic assessment with peritoneal washings for cytology can prevent this and redirect the patient to appropriate palliative systemic therapy.

> 🎯 **CLINICAL PEARL**
>
> Diagnostic laparoscopy changes management in 20-30% of locally advanced gastric cancer patients. It is the single most impactful staging procedure you can perform before starting FLOT.

⚠️ **PITFALL**

Performing D1 instead of D2 in curative gastric surgery: this understages the patient and removes the survival benefit demonstrated in the Dutch D2 trial.

Not testing HER2 before starting palliative chemotherapy: the patient loses access to trastuzumab, which adds 2.7 months of overall survival.

Skipping diagnostic laparoscopy in cT3-T4/N+ gastric cancer: exposes the patient to futile neoadjuvant chemotherapy and unnecessary laparotomy.

Al-Batran SE. Lancet 2019 | Bang YJ. Lancet 2010 | Janjigian YY. Nature 2021 | Songun I. Lancet Oncol 2010 | NCCN Gastric v3.2024

Board Review: High-Yield Pearls

💡 **MUST-KNOW FACTS**

CROSS: neoadjuvant CRT is the standard for cT3+ oesophageal cancer (OS 49 vs 24 months).

CheckMate-577: adjuvant nivolumab x1 year if residual disease after CROSS + surgery.

FLOT4: perioperative FLOT is the standard for gastric cancer (OS 50 vs 35 months).

D2 lymphadenectomy is mandatory with minimum 16 nodes (25+ recommended).

HER2 + MSI + PD-L1 CPS: all three must be tested in gastric/GOJ adenocarcinoma.

Diagnostic laparoscopy: mandatory for locally advanced gastric before neoadjuvant therapy.

⚠ ERRORS TO AVOID

Omitting EUS in oesophageal cancer staging.

D1 instead of D2 for curative gastric surgery.

Not testing HER2 in gastric/GOJ adenocarcinoma before palliative chemo.

Skipping diagnostic laparoscopy in cT3-T4 or N+ gastric cancer.

Missing MSI/dMMR testing (determines chemo vs immunotherapy strategy).

Module 3

Surgical Oncology

Colorectal and Anal Canal

Section III — Colorectal Tumours

3.1. Colon Cancer

NCCN Colon v2.2024 | ESMO Colon 2023

Colon cancer is the third most common malignancy worldwide and one of the most curable when detected at an early stage. The cornerstone of curative treatment is complete mesocolic excision (CME) with central vascular ligation, which provides a standardised oncological resection analogous to total mesorectal excision in rectal cancer. Adequate lymph node harvest is critical for accurate staging: a minimum of 12 lymph nodes must be examined, and retrieval of fewer nodes is associated with understaging and inferior survival outcomes.

Molecular testing is now mandatory at diagnosis for all stages of colon cancer. Microsatellite instability (MSI) and mismatch repair (MMR) status must be assessed in every patient: MSI-high/dMMR tumours have a favourable prognosis in early stages and respond dramatically to immunotherapy in the metastatic setting (KEYNOTE-177). Before initiating anti-EGFR therapy in metastatic disease, extended RAS (KRAS/NRAS exons 2-4) and BRAF V600E testing is mandatory, as RAS mutations predict resistance to cetuximab and panitumumab. Tumour sidedness (right vs left)

independently predicts prognosis and response to biologics: right-sided tumours have worse prognosis and do not benefit from anti-EGFR therapy regardless of RAS status.

3.1.1. NCCN Algorithm by Stage

> 💡 **NCCN COLON CANCER**
>
> **Stage I (T1-T2 N0)** → Surgery alone (CME). No adjuvant chemotherapy. Surveillance.
>
> **Stage II MSI-H** → Surgery + observation. MSI-H confers excellent prognosis. No benefit from 5-FU adjuvant.
>
> **Stage II MSS (high-risk)** → Surgery + consider adjuvant CAPOX 3m or 5-FU/LV 6m if T4, <12 nodes, LVI, PNI, perforation.
>
> **Stage III** → Surgery + adjuvant CAPOX 3m (low-risk T1-3 N1) or CAPOX 6m / FOLFOX 6m (high-risk T4 or N2). MOSAIC/IDEA.
>
> **Stage IV resectable** → Resection of primary + metastases (simultaneous or staged). Perioperative FOLFOX/CAPOX. Sidedness determines biologic.
>
> **Stage IV unresectable MSS** → FOLFOX/FOLFIRI + biologic (left RAS-wt: anti-EGFR; right or RAS-mut: bevacizumab). BRAF-mut: BEACON (encorafenib+cetux).
>
> **Stage IV MSI-H** → First-line pembrolizumab (KEYNOTE-177: PFS 16.5 vs 8.2m, HR 0.60). Superior to

chemotherapy.

3.1.2. Adjuvant Chemotherapy: MOSAIC and IDEA

The MOSAIC trial (Andre, NEJM 2004) established FOLFOX as the adjuvant standard for stage III colon cancer, demonstrating a significant improvement in disease-free survival with the addition of oxaliplatin to 5-FU/LV. The subsequent IDEA collaboration, a prospective pooled analysis of six randomised trials with over 12,000 patients, addressed the optimal duration of adjuvant oxaliplatin-based therapy. For low-risk stage III (T1-3 N1), 3 months of CAPOX was non-inferior to 6 months, with significantly less neurotoxicity. For high-risk stage III (T4 or N2), 6 months remains the standard, though CAPOX 3 months is an acceptable alternative for patients intolerant of prolonged oxaliplatin exposure.

💡 **EVIDENCE SPOTLIGHT**

MOSAIC: FOLFOX adjuvant stage III. DFS HR 0.78. Established oxaliplatin-based adjuvant standard.

IDEA: low-risk stage III (T1-3 N1) → CAPOX 3 months non-inferior. High-risk (T4/N2) → 6 months standard.

KEYNOTE-177: first-line pembrolizumab in MSI-H mCRC. PFS 16.5 vs 8.2 months (HR 0.60).

BEACON-CRC: encorafenib + cetuximab in BRAF V600E mCRC. OS 9.3 vs 5.9 months.

⚠️ **PITFALL**

Not testing MSI/dMMR at diagnosis: this is mandatory for ALL stages. MSI-H stage II patients should NOT receive 5-FU adjuvant (no benefit, possible harm).

Administering anti-EGFR without RAS/BRAF testing or in right-sided tumours: no benefit and potential toxicity.

Harvesting fewer than 12 lymph nodes: leads to understaging and potentially undertreating stage III patients.

Andre T. NEJM 2004 (MOSAIC) | Grothey A. NEJM 2018 (IDEA) | Andre T. NEJM 2020 (KN-177) | Kopetz S. NEJM 2019 (BEACON) | NCCN Colon v2.2024

3.2. Rectal Cancer

NCCN Rectal v1.2024 | ESMO Rectal 2023

Rectal cancer management has evolved dramatically over the past decade with the advent of total neoadjuvant therapy (TNT) and organ-preserving strategies. Total mesorectal excision (TME) remains the oncological gold standard for surgical resection, providing sharp dissection along embryological planes to achieve a complete mesorectal envelope with negative circumferential resection margins

(CRM). MRI pelvis is mandatory for all rectal cancers to assess T stage, N status, CRM involvement, extramural vascular invasion (EMVI), and relationship to the peritoneal reflection. High-resolution MRI directly determines the treatment strategy and is not optional.

Total neoadjuvant therapy (TNT) consolidates all systemic chemotherapy and radiation before surgery, improving compliance, increasing pathological complete response (pCR) rates, and enabling organ preservation in complete responders. The RAPIDO trial demonstrated that short-course radiotherapy (5x5 Gy) followed by 6 cycles of CAPOX achieved a pCR rate of 28% and significantly reduced distant metastasis rates. Similarly, the PRODIGE-23 trial showed that induction mFOLFIRINOX followed by chemoradiotherapy achieved a pCR rate of 28% with improved disease-free survival. For patients achieving clinical complete response (cCR) after TNT, watch-and-wait with strict surveillance is an established alternative to immediate surgery.

3.2.1. NCCN Algorithm by Stage

> 💡 **NCCN RECTAL CANCER**
>
> **cT1-2 N0** → TME surgery alone (or local excision if T1 sm1, well-diff, <3 cm, no LVI). No neoadjuvant.
>
> **cT3 N0** → Neoadjuvant CRT (50.4 Gy + capecitabine) OR TNT (5x5 Gy + CAPOX). Then TME.
>
> **cT3-4 N+** → TNT: RAPIDO (5x5 Gy + CAPOX x6) or PRODIGE-23 (mFOLFIRINOX x6 + CRT). Then TME or W&W if cCR.
>
> **cCR after TNT** → Watch-and-wait: DRE + MRI + endoscopy q3-6 months. Salvage surgery if regrowth. Organ preservation in 40-50%.

3.2.2. Total Neoadjuvant Therapy: RAPIDO and PRODIGE-23

The RAPIDO trial (Bahadoer, Lancet Oncol 2021) randomised patients with locally advanced rectal cancer to either short-course radiotherapy (5x5 Gy) followed by 6 cycles of CAPOX then TME, or standard long-course chemoradiotherapy followed by TME and optional adjuvant chemotherapy. The TNT arm achieved a pCR of 28% versus 14% in the standard arm, and significantly reduced disease-related treatment failure at 3 years (23.7% vs 30.4%). The key advantage of RAPIDO is the delivery of full systemic chemotherapy before surgery, when patient compliance and tolerance are highest.

The PRODIGE-23 trial (Conroy, NEJM 2021) used a complementary approach: induction mFOLFIRINOX for 6 cycles, followed by long-course chemoradiotherapy (50.4 Gy + capecitabine), then TME. This arm achieved a pCR of 28% versus 12% in the standard arm and demonstrated superior 3-year disease-free survival (76% vs 69%, HR 0.69). Both RAPIDO and PRODIGE-23 have fundamentally changed the treatment paradigm for locally advanced rectal cancer, making TNT the preferred approach in most centres.

> 💡 **EVIDENCE SPOTLIGHT**
>
> RAPIDO: 5x5 Gy + CAPOX x6 then TME. pCR 28%. Reduced distant metastasis.
>
> PRODIGE-23: mFOLFIRINOX x6 + CRT then TME. pCR 28%. DFS HR 0.69.
>
> Watch-and-wait: organ preservation in 40-50% of cCR patients. Salvage TME for regrowth maintains oncological outcomes.

⚠️ **PITFALL**

Not performing pelvic MRI: CRM status and EMVI are invisible on CT. MRI is MANDATORY for all rectal cancers.

TME with positive CRM (>1 mm margin required): the strongest predictor of local recurrence.

Offering watch-and-wait without strict surveillance protocol: requires DRE, MRI, and endoscopy every 3-6 months.

Bahadoer RR. Lancet Oncol 2021 (RAPIDO) | Conroy T. NEJM 2021 (PRODIGE-23) | Habr-Gama A. Dis Colon Rectum 2014 | NCCN Rectal v1.2024

3.3. Anal Canal Squamous Cell Carcinoma

NCCN Anal v2.2024 | ESMO Anal 2021

Squamous cell carcinoma (SCC) of the anal canal is an HPV-associated malignancy in approximately 90% of cases, with HPV-16 being the predominant serotype. Unlike most gastrointestinal malignancies, the primary treatment is definitive concurrent chemoradiotherapy (CRT), not surgery. The Nigro protocol, first described in 1974, combined 5-fluorouracil, mitomycin C, and radiation, and remains the

foundation of current treatment. This approach achieves complete response rates of 80-90%, with sphincter and organ preservation being the primary advantage over abdominoperineal resection (APR).

Response assessment timing is critical: the ACT II trial demonstrated that tumour regression continues for several weeks after completing CRT. The NCCN recommends formal response evaluation at 8-12 weeks post-treatment, not earlier. Premature assessment leads to unnecessary biopsies and potentially inappropriate salvage surgery for tumours that would have achieved complete response with time. Only true persistent or recurrent disease after adequate observation should be considered for salvage APR, which is the only surgical option in this setting.

3.3.1. NCCN Algorithm

> 💡 **NCCN ANAL CANAL SCC**
>
> **Localized (T1-2 N0)** → Definitive CRT: 5-FU + mitomycin C + 45-54 Gy (dose based on T stage). CR 80-90%.
>
> **Locally advanced (T3-4 / N+)** → Definitive CRT: 5-FU + MMC + 54 Gy with boost to involved nodes. Extended field radiation.
>
> **Persistent / recurrent** → Re-biopsy at 8-12 weeks. If persistent: salvage APR. If recurrent after CR: salvage APR + inguinal dissection if needed.

3.3.2. The ACT Trials and Current Standard

The ACT I trial (UKCCCR, Lancet 1996) demonstrated the superiority of combined chemoradiotherapy over radiotherapy alone for anal canal SCC, establishing concurrent 5-FU and mitomycin C with radiation as the standard of care. The subsequent ACT II trial (James, Lancet 2013) addressed two important questions: whether cisplatin could replace mitomycin C (it could not, with equivalent outcomes but greater toxicity), and whether adjuvant chemotherapy after CRT improves outcomes (it does not). Thus, the current standard remains definitive CRT with 5-FU and mitomycin C without maintenance chemotherapy.

🎯 **CLINICAL PEARL**

HPV-associated anal SCC has better prognosis and higher response rates to CRT. Always document HPV status (p16 IHC).

Response evaluation MUST be at 8-12 weeks post-CRT, not earlier. Premature biopsy leads to unnecessary salvage APR.

⚠️ **PITFALL**

Performing primary APR for anal SCC: surgery is NOT the first-line treatment. CRT achieves cure in 80-90% with organ preservation.

Assessing response before 8 weeks: tumour regression is ongoing. Early biopsy gives false-positive residual disease.

UKCCCR. Lancet 1996 (ACT I) | James RD. Lancet 2013 (ACT II) | Rao S. Lancet Oncol 2024 | NCCN Anal v2.2024

Board Review: High-Yield Pearls

💡 **MUST-KNOW FACTS**

CME with minimum 12 lymph nodes is the standard for colon cancer surgery.

MSI/dMMR testing is mandatory for ALL stages of colon cancer. MSI-H stage II: no 5-FU benefit.

RAS + BRAF mandatory before anti-EGFR. Sidedness matters: right-sided tumours do not benefit from anti-EGFR.

MOSAIC: FOLFOX adjuvant standard for stage III (DFS HR 0.78).

KEYNOTE-177: first-line pembrolizumab for MSI-H metastatic CRC (PFS 16.5 vs 8.2m).

TME with negative CRM is the oncological standard for rectal cancer surgery.

TNT (RAPIDO or PRODIGE-23) is the preferred approach for locally advanced rectal cancer. pCR 28%.

Watch-and-wait after cCR: organ preservation in 40-50%. Requires strict surveillance.

Anal canal SCC: definitive CRT (5-FU + MMC + 45-54 Gy). CR 80-90%. Surgery only for salvage.

> Response assessment for anal SCC at 8-12 weeks post-CRT, not earlier.

> ⚠️ **ERRORS TO AVOID**
>
> Not testing MSI/dMMR at colon cancer diagnosis (affects adjuvant and metastatic therapy decisions).
>
> Harvesting fewer than 12 nodes in colon cancer (understaging).
>
> Anti-EGFR in right-sided or RAS-mutant colon cancer (no benefit).
>
> Omitting pelvic MRI in rectal cancer (CRM and EMVI invisible on CT).
>
> Primary APR for anal canal SCC instead of definitive CRT.
>
> Assessing anal SCC response before 8 weeks (false-positive residual disease).

Module 4

Surgical Oncology

Peritoneal and Appendiceal

Section IV — Peritoneal Surface Malignancies

4.1. CRC Peritoneal Metastases

NCCN Colon v2.2024 | Verwaal 2003 | PRODIGE-7 2021

Peritoneal metastases from colorectal cancer (CRC) occur in approximately 10-15% of patients at initial presentation and represent a particularly aggressive pattern of disease dissemination. The combination of cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) has transformed the management of selected patients with limited peritoneal disease from a uniformly fatal condition to one with potential for long-term survival. Patient selection is paramount and relies heavily on the Peritoneal Cancer Index (PCI), a standardised scoring system developed by Sugarbaker that divides the abdomen into 13 regions, each scored 0-3 based on tumour burden, yielding a total score of 0-39.

The completeness of cytoreduction score (CC-score) is the strongest prognostic factor after CRS+HIPEC. CC-0 indicates no visible residual disease, CC-1 indicates residual nodules less than 2.5 mm, CC-2 indicates residual nodules between 2.5 mm and 2.5 cm, and CC-3 indicates residual disease greater than 2.5 cm. Only CC-0 and CC-1 are considered curative

resections. The landmark randomised trial by Verwaal (JCO 2003) demonstrated that CRS+HIPEC with mitomycin C versus systemic 5-FU/leucovorin alone achieved a median overall survival of 22.3 versus 12.6 months, establishing CRS+HIPEC as the standard for selected patients with CRC peritoneal metastases.

The PRODIGE-7 trial (Quenet, Lancet Oncol 2021) challenged the added value of HIPEC itself. This landmark French trial randomised patients undergoing complete CRS to CRS alone versus CRS plus oxaliplatin-based HIPEC. There was NO overall survival benefit from the addition of HIPEC (41.7 vs 41.2 months). This pivotal result shifted the paradigm: it demonstrated that the quality and completeness of cytoreductive surgery, not the HIPEC component, is the primary determinant of outcome. However, mitomycin C-based HIPEC (used in the Verwaal trial) was not tested in PRODIGE-7, and many centres continue to use it.

4.1.1. NCCN Algorithm: CRC Peritoneal Metastases

> 💡 **NCCN CRC PERITONEAL DISEASE**
>
> **Limited PM (PCI <20)** → CRS +/- HIPEC at expert centre. Goal CC-0/CC-1. Perioperative systemic chemotherapy.
>
> **Extensive PM (PCI >20)** → Systemic chemotherapy. CRS+HIPEC NOT recommended. Consider palliative surgery only for obstruction.
>
> **PM + Systemic disease** → Systemic chemotherapy. CRS+HIPEC contraindicated. Multidisciplinary discussion for sequencing.

> 💡 **EVIDENCE SPOTLIGHT**
>
> Verwaal 2003: CRS+HIPEC vs systemic chemo. OS 22.3 vs 12.6 months. Landmark trial establishing CRS+HIPEC.
>
> PRODIGE-7: CRS alone vs CRS+oxaliplatin HIPEC. NO OS benefit from HIPEC (41.7 vs 41.2 mo). Quality of CRS is key.
>
> PCI <20 and CC-0/CC-1 are the two strongest predictors of long-term survival after CRS+HIPEC.

> ⚠️ **PITFALL**
>
> Attempting CRS+HIPEC with PCI >20: complete cytoreduction is unachievable, morbidity is high, and survival is not improved.
>
> Confusing PRODIGE-7 results: oxaliplatin HIPEC showed no benefit, but complete CRS remains the standard for limited peritoneal disease.

Verwaal VJ. JCO 2003 | Quenet F. Lancet Oncol 2021 | Sugarbaker PH. Cancer Treat Res 1996 | NCCN Colon v2.2024

4.2. Ovarian Cancer

NCCN Ovarian v2.2024 | ESMO Ovarian 2023

Epithelial ovarian cancer is the most lethal gynaecological malignancy and the fifth leading cause of cancer death in women. The majority of patients present with advanced disease (FIGO stage III-IV), often with extensive peritoneal carcinomatosis. The standard of care centres on maximal surgical cytoreduction combined with platinum-based chemotherapy. The surgical goal is complete resection of all visible disease (R0), as residual tumour is the single most important prognostic factor.

The debate between primary debulking surgery (PDS) and interval debulking surgery (IDS) after neoadjuvant chemotherapy (NACT) remains central to ovarian cancer management. PDS is preferred when complete cytoreduction is achievable with acceptable morbidity. When the tumour burden is deemed too extensive for upfront complete resection, NACT with 3-4 cycles of carboplatin/paclitaxel followed by IDS is an acceptable alternative. The CHORUS and EORTC-55971 trials showed non-inferiority of NACT-IDS versus PDS, though both trials have been criticised for suboptimal surgical effort in the PDS arm.

The OVHIPEC-1 trial (van Driel, NEJM 2018) demonstrated that the addition of cisplatin-based HIPEC at the time of interval debulking surgery improved overall survival by 12 months (45.7 vs 33.9 months, HR 0.67). This is the only randomised trial showing a survival benefit for HIPEC in ovarian cancer and applies specifically to the IDS setting, not primary debulking.

4.2.1. Landmark Trials

> 💡 **EVIDENCE SPOTLIGHT**
>
> OVHIPEC-1: cisplatin HIPEC at IDS. OS 45.7 vs 33.9 months (HR 0.67). +12 months survival benefit.
>
> LION: Systematic LND in advanced ovarian cancer with NORMAL nodes does NOT improve OS and increases morbidity. Do NOT perform LND if nodes appear normal.
>
> SOLO-1: Olaparib maintenance in BRCA-mutated advanced ovarian cancer after 1L platinum response. PFS HR 0.30. Median PFS 56 vs 13.8 months.
>
> PRIMA/ENGOT-OV26: Niraparib maintenance in all-comers advanced ovarian cancer after 1L platinum response. PFS HR 0.62. Benefit regardless of BRCA status.

4.2.2. BRCA Testing: Mandatory

BRCA1/2 germline and somatic testing is mandatory in ALL patients with epithelial ovarian cancer at diagnosis. This is not optional. BRCA-mutated tumours have increased sensitivity to platinum chemotherapy, higher response rates, and critically, qualify for PARP inhibitor maintenance therapy (olaparib,

niraparib). The SOLO-1 trial demonstrated an unprecedented PFS hazard ratio of 0.30 for olaparib maintenance in BRCA-mutated patients, making this the most impactful targeted therapy in ovarian cancer. Homologous recombination deficiency (HRD) testing should also be performed, as HRD-positive patients also benefit from PARP inhibitors even without BRCA mutations.

> ⚠ **PITFALL**
>
> Not testing BRCA at diagnosis: the patient loses access to PARP inhibitor maintenance, which provides the greatest PFS benefit in ovarian cancer.
>
> Performing systematic lymphadenectomy with clinically normal nodes: the LION trial proved this adds morbidity without survival benefit.

van Driel WJ. NEJM 2018 | Harter P. NEJM 2019 (LION) | Moore K. NEJM 2018 (SOLO-1) | Gonzalez-Martin A. NEJM 2019 (PRIMA) | NCCN Ovarian v2.2024

4.3. Appendiceal Neoplasms

PSOGI 2016 | NCCN Colon v2.2024 | WHO 5th Ed.

Appendiceal neoplasms are rare tumours with a complex classification that has undergone significant revision. The

PSOGI (Peritoneal Surface Oncology Group International) 2016 consensus classification categorises epithelial appendiceal neoplasms into three main groups: low-grade appendiceal mucinous neoplasm (LAMN), high-grade appendiceal mucinous neoplasm (HAMN), and goblet cell adenocarcinoma (GCA, formerly known as goblet cell carcinoid). The management of each subtype differs substantially, and accurate pathological classification is essential for appropriate treatment planning.

Goblet cell adenocarcinoma (GCA) is the most aggressive epithelial appendiceal neoplasm and requires right hemicolectomy at ALL stages, regardless of tumour size or depth of invasion. This is because GCA has a high propensity for lymph node metastases and peritoneal dissemination, behaving more like a colorectal adenocarcinoma than a mucinous neoplasm. Appendectomy alone is insufficient even for early-stage GCA. LAMN confined to the appendix is adequately treated with appendectomy alone if margins are clear (R0), while HAMN requires more aggressive follow-up due to higher recurrence risk.

4.3.1. Appendiceal NET Management by Size

Neuroendocrine tumours (NETs) of the appendix are the most common appendiceal neoplasm, often discovered incidentally after appendectomy for acute appendicitis. Management is

stratified by tumour size, which is the strongest predictor of lymph node metastasis and recurrence.

> 💡 **APPENDICEAL NET BY SIZE**
>
> **<1 cm** → Appendectomy alone is curative. No further surgery. Risk of LN metastasis <2%.
>
> **1-2 cm** → Consider right hemicolectomy if: mesoappendiceal invasion >3mm, positive margins, high grade (G2-G3), or LVI present.
>
> **>2 cm** → Right hemicolectomy mandatory. Risk of LN metastasis >20%. Treat as intermediate-risk NET.

> 🎯 **CLINICAL PEARL**
>
> GCA = right hemicolectomy at ALL stages. This is a common board question. Do not confuse GCA with LAMN (which may be cured by appendectomy alone).
>
> Appendiceal NET <1 cm: appendectomy is curative. No right hemicolectomy needed. Size is the single most important factor.

Carr NJ. Am J Surg Pathol 2016 (PSOGI) | NCCN Colon v2.2024 | WHO Classification 5th Ed. 2019 | Pape UF.

4.4. Pseudomyxoma Peritonei

Sugarbaker 2006 | Chua 2012 | PSOGI 2016

Pseudomyxoma peritonei (PMP) is a clinical syndrome characterised by the progressive accumulation of mucinous ascites and peritoneal mucinous implants, almost always arising from a ruptured appendiceal mucinous neoplasm. PMP is classified histologically as disseminated peritoneal adenomucinosis (DPAM, low grade) or peritoneal mucinous carcinomatosis (PMCA, high grade), with an intermediate category (PMCA-I). This classification has direct prognostic implications: DPAM has a significantly better prognosis than PMCA.

CRS+HIPEC is the standard of care for PMP and represents one of the most successful applications of this combined modality. The goal is complete removal of all mucinous disease from the peritoneal surfaces (CC-0 or CC-1 cytoreduction), followed by intraperitoneal chemotherapy (typically mitomycin C). In expert centres, CRS+HIPEC for PMP achieves remarkable long-term outcomes: 10-year overall survival rates of approximately 63% and 5-year OS rates exceeding 70% for DPAM histology. CC-0/CC-1 resection is

essential, as incomplete cytoreduction is associated with significantly worse outcomes and higher recurrence rates.

> 📌 **KEY POINT**
>
> PMP is curable with CRS+HIPEC. 10-year OS ~63% in expert centres. CC-0/CC-1 is the strongest prognostic factor.
>
> DPAM (low-grade) has much better prognosis than PMCA (high-grade). Histological classification matters.
>
> All patients with PMP should be referred to a specialised peritoneal surface malignancy centre.

> ⚠️ **PITFALL**
>
> Repeated debulking operations without CRS+HIPEC: each operation creates adhesions, reduces the chance of complete cytoreduction, and does not change the natural history of PMP.
>
> Treating PMP with systemic chemotherapy alone: PMP is a surgical disease. Systemic chemotherapy has very limited efficacy for mucinous peritoneal disease.

Sugarbaker PH. Ann Surg 2006 | Chua TC. Ann Surg 2012 | Carr NJ. Am J Surg Pathol 2016 (PSOGI) | Moran B. Colorectal Dis 2017

Board Review: High-Yield Pearls

💡 **MUST-KNOW FACTS**

PCI scoring: Sugarbaker, 13 regions, each 0-3, total 0-39. PCI <20 = CRS+HIPEC candidate.

CC-score: CC-0 (no residual) and CC-1 (<2.5mm) are curative. CC-2/CC-3 are palliative.

Verwaal 2003: CRS+HIPEC OS 22.3 vs 12.6 months for CRC peritoneal metastases.

PRODIGE-7: NO OS benefit from oxaliplatin HIPEC. Quality of CRS is what matters.

OVHIPEC-1: cisplatin HIPEC at IDS adds +12 months OS in ovarian cancer (HR 0.67).

LION: Do NOT perform LND if nodes appear normal in advanced ovarian cancer.

SOLO-1: Olaparib BRCA+ ovarian. PFS HR 0.30. Test BRCA in ALL ovarian cancers.

PRIMA: Niraparib maintenance all-comers ovarian. PFS HR 0.62.

GCA = right hemicolectomy at ALL stages (most common board trap).

Appendiceal NET <1cm: appendectomy alone. 1-2cm: consider RHC if adverse features. >2cm: mandatory RHC.

PMP: CRS+HIPEC is curative (10yr OS 63%). Referral to specialised centre mandatory.

⚠ **ERRORS TO AVOID**

Attempting CRS+HIPEC with PCI >20 in CRC peritoneal metastases.

Not testing BRCA in ovarian cancer patients at diagnosis.

Performing systematic LND with clinically normal nodes in ovarian cancer (LION).

Treating GCA with appendectomy alone (requires right hemicolectomy at ALL stages).

Repeated debulking without definitive CRS+HIPEC for PMP.

Module 5

Surgical Oncology

Sarcoma

Section V — Sarcomas and Soft Tissue Tumours

5.1. Soft Tissue Sarcoma Principles

NCCN Soft Tissue Sarcoma v2.2024 | ESMO-EURACAN 2021

Soft tissue sarcomas (STS) are rare mesenchymal neoplasms comprising over 80 histological subtypes. The cornerstone of curative treatment is wide excision with negative margins (R0 resection). An R1 margin (microscopically positive) is associated with significantly higher local recurrence rates but does not necessarily mandate re-excision if further surgery would result in unacceptable functional loss and adjuvant radiotherapy is administered. The goal is always to achieve a wide R0 resection at the first operation, as re-excision after unplanned excision (the so-called "whoops procedure") results in residual disease in 30-50% of cases and compromises subsequent oncological management.

Histological grading uses the FNCLCC system (Federation Nationale des Centres de Lutte Contre le Cancer), which evaluates three parameters: tumour differentiation (scored 1-3), mitotic count (scored 1-3), and tumour necrosis (scored 0-2). The total score classifies sarcomas as Grade 1 (2-3 points), Grade 2 (4-5 points), or Grade 3 (6-8 points). This grading system is the single most important prognostic factor for

distant metastasis and overall survival in localised STS, and directly determines whether adjuvant therapy should be considered.

Molecular testing is essential for certain subtypes. MDM2 amplification by FISH and CDK4 overexpression by immunohistochemistry are critical for distinguishing well-differentiated liposarcoma (WDLPS) and dedifferentiated liposarcoma (DDLPS) from benign lipomatous tumours and other sarcoma subtypes. This distinction has direct therapeutic implications, as WDLPS/DDLPS are uniquely sensitive to MDM2 and CDK4 inhibitors currently under investigation.

5.1.1. NCCN Algorithm — Localised STS

> 💡 **NCCN SOFT TISSUE SARCOMA — EXTREMITY/TRUNK**
>
> **Low-grade, superficial** → Wide excision R0. No adjuvant therapy. Surveillance.
>
> **High-grade, >5 cm, deep** → Preoperative RT (50 Gy) preferred (OSullivan 2002) then wide excision R0.
>
> **Positive margins (R1)** → Re-excision if feasible. If not: postoperative RT boost.
>
> **Metastatic** → Anthracycline-based (doxorubicin). 2L: trabectedin, gemcitabine/docetaxel, pazopanib.

> 💡 **EVIDENCE SPOTLIGHT**
>
> *OSullivan 2002 (Lancet): Preoperative RT (50 Gy) vs postoperative RT (66 Gy). Equal local control but preop RT has lower late morbidity (fibrosis, joint stiffness). Preop RT is PREFERRED.*
>
> FNCLCC Grade is the strongest predictor of distant metastasis and survival in localised STS.

OSullivan B. Lancet 2002 | Coindre JM. J Clin Oncol 2001 | NCCN STS v2.2024 | ESMO-EURACAN 2021

5.2. Retroperitoneal Sarcoma

NCCN Retroperitoneal Sarcoma v2.2024 | Trans-Atlantic RPS Working Group

Retroperitoneal sarcomas (RPS) are dominated by three histological subtypes: well-differentiated liposarcoma (WDLPS), dedifferentiated liposarcoma (DDLPS), and leiomyosarcoma (LMS). Together these account for approximately 75% of all retroperitoneal sarcomas. Each has a distinct biological behaviour: WDLPS recurs locally but almost never metastasises, DDLPS has both local and distant recurrence potential, and LMS tends to metastasise haematogenously (particularly to the lungs and liver) more than it recurs locally.

The surgical principle for RPS is compartmental resection: en bloc removal of the tumour with all involved and adjacent organs, even if not directly invaded, to achieve complete macroscopic clearance. This approach was championed by the Trans-Atlantic RPS Working Group and has been shown to reduce local recurrence rates compared with simple tumour enucleation. For retroperitoneal liposarcomas, this typically involves nephrectomy, colectomy, and psoas muscle resection as needed.

The STRASS trial (Bonvalot, Lancet Oncol 2020) evaluated neoadjuvant radiotherapy for retroperitoneal sarcoma. In the overall population, neoadjuvant RT did not improve abdominal recurrence-free survival. Critically, in the pre-specified subgroup analysis, WDLPS patients showed absolutely no benefit from

neoadjuvant RT. Currently, neoadjuvant RT is NOT standard for retroperitoneal WDLPS and should be discussed in a multidisciplinary tumour board for other subtypes.

> 💡 **CRITICAL RULE**
>
> NEVER perform a transperitoneal biopsy of a retroperitoneal sarcoma. This seeds the peritoneal cavity and converts a potentially curable disease into peritoneal sarcomatosis. Always use a retroperitoneal (posterior) image-guided core needle biopsy approach.

> 💡 **EVIDENCE SPOTLIGHT**
>
> STRASS trial: No benefit of neoadjuvant RT for retroperitoneal WDLPS. Do NOT irradiate WDLPS.
>
> Compartmental resection reduces local recurrence vs simple tumour excision in RPS.
>
> MDM2/CDK4 testing is mandatory for all retroperitoneal lipomatous tumours.

Bonvalot S. Lancet Oncol 2020 | Gronchi A. Ann Surg 2009 | Trans-Atlantic RPS Working Group 2015 | NCCN RPS v2.2024

5.3. Gastrointestinal Stromal Tumour (GIST)

NCCN GIST v1.2024 | ESMO-EURACAN GIST 2021

Gastrointestinal stromal tumours (GISTs) are the most common mesenchymal tumours of the gastrointestinal tract. They arise from the interstitial cells of Cajal and are driven by activating mutations in KIT (approximately 80%) or PDGFRA (approximately 10%). The mutational status is not merely academic: it directly determines the dose of imatinib and eligibility for alternative targeted therapies. KIT exon 11 mutations (the most common) respond to standard-dose imatinib 400 mg daily. KIT exon 9 mutations require 800 mg daily (NOT 400 mg), as demonstrated in the MetaGIST meta-analysis showing significantly better PFS with the higher dose. This is a critical prescribing point that is frequently tested on board examinations.

The PDGFRA D842V mutation is uniquely resistant to imatinib and all other standard TKIs. The only approved effective therapy is avapritinib, validated in the NAVIGATOR trial (Heinrich, Lancet Oncol 2020), which demonstrated a 91% overall response rate in PDGFRA D842V-mutant GIST. This underscores why mutational analysis must be performed before initiating any systemic therapy: a patient with PDGFRA D842V mutation treated with imatinib will have zero benefit and will lose valuable time while the disease progresses.

Adjuvant imatinib for 3 years is the standard of care for high-risk resected GIST. The Z9001 trial (DeMatteo, Lancet 2009) first demonstrated the benefit of adjuvant imatinib in reducing recurrence, while the SSGXVIII/AIO trial (Joensuu, JAMA 2012) established that 3 years of adjuvant imatinib is superior to 1 year, with improved recurrence-free survival and overall survival. Risk stratification

uses the modified NIH criteria (Joensuu) incorporating tumour size, mitotic rate, location, and rupture status.

5.3.1. NCCN GIST Algorithm

> 💡 **NCCN GIST MANAGEMENT ALGORITHM**
>
> **Localised resectable** → Mutational analysis. Surgery (R0, no LN dissection). Risk-stratify for adjuvant.
>
> **High-risk adjuvant** → Imatinib 3 years (400 mg; 800 mg if exon 9). Z9001 + Joensuu 2012.
>
> **Metastatic 1L** → Imatinib 400 mg (exon 11) or 800 mg (exon 9). PDGFRA D842V: avapritinib.
>
> **Metastatic 2L** → Sunitinib (after imatinib failure/intolerance).
>
> **Metastatic 3L** → Regorafenib (GRID trial).
>
> **Metastatic 4L** → Ripretinib (INVICTUS trial). Clinical trial.

> 📌 **KEY POINT**
>
> KIT exon 9 mutations: imatinib 800 mg daily, NOT 400 mg. This is the most commonly tested prescribing error in board examinations.
>
> PDGFRA D842V: resistant to ALL standard TKIs. Avapritinib is the ONLY effective agent (NAVIGATOR: ORR 91%).
>
> Adjuvant imatinib: 3 years, not 1 year (Joensuu 2012). Only for high-risk GIST.

DeMatteo RP. Lancet 2009 | Joensuu H. JAMA 2012 | Heinrich MC. Lancet Oncol 2020 | MetaGIST. J Clin Oncol 2010 | NCCN GIST v1.2024

5.4. Desmoid Tumour (Aggressive Fibromatosis)

NCCN Soft Tissue Sarcoma v2.2024 | ESMO-EURACAN 2021

Desmoid tumours (aggressive fibromatosis) are locally invasive but non-metastasising monoclonal fibroblastic proliferations. Despite their inability to metastasise, they can cause significant morbidity through local infiltration of vital structures. The critical paradigm shift in desmoid management is that active surveillance is now the recommended first-line approach. Approximately 30% of

desmoid tumours undergo spontaneous regression, and many others remain stable for years. Initiating surgery as a first-line treatment is no longer recommended because surgical resection carries a 40-60% local recurrence rate, often resulting in repeated operations with increasing morbidity.

For patients with progressive or symptomatic desmoid tumours that fail active surveillance, the DeFi trial (Gounder, NEJM 2023) demonstrated that nirogacestat, a gamma-secretase inhibitor, achieved a progression-free survival hazard ratio of 0.29 compared with placebo, with a confirmed objective response rate of 41%. This trial established nirogacestat as the first FDA-approved systemic therapy specifically for desmoid tumours and represents a major advance for patients with unresectable or recurrent disease.

> 🎯 **CLINICAL PEARL**
>
> Active surveillance FIRST for desmoid tumours. Do NOT operate as first-line: 30% regress spontaneously, surgery has 40-60% recurrence.
>
> DeFi trial: nirogacestat PFS HR 0.29, ORR 41%. First approved systemic therapy for desmoid tumours.

Gounder MM. NEJM 2023 | Bonvalot S. Eur J Cancer 2020 | Kasper B. Ann Oncol 2017 | NCCN STS v2.2024

5.5. Bone Sarcomas

NCCN Bone Cancer v2.2024 | ESMO-EURACAN 2021

Osteosarcoma is the most common primary malignant bone tumour, typically affecting adolescents and young adults with a peak incidence around the knee (distal femur, proximal tibia). The standard of care is neoadjuvant chemotherapy with the MAP regimen (high-dose methotrexate, doxorubicin [adriamycin], and cisplatin), followed by wide surgical resection, followed by adjuvant MAP. Pathological response to neoadjuvant chemotherapy (percentage of necrosis) is the most important prognostic factor: greater than 90% necrosis indicates a good response. Despite decades of research, no regimen has been shown to be superior to MAP, and the 5-year survival for localised disease remains approximately 60-70%.

Ewing sarcoma is the second most common bone malignancy in children and young adults. It is defined by EWSR1-FLI1 (or variant) translocations, which are pathognomonic and should be confirmed by FISH or molecular testing in all suspected cases. Treatment follows a chemotherapy-surgery-chemotherapy sandwich: neoadjuvant VDC/IE (vincristine, doxorubicin, cyclophosphamide alternating with ifosfamide and etoposide), followed by surgery or radiotherapy for local control, followed by adjuvant chemotherapy. Ewing sarcoma is highly chemosensitive and radiosensitive, distinguishing it from osteosarcoma.

Chondrosarcoma is the third major primary bone malignancy and is uniquely resistant to both chemotherapy and

radiotherapy. Surgery is the ONLY effective treatment. Wide resection with negative margins is mandatory. For low-grade (Grade 1) central chondrosarcomas of the extremities, extended intralesional curettage may be acceptable. For Grade 2-3 tumours, wide en bloc resection is required. There is no role for systemic chemotherapy or radiotherapy in conventional chondrosarcoma, making surgical planning and execution critical.

Bone Sarcoma	Chemotherapy	Radiosensitive	Key Feature
Osteosarcoma	MAP (MTX + doxo + cisplatin)	No	Necrosis >90% = good response
Ewing sarcoma	VDC/IE	Yes	EWSR1-FLI1 translocation
Chondrosarcoma	None (resistant)	No	Surgery ONLY treatment

⚠️ **PITFALL**

Prescribing chemotherapy for conventional chondrosarcoma: it is completely resistant. Surgery is the ONLY treatment.

Forgetting molecular confirmation (EWSR1-FLI1) in suspected Ewing sarcoma: this translocation is pathognomonic and required for diagnosis.

Marina NM. J Clin Oncol 2016 | Gaspar N. Lancet Oncol 2021 | NCCN Bone Cancer v2.2024 | ESMO-EURACAN 2021

Board Review: High-Yield Pearls

💡 **MUST-KNOW FACTS**

STS: Wide excision R0 is the cornerstone. FNCLCC grade (mitoses + necrosis + differentiation) is the strongest prognostic factor.

Preoperative RT preferred over postoperative RT for extremity STS (OSullivan 2002): lower late morbidity.

Retroperitoneal sarcoma: compartmental resection. NEVER transperitoneal biopsy. STRASS: no benefit neoadj RT for WDLPS.

GIST KIT exon 9: imatinib 800 mg (NOT 400 mg). PDGFRA D842V: avapritinib ONLY (NAVIGATOR: ORR 91%).

GIST adjuvant imatinib: 3 years for high-risk (Z9001 + Joensuu 2012).

Desmoid: active surveillance FIRST (30% regression). Surgery: 40-60% recurrence. DeFi: nirogacestat PFS HR 0.29.

Osteosarcoma: MAP. Ewing: VDC/IE (EWSR1-FLI1). Chondrosarcoma: surgery ONLY (chemo/RT resistant).

⚠️ **ERRORS TO AVOID**

Unplanned excision of STS ("whoops procedure"): residual disease in 30-50% of cases.

Transperitoneal biopsy of retroperitoneal sarcoma: seeds the peritoneal cavity.

Imatinib 400 mg for KIT exon 9 GIST: must be 800 mg.

Treating PDGFRA D842V GIST with imatinib: zero response. Use avapritinib only.

Operating first on desmoid tumours: 40-60% recurrence. Active surveillance is first-line.

Chemotherapy for chondrosarcoma: completely resistant. Surgery only.

Module 6

Surgical Oncology

Breast Cancer

Section VI — Breast Cancer

6.1. Molecular Subtypes

NCCN Breast v4.2024 | St Gallen 2023 | ESMO Breast 2023

Breast cancer is not a single disease but a collection of biologically distinct entities defined by hormone receptor (HR) status, HER2 expression, and proliferation index. Accurate molecular subtyping is the foundation of treatment planning, as it determines systemic therapy, surgical extent, and prognosis. Every newly diagnosed breast cancer must be tested for oestrogen receptor (ER), progesterone receptor (PR), HER2 (IHC and FISH if 2+), and Ki-67 proliferation index before any treatment decision is made.

Subtype	ER	PR	HER2	Ki-67	Prognosis
Luminal A	+	+	–	Low (<14%)	Best
Luminal B (HER2–)	+	+/–	–	High (≥14%)	Intermediate
Luminal B (HER2+)	+	+/–	+	Any	Intermediate
HER2-enriched	–	–	+	High	Poor (improved with anti-HER2)
Triple-negative (TNBC)	–	–	–	High	Worst

Luminal A tumours are characterised by strong ER and PR expression, absence of HER2 overexpression, and low proliferation (Ki-67 below 14%). They represent approximately 40% of all breast cancers and carry the best prognosis with endocrine therapy alone. Luminal B tumours share ER positivity but display higher Ki-67 or HER2 co-expression, necessitating the addition of chemotherapy. HER2-enriched

tumours lack hormone receptors but overexpress HER2, and their prognosis has been dramatically improved by targeted anti-HER2 therapies. Triple-negative breast cancer (TNBC) lacks all three receptors and historically carried the worst prognosis, though immunotherapy and PARP inhibitors have expanded therapeutic options.

Perou CM. Nature 2000 | Goldhirsch A. Ann Oncol 2013 | NCCN Breast v4.2024

6.2. Surgical Management

NCCN Breast v4.2024 | NSABP B-06 | ACOSOG Z0011 | AMAROS

The surgical management of breast cancer has evolved from radical mastectomy to breast-conserving surgery (BCS) as the preferred approach for early-stage disease. The NSABP B-06 trial (Fisher, NEJM 2002) with 20-year follow-up definitively demonstrated that lumpectomy plus whole-breast radiation achieves equivalent overall survival to mastectomy. BCS is now indicated for all patients with a favourable tumour-to-breast ratio who can achieve negative margins and receive adjuvant radiation. Mastectomy remains indicated for multicentric disease, large tumour-to-breast ratio, contraindication to radiation therapy, patient preference, or BRCA carriers opting for risk-reducing surgery.

Sentinel lymph node biopsy (SLNB) has replaced routine axillary lymph node dissection (ALND) for clinically node-negative patients. The landmark ACOSOG Z0011 trial (Giuliano, JAMA 2011) demonstrated that patients with 1-2 positive sentinel lymph nodes undergoing BCS with whole-breast radiation can safely omit ALND with no difference in overall survival or locoregional recurrence at 10-year follow-up. The AMAROS trial (Donker, Lancet Oncol 2014) further showed that axillary radiation therapy provides equivalent regional control to ALND in SLN-

positive patients, with significantly less morbidity including lower rates of lymphoedema.

6.2.1. NCCN Algorithm by Stage

> 💡 **NCCN BREAST CANCER**
>
> **DCIS** → BCS + RT (preferred) OR mastectomy. No SLNB for BCS; SLNB if mastectomy. No systemic therapy.
>
> **Stage I-II (BCS candidate)** → BCS + SLNB + whole-breast RT. If 1-2 SLN+: omit ALND (Z0011). Adjuvant systemic per subtype.
>
> **Stage I-II (mastectomy)** → Mastectomy + SLNB. Consider reconstruction. PMRT if T3/4 or >=4 N+.
>
> **Stage III (LABC)** → Neoadjuvant chemotherapy (per subtype) then surgery + ALND. Assess pathological response.
>
> **Stage IV** → Systemic therapy per subtype. Surgery only for palliation or oligometastatic disease (select cases).

> 🎯 **CLINICAL PEARL**
>
> Z0011 criteria: 1-2 positive SLN + BCS + whole-breast RT + T1-T2 = no ALND. This does NOT apply to mastectomy patients, those receiving neoadjuvant chemotherapy, or patients with 3+ positive SLN.
>
> AMAROS: axillary RT equals ALND for regional control in SLN+ patients, with 50% less lymphoedema.

Fisher B. NEJM 2002 | Giuliano AE. JAMA 2011 | Donker M. Lancet Oncol 2014 | NCCN Breast v4.2024

6.3. HER2-Positive Breast Cancer

NCCN Breast v4.2024 | KATHERINE | DESTINY-Breast03 | CLEOPATRA

HER2-positive breast cancer represents approximately 15-20% of all breast cancers and was historically associated with aggressive behaviour and poor prognosis. The development of targeted anti-HER2 therapies has transformed this subtype into one of the most treatable. The current standard for early-stage HER2+ breast cancer is neoadjuvant chemotherapy with dual HER2 blockade (TCHP: docetaxel, carboplatin, trastuzumab, and pertuzumab) followed by surgery and completion of one year of anti-HER2 therapy.

The KATHERINE trial (von Minckwitz, NEJM 2019) established that patients with residual invasive disease after neoadjuvant therapy should switch to T-DM1 (ado-trastuzumab emtansine) for 14 cycles rather than completing trastuzumab alone. This strategy reduced the risk of recurrence by 50% (invasive DFS HR 0.50), making pathological response assessment after neoadjuvant therapy a critical treatment decision point. Patients achieving pathological complete response (pCR) continue trastuzumab plus or minus pertuzumab.

In the metastatic setting, DESTINY-Breast03 (Cortes, NEJM 2022) revolutionised second-line treatment. Trastuzumab deruxtecan (T-DXd) demonstrated an unprecedented progression-free survival hazard ratio of 0.28 compared with T-DM1 (median PFS 28.8 vs 6.8 months), establishing T-DXd as the new standard after progression on trastuzumab-based first-line therapy. For first-line metastatic HER2+, the CLEOPATRA regimen (pertuzumab + trastuzumab + docetaxel) remains standard, with a median overall survival of 57 months.

> 💡 **EVIDENCE SPOTLIGHT**
>
> KATHERINE: T-DM1 for residual disease after neoadjuvant. iDFS HR 0.50. Switch from trastuzumab if non-pCR.
>
> DESTINY-Breast03: T-DXd vs T-DM1 in 2L metastatic. PFS HR 0.28 (28.8 vs 6.8 months). Practice-changing.
>
> CLEOPATRA: pertuzumab + trastuzumab + docetaxel 1L metastatic. OS 57 months.

von Minckwitz G. NEJM 2019 | Cortes J. NEJM 2022 | Swain SM. NEJM 2015 | NCCN Breast v4.2024

6.4. Triple-Negative Breast Cancer

NCCN Breast v4.2024 | KEYNOTE-522 | CREATE-X | OlympiA

Triple-negative breast cancer (TNBC) accounts for 10-15% of all breast cancers and is defined by the absence of oestrogen receptor, progesterone receptor, and HER2 expression. TNBC is characterised by aggressive biology with higher rates of visceral metastasis, brain involvement, and early recurrence. Historically, cytotoxic chemotherapy was the only systemic option, but the therapeutic landscape has been transformed by immunotherapy and targeted agents.

The KEYNOTE-522 trial (Schmid, NEJM 2022) established pembrolizumab combined with neoadjuvant chemotherapy followed by adjuvant pembrolizumab as the new standard for early-stage TNBC (stage II-III). The addition of pembrolizumab improved event-free survival significantly (EFS HR 0.63), regardless of PD-L1 status, and increased the pathological complete response rate from 51.2% to 64.8%. This trial shifted the paradigm: immunotherapy is now incorporated into the neoadjuvant backbone for all stage II-III TNBC.

For patients with residual disease after neoadjuvant therapy, the CREATE-X trial (Masuda, NEJM 2017) demonstrated that adjuvant capecitabine for 6-8 cycles significantly improves overall survival (OS HR 0.59). In BRCA-mutated TNBC, the OlympiA trial (Tutt, NEJM 2021) showed that adjuvant olaparib for one year reduces the risk of death (OS HR 0.68), establishing PARP inhibition as a standard post-neoadjuvant strategy for BRCA carriers with high-risk disease.

> 💡 **EVIDENCE SPOTLIGHT**
>
> KEYNOTE-522: pembro + neoadjuvant chemo for stage II-III TNBC. EFS HR 0.63. pCR 64.8% vs 51.2%.
>
> CREATE-X: adjuvant capecitabine for residual TNBC after neoadjuvant. OS HR 0.59.
>
> OlympiA: adjuvant olaparib x1yr for BRCA+ high-risk. OS HR 0.68.

> ⚠️ **PITFALL**
>
> Not testing germline BRCA in all TNBC patients: misses candidates for olaparib (OlympiA) and platinum-based chemotherapy.
>
> Omitting pembrolizumab in stage II-III TNBC neoadjuvant: KEYNOTE-522 benefit is independent of PD-L1 status.

Schmid P. NEJM 2022 | Masuda N. NEJM 2017 | Tutt ANJ. NEJM 2021 | NCCN Breast v4.2024

6.5. Hormone Receptor-Positive Breast Cancer

NCCN Breast v4.2024 | TAILORx | monarchE

Hormone receptor-positive (HR+) breast cancer is the most common subtype, representing approximately 70% of all cases. The central therapeutic question in early-stage HR+ disease is whether a patient benefits from the addition of chemotherapy to endocrine therapy. The TAILORx trial (Sparano, NEJM 2018) definitively answered this question using the Oncotype DX 21-gene recurrence score. Patients with a recurrence score of 0-25 derive no meaningful benefit from adding chemotherapy to endocrine therapy and can be safely treated with endocrine therapy alone. This result spares the majority of early-stage HR+/HER2- patients from unnecessary chemotherapy and its associated toxicity.

For high-risk HR+ early breast cancer, the monarchE trial (Johnston, NEJM 2023) demonstrated that the addition of abemaciclib (a CDK4/6 inhibitor) to endocrine therapy for two years significantly improves invasive disease-free survival (iDFS HR 0.664). High-risk was defined as four or more positive axillary nodes, or one to three positive nodes with tumour size 5 cm or larger, or Ki-67 of 20% or higher. This represents the first CDK4/6 inhibitor approved in the adjuvant setting and expands the treatment paradigm beyond endocrine therapy alone for high-risk patients.

> 💡 **KEY CONCEPT**
>
> TAILORx: Oncotype DX recurrence score 0-25 = endocrine therapy alone (no chemotherapy benefit). Score 26-100 = add chemotherapy.
>
> monarchE: abemaciclib x2yr + endocrine for high-risk HR+/HER2- (>=4 N+, or 1-3 N+ with T>=5cm or Ki-67>=20%). iDFS HR 0.664.

Sparano JA. NEJM 2018 | Johnston SRD. NEJM 2023 | NCCN Breast v4.2024

6.6. Hereditary Breast Cancer

NCCN Genetic/Familial High-Risk v3.2024 | ESMO Hereditary 2023

Approximately 5-10% of all breast cancers are hereditary, with BRCA1 and BRCA2 germline mutations accounting for the majority of identifiable cases. BRCA1 carriers have a cumulative lifetime breast cancer risk of 55-72% and an ovarian cancer risk of 39-44%. BRCA2 carriers have a breast cancer risk of 45-69% and an ovarian cancer risk of 11-17%. Genetic testing should be offered to all patients meeting NCCN criteria, including those diagnosed before age 50, with triple-negative histology at any age, with bilateral breast cancer, or with a significant family history of breast and ovarian cancer.

Risk-reducing bilateral mastectomy decreases breast cancer risk by approximately 90-95% in BRCA carriers. Risk-reducing bilateral salpingo-oophorectomy (RRSO) is recommended by age 35-40 for BRCA1 carriers and by age 40-45 for BRCA2 carriers, and reduces ovarian cancer risk by 80% and breast cancer risk by an additional 50% when performed premenopausally. For BRCA carriers who choose surveillance over risk-reducing surgery, annual breast MRI alternating with mammography every six months starting at age 25-30 is recommended.

> 🎯 **CLINICAL PEARL**
>
> Test germline BRCA in ALL TNBC regardless of age or family history: it determines eligibility for olaparib (OlympiA) and platinum-based chemotherapy.
>
> BRCA carriers with breast cancer: offer bilateral mastectomy. Contralateral breast cancer risk is 40-60% at 20 years.

Kuchenbaecker KB. JAMA 2017 | Domchek SM. JAMA 2010 | NCCN Genetic/Familial High-Risk v3.2024

Board Review: High-Yield Pearls

💡 **MUST-KNOW FACTS**

NSABP B-06: BCS + RT = mastectomy in overall survival (20-year follow-up).

Z0011: 1-2 positive SLN + BCS + whole-breast RT = omit ALND. No OS or LRR difference.

KATHERINE: T-DM1 for residual HER2+ disease after neoadjuvant. iDFS HR 0.50.

DESTINY-Breast03: T-DXd vs T-DM1 in 2L metastatic HER2+. PFS HR 0.28.

KEYNOTE-522: pembrolizumab + neoadjuvant chemo for stage II-III TNBC. EFS HR 0.63.

CREATE-X: capecitabine for residual TNBC after neoadjuvant. OS HR 0.59.

OlympiA: olaparib x1yr adjuvant for BRCA+ high-risk. OS HR 0.68.

TAILORx: Oncotype DX 0-25 = endocrine alone. No chemotherapy benefit.

monarchE: abemaciclib x2yr for high-risk HR+/HER2-. iDFS HR 0.664.

⚠ ERRORS TO AVOID

Performing ALND when Z0011 criteria are met (1-2 SLN+, BCS, whole-breast RT).

Not switching to T-DM1 after non-pCR in HER2+ neoadjuvant (KATHERINE).

Omitting germline BRCA testing in TNBC patients regardless of age.

Adding chemotherapy to HR+/HER2- with Oncotype DX score 0-25 (TAILORx).

Omitting pembrolizumab in stage II-III TNBC neoadjuvant regimen.

Module 7

Surgical Oncology

Endocrine Tumours

Section VII — Endocrine Tumours

7.1. Thyroid Cancer

NCCN Thyroid v3.2024 | ATA 2015 Guidelines | ESMO 2022

Thyroid cancer encompasses four major histological subtypes with vastly different biological behaviour. Papillary thyroid carcinoma (PTC) accounts for 80-85% of cases, has excellent prognosis, and frequently harbours BRAF V600E mutations (40-60%). Follicular thyroid carcinoma (FTC) represents 10-15%, tends to spread haematogenously to bone and lung, and is driven by RAS mutations and PAX8-PPARG rearrangements. Medullary thyroid carcinoma (MTC) arises from parafollicular C-cells, produces calcitonin, and carries RET mutations (germline in MEN2, somatic in 50-60% of sporadic cases). Anaplastic thyroid carcinoma (ATC) is one of the most aggressive human malignancies, with a median survival of 3-5 months, and BRAF V600E is found in approximately 40% of cases.

The AJCC 8th edition staging system introduced a critical age threshold of 55 years for differentiated thyroid cancer (DTC). Patients under 55 can only be classified as Stage I (any T, any N, M0) or Stage II (any T, any N, M1). This reflects the outstanding prognosis of DTC in younger patients, where even

nodal metastases do not significantly worsen survival. For patients aged 55 and older, staging follows the standard TNM progression from Stage I through Stage IVB.

7.1.1. Surgical Management

The extent of thyroidectomy depends on tumour size, risk factors, and histological subtype. Total thyroidectomy is indicated for tumours >4 cm, bilateral disease, extrathyroidal extension, clinically apparent nodal metastases, distant metastases, or prior head/neck radiation. Lobectomy (hemithyroidectomy) is appropriate for unifocal PTC 1-4 cm without adverse features. For tumours <1 cm (papillary microcarcinoma) without aggressive features, active surveillance is increasingly accepted as an alternative to surgery based on data from the Kuma Hospital and Memorial Sloan Kettering series.

Radioactive iodine (RAI) ablation with I-131 is administered after total thyroidectomy in intermediate and high-risk DTC to ablate remnant thyroid tissue and treat microscopic residual disease. It is NOT indicated for low-risk PTC. Risk stratification follows the ATA three-tier system: low risk (intrathyroidal DTC without aggressive histology, no vascular invasion, N0 or small-volume N1), intermediate risk (microscopic extrathyroidal extension, N1, aggressive histology, or vascular invasion), and high risk (gross

extrathyroidal extension, incomplete resection, or distant metastases).

7.1.2. NCCN Algorithm: Differentiated Thyroid Cancer

> 💡 **NCCN DTC BY ATA RISK**
>
> **Low Risk** → Lobectomy or total thyroidectomy. NO RAI. TSH suppression to 0.5-2. Surveillance with Tg + US.
>
> **Intermediate Risk** → Total thyroidectomy + central neck dissection. RAI 30-150 mCi. TSH suppression to 0.1-0.5.
>
> **High Risk** → Total thyroidectomy + compartment-oriented neck dissection. RAI 100-200 mCi. TSH <0.1.

> 💡 **NCCN MTC BY STAGE**
>
> **Localized MTC** → Total thyroidectomy + central neck dissection. Calcitonin/CEA baseline. RET testing.
>
> **Regional N+** → Total thyroidectomy + central + lateral neck dissection. No role for RAI. Consider XRT if R1.
>
> **Metastatic MTC** → Systemic: selpercatinib (RET+) or cabozantinib/vandetanib. LIBRETTO-001: ORR 69%.

> 💡 **NCCN ATC**
>
> **Resectable ATC** → Surgery if R0 feasible + adjuvant CRT. BRAF+: dabrafenib/trametinib (ORR 56%).
>
> **Unresectable ATC** → Palliative CRT. Test BRAF V600E (40%). If BRAF+: dabrafenib + trametinib.

7.1.3. Molecular Landscape and Targeted Therapy

Molecular profiling has transformed the management of advanced thyroid cancer. In DTC, BRAF V600E is the most common driver and predicts response to dabrafenib/trametinib (particularly relevant in ATC where ORR is 56%). RAS mutations (NRAS, HRAS, KRAS) are found

in follicular-patterned tumours and are targetable with MEK inhibitors. RET fusions occur in 10-20% of PTC and are targetable with selpercatinib or pralsetinib. In MTC, RET point mutations are the dominant drivers: germline RET mutations define MEN2 syndromes, while somatic RET mutations occur in 50-60% of sporadic MTC. The LIBRETTO-001 trial established selpercatinib as a breakthrough therapy for RET-mutant MTC, achieving an objective response rate of 69% in previously treated patients.

> 💡 **EVIDENCE SPOTLIGHT**
>
> *LIBRETTO-001 (Wirth, NEJM 2020): Selpercatinib in RET-mutant MTC. ORR 69% (previously treated), 73% (treatment-naive). Durable responses.*
>
> ATC + BRAF: Dabrafenib/trametinib ORR 56% in BRAF V600E ATC. Median OS improved from 5 to 14 months.

Haugen BR. Thyroid 2016 (ATA) | Wirth LJ. NEJM 2020 | Subbiah V. NEJM 2018 | NCCN Thyroid v3.2024

7.2. Adrenal Incidentaloma

ESE/ENSAT Guidelines 2016 | NCCN Adrenal v2.2024

An adrenal incidentaloma is an adrenal mass discovered on imaging performed for unrelated indications, found in 4-5% of CT scans. The two critical questions to answer are: is it

functional? and is it malignant? The single most important rule is: ALWAYS rule out phaeochromocytoma FIRST, before any intervention or biopsy, because undiagnosed phaeochromocytoma carries a risk of lethal hypertensive crisis during manipulation. The workup must proceed in a systematic order: phaeochromocytoma first, then cortisol excess, then aldosterone excess (if hypertensive), then imaging characteristics for malignancy.

Biochemical workup: 24-hour urinary fractionated metanephrines or plasma free metanephrines rule out phaeochromocytoma (sensitivity >97%). The 1 mg overnight dexamethasone suppression test (DST) screens for Cushing syndrome: cortisol <1.8 mcg/dL (50 nmol/L) is normal, >5 mcg/dL confirms hypercortisolism. For hypertensive patients, aldosterone-to-renin ratio screens for Conn syndrome. On imaging, unenhanced CT Hounsfield units (HU) <10 is highly specific for lipid-rich adenoma and essentially excludes malignancy. Size >4 cm, HU >20, heterogeneous enhancement, irregular margins, or interval growth all raise suspicion for adrenocortical carcinoma or metastasis.

> 💡 **CRITICAL RULE**
>
> NEVER biopsy or operate on an adrenal mass without first excluding phaeochromocytoma. A biopsy of an undiagnosed phaeo can trigger fatal hypertensive crisis.
>
> Workup order: (1) Phaeochromocytoma (24h metanephrines), (2) Cushing (1mg DST), (3) Conn (ARR if hypertensive), (4) Imaging characterisation.

Feature	Benign Adenoma	Suspicious/Malignant
Size	< 4 cm	> 4 cm
CT density (unenhanced)	< 10 HU (lipid-rich)	> 20 HU
Washout	> 60% absolute washout	< 60% washout
Growth	Stable over 12 months	Interval growth
Management	Surveillance	Adrenalectomy

Fassnacht M. Eur J Endocrinol 2016 (ESE/ENSAT) | NCCN Adrenal v2.2024 | Grumbach MM. Ann Intern Med 2003

7.3. Adrenocortical Carcinoma

NCCN Adrenal v2.2024 | ESMO-EURACAN 2020 | ENSAT

Adrenocortical carcinoma (ACC) is a rare but highly aggressive endocrine malignancy with an incidence of 1-2 per million per year. The Weiss score is the histopathological gold standard for distinguishing benign adrenocortical adenoma from carcinoma: a score of 3 or more out of 9 criteria (high mitotic rate, atypical mitoses, high nuclear grade, low percentage of clear cells, necrosis, diffuse architecture, capsular invasion, sinusoidal invasion, venous invasion) diagnoses ACC. Most ACCs present as large tumours (>6 cm), and approximately 60% are hormonally functional, most commonly producing cortisol or androgens.

Complete surgical resection with en-bloc removal of adjacent structures (kidney, spleen, distal pancreas, liver segment) when involved is the only potentially curative treatment. R0 resection is the strongest prognostic factor. Open adrenalectomy is preferred over laparoscopic for suspected ACC to minimise capsular disruption and tumour spillage. The FIRM-ACT trial (Fassnacht, NEJM 2012) compared etoposide/doxorubicin/cisplatin plus mitotane (EDP-M) versus streptozocin plus mitotane in advanced ACC: EDP-M showed superior response rate (23% vs 9%) and is the standard first-line regimen for advanced disease. Adjuvant mitotane is recommended for high-risk ACC (Ki-67 >10%, R1 resection, stage III) based on retrospective data showing improved recurrence-free survival.

> 💡 **EVIDENCE SPOTLIGHT**
>
> *FIRM-ACT (Fassnacht, NEJM 2012): EDP-M vs streptozocin-M in advanced ACC. ORR 23% vs 9%. EDP-M is the standard 1L regimen.*
>
> Weiss score >= 3 = ACC. En-bloc R0 resection is the single most important prognostic factor.

Fassnacht M. NEJM 2012 | Else T. Endocr Rev 2014 | NCCN Adrenal v2.2024 | Berruti A. JCEM 2005

7.4. Phaeochromocytoma and Paraganglioma

Endocrine Society Guidelines 2014 | NCCN Pheochromocytoma 2024

Phaeochromocytomas are catecholamine-producing tumours arising from chromaffin cells of the adrenal medulla. Paragangliomas arise from extra-adrenal sympathetic (abdominal) or parasympathetic (head and neck) ganglia. The classic presentation includes episodic hypertension, headache, diaphoresis, and palpitations, although many patients present atypically. Approximately 40% of cases have a hereditary basis, involving mutations in SDHx genes (SDHA, SDHB, SDHC, SDHD, SDHAF2), VHL, RET, NF1, MAX, TMEM127, and others. SDHB mutations carry the highest risk of malignant disease (up to 40% lifetime risk of metastatic paraganglioma).

The cardinal surgical principle is: NEVER operate on a phaeochromocytoma without adequate alpha-adrenergic blockade. Preoperative alpha-blockade with phenoxybenzamine (irreversible, non-selective alpha antagonist) or doxazosin (selective alpha-1 antagonist) must be initiated 10-14 days before surgery. Only AFTER alpha-blockade is established should beta-blockade be added if tachycardia persists. Beta-blockade without prior alpha-blockade causes unopposed alpha-receptor stimulation and can precipitate a fatal hypertensive crisis. The target preoperative blood pressure is <130/80 seated with orthostatic hypotension (systolic >90 standing), and patients should be liberally salt- and fluid-loaded.

> 💡 **CRITICAL RULE**
>
> NEVER operate without phaeo workup. NEVER give beta-blockers before alpha-blockade is established.
>
> Alpha-blockade 10-14 days preop: phenoxybenzamine 10 mg BID, titrate to BP <130/80 seated.
>
> SDHB mutation = highest malignancy risk (up to 40%). All patients need germline testing.

Lenders JW. JCEM 2014 | Neumann HP. NEJM 2019 | NCCN Pheochromocytoma 2024 | Eisenhofer G. JCEM 2003

7.5. Pancreatic Neuroendocrine Tumours

NCCN NET v2.2024 | ENETS Guidelines 2023 | WHO 2022

Pancreatic neuroendocrine tumours (pNETs) are categorised by the WHO 2022 classification based on Ki-67 index and mitotic rate: Grade 1 (Ki-67 <3%, mitoses <2/10 HPF), Grade 2 (Ki-67 3-20%, mitoses 2-20/10 HPF), and Grade 3 (Ki-67 >20%, mitoses >20/10 HPF). A critical distinction exists between well-differentiated neuroendocrine tumours (NETs, G1-G3) and poorly differentiated neuroendocrine carcinomas (NECs), which have different biology, molecular drivers, and treatment strategies. NETs are driven by MEN1, DAXX/ATRX, and mTOR pathway alterations, while NECs harbour TP53 and RB1 mutations similar to small-cell carcinoma.

Functional pNETs present with clinical syndromes related to hormone overproduction: insulinoma (hypoglycaemia), gastrinoma (Zollinger-Ellison syndrome with refractory peptic ulcers), glucagonoma (necrolytic migratory erythema, diabetes), VIPoma (watery diarrhoea, hypokalaemia), and somatostatinoma (diabetes, gallstones, steatorrhoea). Non-functional pNETs account for 60-90% of cases and are often diagnosed incidentally or due to mass effect. For localised disease, surgery is curative. For advanced well-differentiated pNETs, somatostatin analogues (SSAs), targeted therapy, and

peptide receptor radionuclide therapy (PRRT) form the backbone of systemic treatment.

7.5.1. NCCN pNET Algorithm

> 💡 **NCCN PANCREATIC NET**
>
> **Localized G1-G2** → Surgical resection (enucleation if <2 cm, distal pancreatectomy, or Whipple). Observe if <1 cm, G1, non-functional.
>
> **Locally Advanced** → SSA (octreotide LAR or lanreotide). Consider resection if downstaged. Everolimus or sunitinib if progressive.
>
> **Metastatic G1-G2** → 1L: SSA (PROMID, CLARINET). 2L: Everolimus (RADIANT-3) or sunitinib. 3L: PRRT Lu-177 (NETTER-1).
>
> **Metastatic G3 NEC** → Platinum-based chemotherapy (cisplatin/etoposide). Treat like small-cell carcinoma. Poor prognosis.

7.5.2. Landmark Trials

> 💡 **EVIDENCE SPOTLIGHT**
>
> PROMID (Rinke, JCO 2009): Octreotide LAR vs placebo in midgut NET. TTP 14.3 vs 6.0 months. Established SSA as antiproliferative.
>
> *CLARINET (Caplin, NEJM 2014): Lanreotide vs placebo in G1-G2 GEP-NET. PFS not reached vs 18 months. Confirmed SSA antiproliferative role.*
>
> *NETTER-1 (Strosberg, NEJM 2017): Lu-177 DOTATATE (PRRT) vs high-dose octreotide in midgut NET. PFS HR 0.18. Landmark result for PRRT.*
>
> *RADIANT-3 (Yao, NEJM 2011): Everolimus vs placebo in progressive pNET. PFS 11.0 vs 4.6 months (HR 0.35).*

Rinke A. JCO 2009 | Caplin ME. NEJM 2014 | Strosberg J. NEJM 2017 | Yao JC. NEJM 2011 | NCCN NET v2.2024

7.6. Multiple Endocrine Neoplasia Syndromes

ATA MTC Guidelines 2015 | NCCN Thyroid 2024 | Expert Consensus

The MEN syndromes are autosomal dominant inherited cancer predisposition syndromes characterised by tumours in multiple endocrine glands. MEN1 is caused by inactivating mutations in the MEN1 gene (menin, chromosome 11q13) and classically presents with the triad of the 3 Ps: parathyroid

hyperplasia (95%, primary hyperparathyroidism), pancreatic neuroendocrine tumours (40-70%, most commonly gastrinoma and insulinoma), and pituitary adenomas (30-40%, most commonly prolactinoma). The penetrance of primary hyperparathyroidism approaches 100% by age 50.

MEN2 is caused by activating mutations in the RET proto-oncogene and is subdivided into MEN2A and MEN2B. MEN2A (95% of MEN2 cases) is characterised by medullary thyroid carcinoma (virtually 100% penetrance), phaeochromocytoma (50%), and primary hyperparathyroidism (20-30%). The most common mutation is at codon 634 (C634R), and prophylactic thyroidectomy is recommended by age 5 years. MEN2B is the most aggressive form, caused by the M918T RET mutation, presenting with MTC (100%, earliest onset and most aggressive), phaeochromocytoma (50%), mucosal neuromas, marfanoid habitus, and intestinal ganglioneuromatosis. Prophylactic thyroidectomy in MEN2B should be performed within the FIRST YEAR of life, ideally within the first 6 months.

Syndrome	Gene	Key Features	Prophylactic Thyroidectomy
MEN1	MEN1 (11q13)	3 Ps: Parathyroid + Pancreatic NET + Pituitary	N/A
MEN2A	RET codon 634	MTC + Phaeo + Hyperparathyroidism	By age 5 years
MEN2B	RET M918T	MTC + Phaeo + Mucosal neuromas + Marfanoid	FIRST YEAR of life

> 🎯 **CLINICAL PEARL**
>
> In MEN2: ALWAYS rule out phaeochromocytoma BEFORE thyroidectomy. Undiagnosed phaeo during thyroidectomy = intraoperative crisis.
>
> MEN2B (M918T): most aggressive MTC. Prophylactic thyroidectomy in FIRST YEAR, ideally <6 months of age.

Wells SA. Thyroid 2015 (ATA MTC) | Thakker RV. JCEM 2012 | Brandi ML. JCEM 2001 | NCCN Thyroid v3.2024

Board Review: High-Yield Pearls

💡 MUST-KNOW FACTS

AJCC 8th thyroid: age <55 can only be Stage I (M0) or Stage II (M1). Even N1 does not upstage.

Total thyroidectomy for DTC >4 cm, bilateral, extrathyroidal extension, N1, or M1. Lobectomy for 1-4 cm unifocal PTC.

LIBRETTO-001: selpercatinib in RET-mutant MTC. ORR 69%. New standard for advanced RET+ MTC.

Adrenal incidentaloma: rule out phaeo FIRST (24h metanephrines). HU <10 = adenoma. >4 cm = surgery.

ACC: Weiss >= 3. En-bloc R0 resection. FIRM-ACT: EDP-M is standard 1L for advanced ACC.

Phaeo: alpha-blockade 10-14 days preop. NEVER beta before alpha. SDHB = malignant risk.

pNET WHO grading: G1 Ki-67<3%, G2 3-20%, G3 >20%. NETTER-1: Lu-177 PFS HR 0.18.

MEN1: 3 Ps (Parathyroid, Pancreas, Pituitary). MEN2A codon 634: thyroidectomy age 5. MEN2B M918T: thyroidectomy FIRST YEAR.

⚠ ERRORS TO AVOID

Operating on adrenal mass without ruling out phaeochromocytoma.

Beta-blockers before alpha-blockade in phaeochromocytoma.

RAI for low-risk PTC (not indicated, ATA 2015).

Not testing RET in all MTC patients (misses hereditary syndromes).

Laparoscopic adrenalectomy for suspected ACC (risk of capsular disruption and spillage).

Thyroidectomy in MEN2 without first excluding phaeochromocytoma.

Module 8

Surgical Oncology

Melanoma and Skin Cancer

Section VIII — Skin Tumours and Melanoma

8.1. Melanoma Subtypes

NCCN Melanoma v2.2024 | AJCC 8th Edition | WHO 2018

Cutaneous melanoma is classified into distinct histopathological subtypes with different clinical behaviour, anatomical distribution, and molecular profiles. Superficial spreading melanoma (SSM) is the most common subtype (approximately 70%), typically arising on intermittently sun-exposed skin, and characterised by a prolonged radial growth phase before vertical invasion. Nodular melanoma (NM) accounts for 15-30% of cases and is the most aggressive subtype, presenting as a rapidly growing elevated or polypoid lesion with early vertical growth phase and no preceding radial growth, which explains its disproportionate contribution to melanoma mortality.

Lentigo maligna melanoma (LMM) occurs on chronically sun-damaged skin of elderly patients, predominantly on the head and neck. It has the longest radial growth phase and the best prognosis when excised adequately. Acral lentiginous melanoma (ALM) is the most common subtype in non-Caucasian populations, arising on palms, soles, and subungual regions. It is frequently diagnosed late due to its location and

may lack typical pigmentation. Desmoplastic melanoma is a rare neurotropic variant characterised by spindle cells in a collagenous stroma, commonly associated with perineural invasion and high local recurrence rates. Desmoplastic melanoma has a lower rate of nodal metastasis but a higher propensity for local recurrence, and adjuvant radiation should be considered for lesions with positive or close margins.

Subtype	Frequency	Key Features	Molecular
SSM	~70%	Radial then vertical growth; ABCDE criteria	BRAF V600E ~50%
Nodular	15-30%	De novo vertical growth; rapid progression	BRAF ~40%
LMM	5-15%	Chronic sun damage; head/neck; elderly	BRAF ~10%, NRAS higher
ALM	2-8%	Palms, soles, subungual; non-Caucasian	KIT mutations ~15-20%
Desmoplastic	1-4%	Neurotropic; spindle cells; high local recurrence	Low BRAF; NF1 common

NCCN Melanoma v2.2024 | WHO Classification of Skin Tumours 2018 | Elder DE. Arch Pathol Lab Med 2020

8.2. AJCC 8th Edition Melanoma Staging

Gershenwald JE. CA Cancer J Clin 2017 | AJCC 8th Ed. 2017

The AJCC 8th edition melanoma staging system, effective since January 2018, introduced several critical changes that directly impact clinical decision-making. The most important conceptual change is that Breslow thickness remains the primary determinant of T category and prognosis. Mitotic rate was removed as a criterion for T1b classification; instead, T1 is now substratified by thickness alone at the 0.8 mm threshold (T1a: <0.8 mm without ulceration; T1b: 0.8-1.0 mm or <0.8 mm with ulceration). This simplification was supported by multivariate analyses showing that ulceration status was a stronger independent predictor than mitotic rate.

Another key change is the addition of M1d for central nervous system (CNS) metastases, recognising their distinct and particularly poor prognosis. The M1 subcategories now include M1a (distant skin, soft tissue, or non-regional lymph nodes), M1b (lung metastases), M1c (non-CNS visceral metastases), and M1d (CNS metastases with or without any other sites of disease). Elevated serum LDH is designated by a suffix (1) after any M1 category and is an independent adverse prognostic factor in stage IV disease.

T Category	Breslow Thickness	Ulceration	Notes
T1a	< 0.8 mm	No	Low risk; SLNB generally not indicated
T1b	0.8-1.0 mm OR < 0.8 mm	Any OR Yes	Consider SLNB; mitotic rate NO longer a criterion
T2	> 1.0-2.0 mm	a: No / b: Yes	SLNB recommended for all T2
T3	> 2.0-4.0 mm	a: No / b: Yes	SLNB recommended
T4	> 4.0 mm	a: No / b: Yes	High risk; consider adjuvant therapy

> 💡 **KEY CHANGE**
>
> Mitotic rate REMOVED from T1b criteria in AJCC 8th edition. T1b is now defined by Breslow >= 0.8 mm OR ulceration in thinner lesions.
>
> New M1d category: CNS metastases now have their own category, reflecting their uniquely poor prognosis.

Gershenwald JE. CA Cancer J Clin 2017 | Amin MB. AJCC Cancer Staging Manual 8th Ed. 2017

8.3. Wide Local Excision Margins (UICC)

NCCN Melanoma v2.2024 | UICC/WHO Guidelines

Wide local excision (WLE) is the definitive treatment for primary melanoma after diagnostic biopsy. Excision margins are determined exclusively by Breslow thickness and have been established through multiple randomised controlled trials. Wider margins do not improve survival but increase morbidity, wound closure complexity, and the need for skin grafts or flaps. The goal is to achieve clear histological margins with the minimum morbidity necessary.

Breslow Thickness	Recommended Margin	Evidence	Notes
In situ	0.5 cm (up to 1 cm)	Consensus	Consider Mohs for head/neck LMM
<= 1.0 mm	1 cm	RCTs: no benefit > 1 cm	WLE at time of SLNB
1.01-2.0 mm	1-2 cm	WHO trial, Swedish trial	1 cm acceptable if anatomically constrained
> 2.0 mm	2 cm	Intergroup, UK MelaST	No survival benefit beyond 2 cm

> 🎯 **CLINICAL PEARL**
>
> For melanoma in situ (especially lentigo maligna) on the head and neck, consider Mohs micrographic surgery or staged excision with margin control, as subclinical extension can be substantial and standard 0.5 cm margins may be inadequate.
>
> WLE should be performed down to but NOT including the deep fascia. Routine fascial excision provides no oncological benefit.

Thomas JM. NEJM 2004 | Gillgren P. Lancet Oncol 2011 | NCCN Melanoma v2.2024 | Hayes AJ. Lancet Oncol 2016

8.4. Sentinel Lymph Node Biopsy

MSLT-I (Morton, NEJM 2014) | MSLT-II (Faries, NEJM 2017) | DeCOG-SLT (Leiter, Lancet Oncol 2016)

Sentinel lymph node biopsy (SLNB) is the most important prognostic procedure in melanoma staging. MSLT-I (Morton, NEJM 2014) established that SLN status is the single strongest predictor of recurrence and survival in clinically node-negative melanoma. The trial demonstrated that SLNB with immediate completion lymph node dissection (CLND) for positive nodes improved 10-year melanoma-specific survival compared with nodal observation alone in intermediate-thickness melanomas (62.1% vs 41.5% in SLN-positive patients). However, the overall survival of the entire randomised population (SLNB vs

observation) was not significantly different, meaning that SLNB provides prognostic information and early regional control, but does not confer an overall survival advantage when analysed on an intention-to-treat basis.

The landmark MSLT-II trial (Faries, NEJM 2017) fundamentally changed practice by demonstrating that completion lymph node dissection (CLND) does NOT improve melanoma-specific survival in patients with a positive sentinel node (HR 1.08, p=0.42). CLND improved regional disease control but at the cost of significantly increased lymphoedema (24.1% vs 6.3%). This means that observation with ultrasound surveillance of the nodal basin is now the standard of care after a positive SLNB. The DeCOG-SLT trial confirmed these findings. CLND is reserved for patients with clinically detected nodal recurrence.

> 💡 **SLNB INDICATIONS**
>
> Breslow > 0.8 mm: SLNB recommended for all patients.
>
> Breslow < 0.8 mm with ulceration: SLNB should be considered.
>
> Breslow < 0.8 mm without ulceration: SLNB generally NOT indicated.
>
> MSLT-II: completion CLND NO survival benefit (HR 1.08). Observation is the standard after positive SLNB.

8.4.1. NCCN Melanoma Algorithm

> 💡 **NCCN CUTANEOUS MELANOMA**
>
> **In situ** → WLE 0.5 cm margins. No SLNB. Surveillance.
>
> **Stage I-II (T1b-T4b, N0)** → WLE (margins by Breslow) + SLNB. If SLN-negative: surveillance. If SLN-positive: observation (NO CLND) + consider adjuvant.
>
> **Stage III (N+)** → Adjuvant: nivolumab, pembrolizumab, or dabrafenib/trametinib (BRAF+). Consider RT for high-risk features.
>
> **Stage III in-transit** → Surgical excision if feasible. T-VEC intralesional. Isolated limb perfusion/infusion. Systemic therapy.
>
> **Stage IV (M1)** → BRAF testing mandatory. BRAF+: targeted therapy OR immunotherapy. BRAF-: nivo+ipi or pembro. CNS mets: consider SRS/surgery.

Morton DL. NEJM 2014 | Faries MB. NEJM 2017 | Leiter U. Lancet Oncol 2016 | NCCN Melanoma v2.2024

8.5. Adjuvant Therapy: Stage III Melanoma

COMBI-AD | KEYNOTE-054 | CheckMate-238

The adjuvant treatment landscape for resected stage III melanoma has been transformed by targeted therapy and immunotherapy. Prior to these agents, interferon-alpha was the only approved adjuvant treatment, with modest and inconsistent benefits. Three landmark trials now define the current standard of care and should be known in detail for board examinations.

COMBI-AD (Long, NEJM 2017) demonstrated that 12 months of adjuvant dabrafenib plus trametinib (dual BRAF/MEK inhibition) significantly improved relapse-free survival in resected BRAF V600E/K-mutant stage III melanoma (HR 0.49 at 3 years). The 5-year relapse-free survival was 52% versus 36% with placebo. This combination is indicated exclusively for BRAF-mutant patients, making BRAF testing mandatory at diagnosis.

KEYNOTE-054 (Eggermont, NEJM 2018) established pembrolizumab as adjuvant immunotherapy for resected stage III melanoma regardless of BRAF status. Pembrolizumab administered for one year significantly improved recurrence-free survival (HR 0.57 at 3.5 years). The benefit was observed across all subgroups including BRAF wild-type patients who are ineligible for targeted therapy.

CheckMate-238 (Weber, NEJM 2017) compared adjuvant nivolumab to ipilimumab in resected stage IIIB-IV melanoma. Nivolumab demonstrated superior recurrence-free survival (HR 0.65) with substantially fewer grade 3-4 adverse events (14.4% vs 45.9% with ipilimumab). This trial established nivolumab as a preferred immunotherapy option and definitively ended the use of adjuvant ipilimumab monotherapy due to its poor toxicity profile.

Trial	Regimen	Population	HR (RFS)	Key Result
COMBI-AD	Dab+Tram x12mo	BRAF+ Stage III	0.49	5yr RFS 52% vs 36%. BRAF+ only.
KEYNOTE-054	Pembro x12mo	Stage III (any BRAF)	0.57	Works regardless of BRAF status.
CheckMate-238	Nivo vs Ipi	Stage IIIB-IV	0.65	Nivo superior; far less toxic than ipi.

> 💡 **EVIDENCE SPOTLIGHT**
>
> BRAF V600 testing is MANDATORY at diagnosis: determines eligibility for dabrafenib/trametinib (COMBI-AD, HR 0.49).
>
> BRAF wild-type patients: pembrolizumab (KEYNOTE-054) or nivolumab (CheckMate-238) are the options.
>
> Interferon-alpha is NO LONGER the standard of care for adjuvant melanoma treatment.

Long GV. NEJM 2017 | Eggermont AMM. NEJM 2018 | Weber J. NEJM 2017 | NCCN Melanoma v2.2024

8.6. Metastatic Melanoma

CheckMate-067 | COMBI-v | KEYNOTE-006 | NCCN v2.2024

The treatment of metastatic melanoma has undergone a revolution with the advent of immune checkpoint inhibitors and BRAF-targeted therapies. BRAF mutation testing is mandatory in all patients with advanced melanoma, as it determines the entire treatment strategy. Approximately 40-50% of cutaneous melanomas harbour BRAF V600 mutations, making them eligible for both targeted therapy and

immunotherapy. BRAF wild-type patients are treated exclusively with immunotherapy.

CheckMate-067 (Larkin/Wolchok, NEJM 2015; 6.5-year update, NEJM 2022) is the definitive immunotherapy trial for advanced melanoma. The combination of nivolumab plus ipilimumab achieved a 5-year overall survival rate of 52%, compared with 44% for nivolumab alone and 26% for ipilimumab alone. The median overall survival for the combination arm exceeded 72 months. However, the combination carries substantial toxicity with grade 3-4 immune-related adverse events in approximately 59% of patients. Single-agent nivolumab showed a favourable toxicity profile with a 5-year OS of 44%, and a formal statistical comparison between nivo+ipi and nivo alone did not reach significance for OS.

For BRAF-mutant melanoma, COMBI-v (Robert, NEJM 2015) established dabrafenib plus trametinib as the standard targeted therapy, demonstrating superior overall survival versus vemurafenib monotherapy (HR 0.69). KEYNOTE-006 (Robert, NEJM 2015) established pembrolizumab as an alternative first-line immunotherapy with superior PFS and OS compared to ipilimumab alone. The choice between targeted therapy and immunotherapy in BRAF-mutant patients remains an active area of investigation; current evidence generally favours immunotherapy first unless rapid response is needed.

Trial	Regimen	5yr OS	Key Finding
CheckMate-067	Nivo+Ipi	52%	Best long-term OS. High toxicity (59% G3-4).
CheckMate-067	Nivo alone	44%	Less toxic; OS not statistically different from combo.
COMBI-v	Dab+Tram	34%	BRAF+ only. HR 0.69 vs vemurafenib.
KEYNOTE-006	Pembro	39%	Superior to ipi. All BRAF subtypes.

⚠️ **PITFALL**

Starting treatment in metastatic melanoma WITHOUT BRAF testing: this is a critical error that may deny the patient access to highly effective targeted therapy.

Using ipilimumab monotherapy as first-line: obsolete after CheckMate-067 and KEYNOTE-006. Nivo+Ipi or single-agent anti-PD1 are the standard.

Larkin J. NEJM 2015 | Wolchok JD. NEJM 2022 | Robert C. NEJM 2015 (COMBI-v) | Robert C. NEJM 2015 (KN-006) | NCCN Melanoma v2.2024

8.7. Non-Melanoma Skin Cancer: BCC, cSCC, MCC

NCCN BCC/SCC v1.2024 | NCCN MCC v1.2024

Basal cell carcinoma (BCC) is the most common human malignancy but rarely metastasises. Surgical excision with 3-4 mm margins achieves cure rates exceeding 95%. For high-risk BCC (aggressive subtypes, perineural invasion, recurrent tumours, critical anatomical locations), Mohs micrographic surgery provides the highest cure rates with maximal tissue conservation. For locally advanced or metastatic BCC not amenable to surgery or radiation, the Hedgehog pathway inhibitor vismodegib (ERIVANCE trial) provides objective response rates of approximately 30-43% in advanced BCC, though adverse effects (muscle spasms, alopecia, dysgeusia) limit tolerability and lead to treatment discontinuation in a significant proportion of patients.

Cutaneous squamous cell carcinoma (cSCC) is the second most common skin cancer. Most are cured by surgical excision, but a subset with high-risk features (diameter > 2 cm, depth > 6 mm, perineural invasion, poor differentiation, immunosuppression) carries significant risk of recurrence and metastasis. EMPOWER-CSCC-1 (Migden, NEJM 2018) established cemiplimab (anti-PD-1) as the first approved systemic therapy for advanced cSCC, demonstrating an overall response rate of 47% in locally advanced disease and 49% in metastatic disease, with durable responses in the majority of responders.

Merkel cell carcinoma (MCC) is a rare but aggressive neuroendocrine skin cancer with a mortality rate exceeding that of melanoma. Approximately 80% of MCC cases are associated with Merkel cell polyomavirus (MCPyV). SLNB is recommended for all clinically node-negative patients, as the SLN positivity rate is

approximately 30%. For metastatic MCC, JAVELIN Merkel 200 (Kaufman, Lancet Oncol 2016) established avelumab (anti-PD-L1) as the first approved therapy, with an overall response rate of 33% in previously treated patients, including complete responses. Pembrolizumab and nivolumab also show activity in MCC.

Cancer	Key Trial	Agent	ORR	Notes
Advanced BCC	ERIVANCE	Vismodegib	30-43%	Hedgehog inhibitor. Toxicity limits use.
Advanced cSCC	EMPOWER-CSCC-1	Cemiplimab	47-49%	Anti-PD-1. First approved for cSCC.
Metastatic MCC	JAVELIN Merkel 200	Avelumab	33%	Anti-PD-L1. Durable responses.

🎯 **CLINICAL PEARL**

MCC has a higher stage-for-stage mortality than melanoma. SLNB is recommended for all clinically node-negative MCC patients. MCPyV-positive tumours have a paradoxically better prognosis.

For transplant recipients with cSCC: higher recurrence and metastasis rates. Consider dose reduction of immunosuppression. Cemiplimab use requires careful risk-benefit analysis due to potential graft rejection.

Migden MR. NEJM 2018 | Kaufman HL. Lancet Oncol 2016 | Sekulic A. NEJM 2012 | NCCN BCC/SCC v1.2024 | NCCN MCC v1.2024

Board Review: High-Yield Pearls

💡 MUST-KNOW FACTS

AJCC 8th: mitotic rate REMOVED from T1b criteria. T1b = Breslow >= 0.8 mm OR ulceration.

WLE margins: in situ 0.5 cm, <= 1 mm 1 cm, 1-2 mm 1-2 cm, > 2 mm 2 cm.

MSLT-II: completion CLND NO survival benefit (HR 1.08). Observation after positive SLNB.

SLNB threshold: > 0.8 mm or ulcerated thin melanomas.

CheckMate-067: nivo+ipi 5yr OS 52%. Best long-term data in metastatic melanoma.

COMBI-AD adjuvant: dab+tram HR 0.49 (BRAF+ only). KEYNOTE-054: pembro HR 0.57 (any BRAF).

BRAF testing is MANDATORY in ALL advanced melanoma before treatment decisions.

Cemiplimab: first approved systemic therapy for advanced cSCC (EMPOWER-CSCC-1, ORR 47-49%).

Avelumab: first approved therapy for metastatic Merkel cell carcinoma (JAVELIN Merkel 200).

⚠ ERRORS TO AVOID

Using mitotic rate to classify T1b melanoma (removed in AJCC 8th edition).

Performing completion CLND after positive SLNB (no survival benefit per MSLT-II).

Excision margins wider than 2 cm for any thickness melanoma (no evidence of benefit).

Not testing BRAF in metastatic melanoma before starting treatment.

Using interferon-alpha as adjuvant when checkpoint inhibitors or targeted therapy are available.

Module 9

Surgical Oncology

Hepatobiliary and CRLM

Section IX — Liver, Biliary Tract and Colorectal Liver Metastases

9.1. Hepatocellular Carcinoma (HCC)

NCCN Hepatocellular v2.2024 | EASL-EORTC 2024 | BCLC 2022

Hepatocellular carcinoma (HCC) accounts for approximately 90% of primary liver cancers and arises almost exclusively in the setting of chronic liver disease. The diagnosis of HCC in cirrhotic patients is unique in oncology: a nodule greater than 1 cm in a cirrhotic liver showing arterial phase hyperenhancement with subsequent washout on portal venous or delayed phases on contrast-enhanced CT or MRI is diagnostic of HCC without the need for biopsy. This radiological diagnosis pathway (LI-RADS 5) avoids the risk of tumour seeding and bleeding associated with percutaneous biopsy in cirrhotic livers. However, biopsy remains mandatory for non-cirrhotic patients and for indeterminate lesions that do not meet classic imaging criteria.

The Barcelona Clinic Liver Cancer (BCLC) staging system is the most widely used classification for HCC because it integrates tumour burden, liver function (Child-Pugh), and performance status into a single framework that directly links to treatment recommendations. Treatment decisions in HCC

cannot be made without assessing hepatic reserve: a patient with a resectable tumour but Child-Pugh C cirrhosis requires transplantation, not resection.

9.1.1. NCCN/BCLC Algorithm

> 💡 **NCCN HCC / BCLC STAGING**
>
> **BCLC 0 (Very Early)** → Single <2 cm, Child-Pugh A, PS 0. Resection or ablation (RFA/MWA). >90% 5-year survival.
>
> **BCLC A (Early)** → Single or up to 3 nodules <=3 cm, Child-Pugh A-B, PS 0. Resection, transplant (Milan criteria), or ablation.
>
> **BCLC B (Intermediate)** → Multinodular, no vascular invasion, Child-Pugh A-B, PS 0. Transarterial chemoembolisation (TACE).
>
> **BCLC C (Advanced)** → Vascular invasion or extrahepatic spread, PS 1-2. Systemic therapy: atezolizumab + bevacizumab (IMbrave150).
>
> **BCLC D (Terminal)** → Child-Pugh C, PS 3-4. Best supportive care only.

9.1.2. Milan Criteria and Transplantation

The Milan criteria define transplant eligibility for HCC: a single tumour up to 5 cm in diameter, or up to 3 tumours each no larger than 3 cm, with no macrovascular invasion and no extrahepatic disease. Patients meeting these criteria achieve 5-year post-transplant survival exceeding 70%, comparable to non-HCC transplant recipients. Bridging therapy with TACE, ablation, or stereotactic body radiation therapy (SBRT) is routinely used to prevent disease progression while awaiting organ allocation, and downstaging protocols are increasingly accepted for patients initially exceeding Milan criteria.

> 💡 **KEY CONCEPT**
>
> Milan criteria: single <=5 cm OR up to 3 nodules each <=3 cm, no macrovascular invasion, no extrahepatic disease.
>
> Radiological diagnosis in cirrhosis: nodule >1 cm + arterial enhancement + washout = HCC. NO biopsy needed.

9.1.3. Systemic Therapy: Landmark Trials

The treatment landscape for advanced HCC has been transformed by immunotherapy. IMbrave150 (Finn, NEJM 2020) established atezolizumab plus bevacizumab as the first-line standard, demonstrating superior overall survival

compared with sorafenib (median 19.2 vs 13.4 months, HR 0.58). This combination requires upper GI endoscopy before initiation to rule out high-risk varices, as bevacizumab carries a bleeding risk. Prior to IMbrave150, sorafenib was the only systemic agent with proven survival benefit, established by the SHARP trial (Llovet, NEJM 2008), which showed a modest but significant improvement in median OS (10.7 vs 7.9 months, HR 0.69).

> 💡 **EVIDENCE SPOTLIGHT**
>
> IMbrave150: atezo+bev vs sorafenib. OS HR 0.58. New first-line standard for advanced HCC.
>
> SHARP: sorafenib vs placebo. OS 10.7 vs 7.9 months (HR 0.69). First systemic agent in HCC.
>
> REFLECT: lenvatinib non-inferior to sorafenib. OS 13.6 vs 12.3 months.
>
> RESORCE: regorafenib 2L after sorafenib. OS 10.6 vs 7.8 months (HR 0.63).

Finn RS. NEJM 2020 | Llovet JM. NEJM 2008 | Kudo M. Lancet 2018 | Bruix J. Lancet 2017 | NCCN Hepatocellular v2.2024

9.2. Biliary Tract Cancers

NCCN Biliary Tract v2.2024 | ESMO BTC 2023

Biliary tract cancers (BTC) encompass a heterogeneous group of malignancies arising from the biliary epithelium: intrahepatic cholangiocarcinoma (iCCA), perihilar cholangiocarcinoma (pCCA, Klatskin tumour), distal cholangiocarcinoma (dCCA), gallbladder carcinoma (GBC), and ampullary carcinoma. Despite sharing a biliary origin, these tumours differ substantially in molecular biology, surgical approach, and prognosis. Intrahepatic cholangiocarcinoma is the second most common primary liver malignancy after HCC and harbours actionable molecular alterations in a significant proportion of patients: FGFR2 fusions are found in 10-15% and IDH1 mutations in 10-20% of iCCA cases, making molecular profiling essential.

9.2.1. Perihilar Cholangiocarcinoma (Klatskin)

Perihilar cholangiocarcinoma is classified by the Bismuth-Corlette system according to the extent of bile duct involvement: Type I involves the common hepatic duct below the confluence, Type II extends to the confluence, Type IIIa involves the right hepatic duct, Type IIIb the left hepatic duct, and Type IV involves both right and left hepatic ducts or is multifocal. The Bismuth-Corlette classification determines the extent of hepatic resection required: Type I may be amenable to bile duct resection alone, while Types III-IV typically require major hepatectomy with caudate lobectomy and bile

duct resection en bloc. Adequate future liver remnant (FLR) assessment with volumetry is mandatory before major resection, and portal vein embolisation (PVE) should be performed if FLR is insufficient.

9.2.2. Gallbladder Carcinoma

Gallbladder carcinoma is frequently diagnosed incidentally after cholecystectomy for presumed benign disease. The management of incidental GBC depends critically on T stage. T1a tumours (invasion limited to the lamina propria) are cured by simple cholecystectomy alone. From T1b onwards (invasion into the muscular layer), re-resection is mandatory and consists of hepatic segments IVb and V resection with portal lymphadenectomy. The cystic duct margin must be assessed: if positive, common bile duct excision is required. Port-site excision was historically performed but is no longer routinely recommended unless there is clinical concern for implantation metastases.

🎯 **CLINICAL PEARL**

Incidental GBC T1a: cholecystectomy alone is curative. T1b and beyond: mandatory re-resection (segments IVb+V + portal lymphadenectomy).

Bismuth-Corlette IV Klatskin: typically requires extended hepatectomy + caudate + bile duct. Always assess FLR with volumetry.

9.2.3. Ampullary Carcinoma

Ampullary carcinoma is treated with pancreaticoduodenectomy (Whipple procedure) and carries a substantially better prognosis than pancreatic ductal adenocarcinoma, with 5-year survival rates of 40-65% for resected disease. The ESPAC-3 trial evaluated adjuvant chemotherapy in periampullary cancers and demonstrated a trend toward improved survival with adjuvant therapy, supporting its use in fit patients after complete resection. Histological subtype (intestinal vs pancreaticobiliary) has important prognostic implications, with the intestinal subtype showing a significantly better outcome.

Bismuth H. Ann Surg 1992 | Ito F. Ann Surg 2009 | Neoptolemos JP. Lancet 2012 (ESPAC-3) | NCCN Biliary Tract v2.2024

9.3. Systemic Therapy for BTC

TOPAZ-1 | BILCAP | FOENIX-CCA2 | ClarIDHy

The systemic therapy landscape for biliary tract cancers has evolved significantly in recent years. TOPAZ-1 (Oh, NEJM Evid 2022) demonstrated that the addition of durvalumab to gemcitabine plus cisplatin improved overall survival across all BTC subtypes (median 12.8 vs 11.5 months, HR 0.80), establishing immunochemotherapy as the new first-line standard. This is the first positive immunotherapy trial in BTC. BILCAP (Primrose, Lancet Oncol 2019) showed that adjuvant capecitabine for 8 cycles after curative resection of BTC improved median overall survival from 36 to 53 months in the per-protocol analysis, making it the standard adjuvant regimen.

For molecularly selected patients with intrahepatic cholangiocarcinoma, targeted therapies offer meaningful clinical benefit. FOENIX-CCA2 (Goyal, Lancet Oncol 2023) demonstrated that futibatinib, a covalent FGFR1-4 inhibitor, achieved an objective response rate of 42% in patients with FGFR2 fusions or rearrangements who had progressed on prior chemotherapy, leading to regulatory approval. ClarIDHy (Abou-Alfa, Lancet Oncol 2020) showed that ivosidenib, an IDH1 inhibitor, improved progression-free survival in IDH1-mutant cholangiocarcinoma (median 2.7 vs 1.4 months, HR 0.37), with an overall survival benefit on crossover-adjusted analysis. These results underscore the critical importance of molecular profiling in all iCCA patients.

> 💡 **EVIDENCE SPOTLIGHT**
>
> TOPAZ-1: durva+gem/cis vs gem/cis. OS HR 0.80. First positive IO trial in ALL BTC subtypes.
>
> BILCAP: adjuvant capecitabine x8 cycles. OS 53 vs 36 months (per-protocol). Standard after R0/R1 resection.
>
> FOENIX-CCA2: futibatinib in FGFR2-fusion iCCA. ORR 42%. FDA approved.
>
> ClarIDHy: ivosidenib in IDH1-mutant CCA. PFS HR 0.37. OS benefit on adjusted analysis.

> 💡 **KEY CONCEPT**
>
> Molecular profiling is MANDATORY in all iCCA: FGFR2 fusions (10-15%) and IDH1 mutations (10-20%) have approved targeted therapies.

Oh DY. NEJM Evid 2022 | Primrose JN. Lancet Oncol 2019 | Goyal L. Lancet Oncol 2023 | Abou-Alfa GK. Lancet Oncol 2020

9.4. Colorectal Liver Metastases: Surgical Management

NCCN Colon v3.2024 | ESMO CRLM Consensus 2023

Resection of colorectal liver metastases (CRLM) offers the only chance of long-term cure, with 5-year survival rates of 40-60% after complete (R0) hepatectomy. The definition of resectability has evolved from anatomical criteria (fewer than 4 metastases, no bilobar disease) to a functional definition: a tumour is resectable if all disease can be cleared with negative margins while preserving an adequate future liver remnant (FLR) with sufficient vascular inflow, outflow, and biliary drainage. This paradigm shift has greatly expanded the proportion of patients eligible for curative surgery.

When FLR is insufficient, volume modulation techniques are employed. Portal vein embolisation (PVE) of the tumour-bearing lobe induces compensatory hypertrophy of the contralateral lobe over 4-6 weeks, typically achieving a 30-40% increase in FLR volume. The two-stage hepatectomy (TSH) strategy is used for bilobar disease: the first stage clears the FLR of metastases (by resection or ablation), followed by PVE, and the second stage resects the tumour-bearing lobe after adequate hypertrophy. ALPPS (Associating Liver Partition and Portal vein Ligation for Staged hepatectomy) is a more aggressive alternative that achieves 40-80% FLR increase in just 7-14 days, but carries higher morbidity and must be reserved for carefully selected patients in expert centres. The liver-first approach reverses the traditional sequence by prioritising hepatic resection before colonic

resection in patients with synchronous CRLM, particularly when hepatic disease determines prognosis.

9.4.1. NCCN CRLM Algorithm

> 💡 **NCCN CRLM MANAGEMENT**
>
> **Resectable Upfront** → Hepatectomy +/- perioperative FOLFOX. R0 resection goal. Consider ablation for small deep lesions.
>
> **Borderline** → PVE (wait 4-6 weeks) or TSH or ALPPS (FLR increase 40-80% in 7-14 days). Reassess volumetry.
>
> **Initially Unresectable** → Conversion chemotherapy (FOLFOXIRI+bev, FOLFOX+anti-EGFR if RAS-wt). Reassess every 2 months.
>
> **Never Resectable** → Palliative systemic therapy. HAI (hepatic arterial infusion) in selected centres. Ablation for oligometastatic.

⚠ **PITFALL**

Using old anatomical criteria (number/size only) to declare CRLM unresectable. Modern resectability is functional: can you achieve R0 with adequate FLR?

Not reassessing resectability after conversion chemotherapy. Up to 30% of initially unresectable patients become resectable after effective systemic therapy.

Adam R. Ann Surg 2004 | Schnitzbauer AA. Ann Surg 2012 (ALPPS) | Mentha G. Ann Surg 2006 | NCCN Colon v3.2024

9.5. Perioperative Chemotherapy for CRLM

EORTC 40983 | EPOC | KEYNOTE-177

EORTC 40983 (Nordlinger, Lancet 2008) is the landmark trial for perioperative chemotherapy in resectable CRLM. This study randomised patients with up to 4 liver metastases to perioperative FOLFOX (6 cycles pre- and 6 post-surgery) versus surgery alone. The primary endpoint showed a significant improvement in progression-free survival (HR 0.77), though the overall survival difference did not reach statistical significance. Despite this, perioperative FOLFOX became widely adopted as standard practice for resectable CRLM, particularly for patients with multiple or bilateral metastases, high CEA, or synchronous presentation.

The EPOC trial (Primrose, Lancet Oncol 2014) provided a crucial negative result: the addition of cetuximab to perioperative chemotherapy in KRAS wild-type patients with resectable CRLM was not only unhelpful but harmful, with significantly worse progression-free survival (HR 1.48). This trial demonstrated that targeted agents beneficial in the metastatic palliative setting do not necessarily translate to the perioperative curative-intent setting, and cetuximab should NOT be added to perioperative chemotherapy for resectable CRLM.

For patients with initially unresectable CRLM, conversion chemotherapy with FOLFOXIRI plus bevacizumab achieves objective response rates exceeding 60% and secondary resection rates of 25-30%. In the subset of MSI-H/dMMR colorectal cancer, KEYNOTE-177 (Andre, NEJM 2020) established pembrolizumab as the first-line standard, with superior PFS (median 16.5 vs 8.2 months, HR 0.60) and fewer treatment-related adverse events compared with chemotherapy. MSI status should be tested in all CRLM patients as it fundamentally changes the treatment paradigm.

> 💡 **EVIDENCE SPOTLIGHT**
>
> EORTC 40983: periop FOLFOX for resectable CRLM. PFS HR 0.77. Standard for high-risk patients.
>
> EPOC: cetuximab + periop chemo in KRAS-wt CRLM. PFS HR 1.48 (WORSE). Do NOT add cetuximab.
>
> FOLFOXIRI+bev: conversion ORR >60%, secondary resection 25-30%.
>
> KEYNOTE-177: pembrolizumab 1L MSI-H CRC. PFS HR 0.60. Test MSI in ALL CRLM patients.

Nordlinger B. Lancet 2008 | Primrose JN. Lancet Oncol 2014 | Andre T. NEJM 2020 | Loupakis F. NEJM 2014

Board Review: High-Yield Pearls

💡 **MUST-KNOW FACTS**

HCC in cirrhosis: >1 cm + arterial enhancement + washout = diagnostic. NO biopsy needed (LI-RADS 5).

Milan criteria: single <=5 cm OR 3 nodules <=3 cm. Post-transplant 5yr survival >70%.

IMbrave150: atezo+bev is 1L standard for advanced HCC (OS HR 0.58).

TOPAZ-1: durva+gem/cis is 1L standard for ALL BTC subtypes (OS HR 0.80).

BILCAP: adjuvant capecitabine x8 cycles after resected BTC. OS 53 vs 36 months.

iCCA molecular profiling: FGFR2 fusions (10-15%) and IDH1 mutations (10-20%) have approved targeted therapies.

Incidental GBC: T1a = cholecystectomy only. T1b+ = re-resection (segments IVb+V + LND).

CRLM resectability is functional, not anatomical. PVE (4-6wk), TSH, or ALPPS (7-14d) if FLR insufficient.

EORTC 40983: perioperative FOLFOX for CRLM (PFS HR 0.77). EPOC: do NOT add cetuximab (HR 1.48).

> KEYNOTE-177: pembrolizumab 1L for MSI-H CRC (PFS HR 0.60). Test MSI in ALL CRLM.

⚠ ERRORS TO AVOID

Biopsying a classic LI-RADS 5 HCC in a cirrhotic patient (risk of seeding and bleeding).

Resecting HCC in Child-Pugh C cirrhosis (transplant, not resection).

Not performing molecular profiling in iCCA (missing FGFR2/IDH1 targeted therapy).

Declaring CRLM unresectable based on number/size alone without functional assessment.

Adding cetuximab to perioperative chemotherapy for resectable CRLM (EPOC: HR 1.48).

Not testing MSI in CRLM patients (misses pembrolizumab eligibility, KEYNOTE-177).