A Brief Introduction to Solid Cancers

a resident's guide to understanding basic principles of diagnosis, staging, prognosis and treatment

Detailed information on disease-specific cancer staging, prognosis and treatment regimens is available in associated lectures

What information do you need to know to treat cancer?

Diagnosis = **WHAT** is the cancer

Staging = **WHERE** is the cancer

Diagnosis = **WHAT** is the cancer

Diagnosis: WHEN & WHEN NOT to biopsy

WHEN to biopsy

Tissue Biopsy is required with few exceptions

WHEN NOT to biopsy

HCC: can be diagnosed on imaging alone

RCC: workup + treatment often requires nephrectomy → can defer biopsy

Testicular: workup + treatment often requires orchiectomy → can defer biopsy

CNS: work up + treatment often requires primary resection → can defer biopsy

example HCC: Triple phase CT or MRI can be used to generate a LIRADS score

LIRADS SCORE	Probability of Malignancy
LIRADS 1	Definitely Benign
LIRADS 2	Likely Benign
LIRADS 3	Intermediate Likelihood of HCC
LIRADS 4	Likely HCC
LIRADS 5	Definitely HCC

Diagnosis: WHERE & HOW to biopsy

* exception: sometimes you need a biopsy of a primary site in addition to or in place of the metastatic site for corollary studies. For example, a bone biopsy for breast cancer can be insensitive for HER2 IHC testing

1. Location

Biopsy of **metastatic site** is preferred when possible. This allows confirmation of diagnosis AND **stage**
Ex: Lymph node

2. Access

Biopsy of site that is **safely** or **easily** accessible by an interventional team
Ex: Liver lesion

3. Quality

Excisional biopsy is often preferred over FNA (fine needle aspiration)
Ex: Sufficient tissue is required for diagnostic studies such as IHC (immunohistochemistry) or NGS (next generation sequencing)

Diagnosis: INTERPRETING a biopsy

Histology

IHC

Molecular

Histology

Microscopic Appearance

of the cells and tissue architecture

Carcinoma: originating from

Solid Organs or Glands

Adenocarcinoma is a cancer of an **organ**

Neuroendocrine Carcinoma is a cancer of a **gland**

Squamous Cell Carcinoma is a cancer of **epithelium**

Sarcoma: originating from

Connective Tissues

- Muscle
- Fat
- Bone
- Vasculature

IHC

IHC = Immunohistochemistry

Antibodies to cell surface proteins

IHC expression patterns help determine origin of cancer

CK7 and CK20 are common IHC markers	
CK7+	Lung, Breast
CK20+	GI
CK7+/CK20+	Bladder, Prostate, Ovarian
CK7-/CK20-	Renal, HCC

- **CK7** often cancers **above diaphragm**
- **CK20** often cancers **below diaphragm**
- **Bladder** is **BOTH**
- **Gender-Specific** is **BOTH**
- **RCC & HCC** are **C for secretive NEITHER**

Other Notable Markers	
TTF, Napsin	Lung Adenocarcinoma
p40, p63, CK5/6	Lung Squamous
CD56, Chromogranin, Synaptophysin	Small Cell
GATA3	Breast
S-100	Melanoma, Sarcoma
Androgen Receptor	Prostate
PAX8	Renal

Histology, IHC and Molecular data together determine the sub-types of lung cancer

1. Non-Small Cell Lung Cancer = NSCLC

- Squamous
- Adenocarcinoma

- No Driver Mutation
- Driver Mutation

2. Large Cell Lung Cancer = LCLC

Distinct entity between NSCLC and SCLC. Treated more like SCLC

3. Small Cell Lung Cancer = SCLC

Spectrum of Pulmonary Neuroendocrine Tumors (NET)

- Carcinoid low-grade NET
- Atypical intermediate-grade NET
- Small Cell high-grade NET

increasing grade

For many cancers there are additional diagnostic tests needed to direct therapy
re: (1) disease subtype or (2) disease risk stratification

Breast

Receptor Status determines breast cancer subtype

Estrogen Receptor (ER)
Progesterone Receptor (PR)
HER2 Receptor (HER2)

} hormone receptors

1. Hormone Receptor Positive (HR+/HER2-)
2. HER2 Positive (HR-/HER2+, HR+/HER2+)
3. Triple Negative (HR-/HER2-)

Prostate

PSA & Gleason Score determine prostate cancer risk

PSA = Prostate Specific Antigen

PSA <10 = Low Risk
PSA 10-20 = Intermediate Risk
PSA >20 = High Risk

Gleason Score = Gland Formation Grade

1 = well differentiated; 5 = poorly differentiated

Two morphologies on biopsy sample are added together to make a composite score, the first number is the more predominant morphology. Ex: 3+4 is different than 4+3

Gleason <6 = Low Risk
Gleason 7 = Intermediate Risk
Gleans >8 = High Risk

Molecular

Genetic analysis of:

1. **Tumor Tissue**
2. **ctDNA (circulating tumor DNA in serum)**

Inheritance

1. **Germline:** Inherited from parents
2. **Somatic:** Developed spontaneously

Pathogenicity

1. **Benign:** Doesn't cause cancer
2. **Pathogenic:** Known to cause cancer
3. **Variant of Unknown Significance:** Not enough info

* Classification of germline/somatic and benign/pathogenic/VUS is based predominantly on historical databases of founder mutations, as well as the source of the sample, and other characteristics like VAF (variant allele frequency, or % of mutation present in specimen)

Diagnosis: Tumor Markers

Used primarily for:

1. **MONITORING** treatment response in already diagnosed advanced disease
2. **SURVEILLANCE** of recurrence in previously treated early-stage disease

   NOT Diagnosis

Common Tumor Markers: Neither sensitive nor specific	
CEA	GI, Breast, Lung, Thyroid
CA 19-9	Pancreatic, Biliary, Colon
CA 27-29, CA 15-3	Breast
CA-125	Ovarian, Lung, Breast, Pancreatic
PSA	Prostate
AFP	Liver
AFP, HCG, LDH	Testicular, Choriocarcinoma

Staging = **WHERE** is the cancer

Staging: PARADIGM

TNM

TNM is a staging system

T = tumor size
N = node status
M = metastases

T, N, M cut-offs are different for each cancer

Clinical vs Pathologic Staging

Clinical Staging

Clinical Staging is an estimate of TNM based on clinical exam and imaging studies

cTNM is the notation for clinical staging

Pathologic Staging

Pathologic Staging is a measurement of TNM involvement based on a resected surgical specimen

pTNM is the notation for pathological staging
ypTNM is the notation for pathologic staging for a patient who has received neoadjuvant therapy

	Early Stage (I-II)	Locally Advanced (II-III)	Metastatic (IV)
Staging Classifications	**T = T1-T2 = Small** **N = N0-N1 = None or Few** **M** = M0 = None	**T = T3-T4 = Large or Locally Invasive** **N = N1-N3 = Many or Large** **M** = M0 = None	**T** = Any **N** = Any **M = M1 = Distant Mets**

	Early Stage	Locally Advanced	Metastatic
Treatment Implications	Often only treated with **Local Therapy**	Often treated with **Local Therapy + Systemic Therapy**	Often only treated with **Systemic Therapy**
Prognostic Implications	Often **Curable**	Sometimes **Curable**	Often **Incurable**

* Incurable does NOT always mean a terrible prognosis (weeks-months) to live. Certain metastatic cancers can have good prognoses (several-many years). for ex: low-grade neuroendocrine tumors, prostate cancer or HR+ breast cancer.

Treatment

Treatment

LOCAL

Treatment for local or locally advanced disease usually requires **local therapies** such as surgery or radiation therapy

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SYSTEMIC

Treatment for locally advanced or metastatic disease usually requires **systemic therapy** such as chemotherapy, immunotherapy or molecularly targeted therapy

Treatment

CURATIVE INTENT

Treatment aimed to **cure** the cancer
Goal is to eradicate cancer and reduce risk of recurrence

PALLIATIVE INTENT

Treatment aimed to **control** the cancer
Goal is to limit or stabilize cancer growth

Chemotherapy

Mechanism

Usually a systemic therapy that is non-specifically cytotoxic
attacks step in cell division thus kills rapidly dividing cells faster and better than slower growing cells

Toxicity

Naturally occurring quickly dividing cells include GI mucosa, hair cells, blood cells
thus the common side affects of diarrhea, constipation, nausea, vomiting, hair loss, cytopenias

Metabolism

Metabolized by the kidney or liver
thus sometimes require dose adjustment for renal/hepatic function
often cannot be given in kidney/liver failure

Delivery

Often, but not always, IV

Regimens

Can be used as monotherapy or more often in doublet or triplet combinations.
named via acronym when in combination.

Example “ACT” Anthracycline, Cyclophosphamide, Paclitaxel (regimen used in Breast Cancer)

Can be combined with non-chemotherapeutic agents, such as immunotherapy.
usually not combined with molecularly targeted therapies

Common Chemotherapy Drugs & Toxicities

General	**Blood:** Myelosuppression **GI:** Mucositis, Nausea, Vomiting, Diarrhea, Constipation **Gyn:** Infertility
Anti-Tubulin Agents Docetaxel (Taxotere) Paclitaxel (Taxol) Abraxane	Neuropathy Alopecia Nail Changes * Docetaxel: Fluid accumulation, Asthenia, Epiphora
Alkylating Agents Carboplatin Cisplatin Oxaliplatin	Neuropathy, Nephropathy, Otoxicity (Cis is stronger than Carbo) * Oxaliplatin: Cold Hypersensitivity
Topoisomerase Inhibitors Irinotecan	Watery Diarrhea Early Diarrhea = Cholinergic surge Late Diarrhea = SN38 active metabolite
Anthracyclines/DNA Damaging Doxorubicin Doxil	Cardiomyopathy (lower risk with doxil) Leukemia
Fluropyrimidines 5FU Capecitabine	Hand-Foot Syndrome (Palmar-Plantar Erythrodesia)

Antibody Drug Conjugates

Mechanism

An antibody targeted to a neoplastic antigen
conjugated to a chemotherapy drug that gets delivered directly to the cancer cell

example: *enhertu* an ADC of trastuzumab (a HER2 antibody) conjugated to a topoisomerase I inhibitor used in HER2+ breast cancer

Toxicity

Despite being “directed” chemotherapy, can still cause systemic side effects such as liver dysfunction

Delivery

Often IV

Immunotherapy

Mechanism	Usually a systemic therapy that activates the body's immune system to target malignant cells
	Example: Checkpoint inhibitors (CPI) such as pembrolizumab, nivolumab, ipilimumab
Toxicity	Can cause new onset autoimmune reactions or flair of underlying autoimmune conditions toxicity can occur at *any time* and in *any organ* of the body most common toxicities: thyroiditis, dermatitis, colitis, hepatitis
Delivery	Often IV
Dosing	Can be less effective iso immunosuppressive medications
Regimens	Can sometimes be combined with chemotherapy

Targeted Therapy

Mechanism

A systemic targeted drug that acts on a specific molecular pathway

Targets “driver mutations” = mutations that are primarily “driving” the cancer

Example: Osimertinib (EGFR inhibitor used in NSCLC)

Regimen

Usually not combined with other therapies

Delivery

Often PO

Palliative Therapy

Definition

Any treatment that improves comfort without necessarily improving survival

Does NOT necessarily equate with hospice care

Example: Radiation therapy to a painful bone metastasis

Treatment Terminology

Neoadjuvant: Systemic Treatment **before** a surgical resection (ex: can be radiation therapy or chemotherapy).

Technically implies curative intent treatment.

If patient received neoadjuvant tx, pathologic staging is **yp**TNM on surgical specimen

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Adjuvant: Systemic treatment **after** a surgical resection (ex: can be radiation therapy or chemotherapy).

Technically implies curative intent treatment.

If patient did NOT receive neoadjuvant tx, pathologic staging is **p**TNM on surgical specimen

Common Oncologic Acronyms

LN	Lymph Node
LVI	Lymphovascular Invasion
PNI	Perineural Invasion
LMD	Leptomeningeal Disease
RT	Radiation Therapy
XRT	ChemoRT Chemotherapy given in conjunction with RT, different from adjuvant chemotherapy followed by RT
SD	Stable Disease
RD	Residual Disease some cancer left at time of surgical resection
PCR	Pathologic Complete Response no cancer left at time of surgical resection
POD	Progression of Disease
PFS	Progression Free Survival
OS	Overall Survival
CPI	Checkpoint Inhibitor
IO	Immuno-Oncology
NGS	Next Generation Sequencing often referred to by the testing company name such as “foundation” or “guardant”

Available Online Introductory Oncology Lectures

adapted to both resident and fellow levels

1. Breast Cancer

2. Lung Cancer

3. GI Cancers
Gastroesphoageal, Colorectal, Pancreatic, Hepatobiliary, Hepatocellular

4. GU Cancers
Prostate, Renal Cell, Bladder Cancer, Testicular Cancer

5. GYN Cancers

5. Miscellaneous
Head & Neck, Sarcoma, Melanoma, CNS