LECTURE #5
BMI FORMULA

USA  \[ \text{BMI} = 703 \times \frac{\text{weight (lb)}}{\text{height}^2 \ (\text{in}^2)} \]

METRIC  \[ \text{BMI} = \frac{\text{weight (kg)}}{\text{height}^2 \ (\text{m}^2)} \]
OBESITY
Body Mass Index (BMI)

<table>
<thead>
<tr>
<th>BMI</th>
<th>NIH Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18.5</td>
<td>Underweight</td>
</tr>
<tr>
<td>18.5-24.9</td>
<td>Normal Weight</td>
</tr>
<tr>
<td>25-29.9</td>
<td>Overweight</td>
</tr>
<tr>
<td>30-34.9</td>
<td>Obesity I</td>
</tr>
<tr>
<td>35-39.9</td>
<td>Obesity II</td>
</tr>
<tr>
<td>&gt;40</td>
<td>Extreme Obesity</td>
</tr>
</tbody>
</table>

BMI = \frac{\text{weight (kg)}}{\text{height}^2 \text{ (m)}}
OBESITY AND CANCER
NEW FINDINGS

• ~30% of adults are obese (BMI > 30)
• ~35% of adults are overweight (BMI 25 - 30)

• **Women**: Uterine cancer 6-fold
  Kidney cancer 5-fold

• **Men**: Liver cancer 6-fold
  Colorectal cancer ~1.75-fold
Cancer Death Rates of Obese Compared to that of Individuals with Normal Body Weight (BMI < 25)

![Bar chart showing cancer death rates by BMI category and gender.]

- Men:
  - 30.0-34.9: 52%
  - 35.0-39.9: 52%
  - 40 or more: 62%

- Women:
  - 30.0-34.9: 62%
  - 35.0-39.9: 52%
  - 40 or more: 62%

E. Moran 2018
CANCER TREATMENT
Is cancer a curable disease?
Cancer is no longer the most lethal of chronic diseases

Cancer is now the most chronic of lethal diseases
CHEMOTHERAPY OF ADVANCED CANCER

CURABLE

Choriocarcinoma
A.L.L. in Children
Hodgkin's Disease
Histiocytic Lymphoma
Mixed Lymphoma
Burkitt's Lymphoma
A.M.L.
Testicular Cancer
Ovarian Carcinoma
Wilms' Tumor
Embryonal Rhabdomyosarcoma
Ewing's Sarcoma
CHEMOTHERAPY OF ADVANCED CANCER
IMPROVED SURVIVAL

Breast Carcinoma
C.M.L.
P. Vera
C.L.L.
Lymphocytic Lymphoma
Multiple Myeloma
Small Cell Lung Ca
Prostatic Carcinoma
Soft Tissue Sarcomas
CONTINUUM OF CANCER CARE

PREVENTION
SCREENING
DIAGNOSIS
STAGING
TREATMENT
REHABILITATION
FOLLOW-UP
CANCER TREATMENT PRINCIPLES

Localized – Adjuvant ChemoRx. + Surgery +/- RT

Regional (N+) – Surgery + Adjuvant RT + CT +/- ImmunoRx.

Metastatic (spread +) – ChemoRx, Biologicals, Immunotherapy +/- Surgery for “debulking” + ChemoRx. +/- Radiation
Cancer Prognosis and Survival

Patient’s general condition, co-morbidities
Performance status
Psychological index
Tumor histology, grade of aggressiveness
Tumor stage (T, N, and M)
Treatment modality available
Responsiveness to treatment

Cancer is no longer the most lethal of chronic diseases.
Cancer is now the most chronic of lethal diseases.
SURGERY

What should we know?

• Disease control - rates?
• Side effects?
• Indicated for the particular patient?
• Quality of life?

Radical prostatectomy with removal of seminal vesicles

• Retropubic prostatectomy
• Perineal prostatectomy
• Laparoscopic/robotic prostatectomy

(Nerve-sparing technique and Pelvic lymph node sampling are necessary)
NEW SURGICAL TREATMENTS

Debulking the tumor mass
Removal of the primary tumor in presence of metastases
Removal of metastases in liver, lungs, brain
The drug, HN₂, nitrogen mustard, is called an alkylating agent because of its ability to react with, or alkylate, chemical groupings in a cell. Studies have suggested that
Chain splitting (x rays, Mitomycin)

Cross-linking (Alkylation agents, Mitomycin)

Base-substitution (Antimetabolites)

Complex-formation (Actinomycins)
Principles of Combination Chemotherapy

1. Each drug should be active when used alone against the tumor.

2. The drugs should have different mechanisms of action.

3. The toxic effects of the drugs should not overlap, so that each can be administered at or near its maximum tolerated dose.
## ADJUVANT CHEMOTHERAPY

### Effectiveness

<table>
<thead>
<tr>
<th>Condition</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Cancer</td>
<td>CMF, TMX (?)</td>
</tr>
<tr>
<td>Head and Neck</td>
<td>preop + RT</td>
</tr>
<tr>
<td>Bone &amp; Soft Tissue Sarcomas</td>
<td>preop + RT</td>
</tr>
<tr>
<td>Small Cell Lung</td>
<td>postop</td>
</tr>
<tr>
<td>Colon</td>
<td>postop</td>
</tr>
<tr>
<td>Brain</td>
<td>postop</td>
</tr>
</tbody>
</table>
CELL-MEDIATED IMMUNITY

**T-lymphocytes** identify aggressors and try to destroy them through the production of **lymphokines** (synthesized proteins)

- Killer T-cells
- Helper T-cells
- Suppressor cells
B-lymphocytes synthesize immunoglobulins which function as antibodies combining with foreign antigens (bacteria and viruses):

IgG – major immunoglobulin (80%)
IgM – mostly intravascular
IgA – in body secretions, GI and respiratory tract
IgE – active in hypersensitivity (allergy)
CELL MEMBRANE RECEPTORS
Immunoglobulin Molecule, Antigen, and Antibody
IMMUNOTHERAPY OF CANCER (1)

Active immunotherapy:

Non-specific: BCG
Levamisole
Interferon
Interleukin 2

Specific: Tumor antigen vaccines
Immunotherapy of Cancer (2)

Passive immunotherapy

**Antibodies:** Monoclonal or Polyclonal Antibodies
Conjugated with toxins
Radiolabeled

**Cells:** Tumor-infiltrating lymphocytes
# Response to Cancer Immunotherapy

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary bladder</td>
<td>60-70</td>
</tr>
<tr>
<td>Kidney cancer</td>
<td>15-20</td>
</tr>
<tr>
<td>Malignant melanoma</td>
<td>10-15</td>
</tr>
<tr>
<td>Cutaneous T-cell lymphoma</td>
<td>80</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>40-50</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>50</td>
</tr>
</tbody>
</table>
Monoclonal Antibodies to Cancer Cell
Development of a Malignant Tumor

Figure 1. Development of a tumor.
Anti-angiogenesis
TREATMENT OF FEMALE BREAST CANCER
BREAST CANCER - Risk Factors (1)

• Previous breast cancer, atypical hyperplasia.
• Family history: 1st degree relative $\Rightarrow$ x 2-3 fold
• Susceptibility genes: risk = 50% - 85%
• BRCA-1 occurs in 5% of women <70 y.o. w/ ovarian ca.
• Chromosome #17q = lifetime risk of 85% for breast ca. and 45% for ovarian cancer in families with multiple cases of cancer
BREAST CANCER – Risk Factors (2)

- Older age at pregnancy, nulliparity
- High socioeconomic status (diet? lifestyle?)
- History of high-dose radiation exposure
- Oral contraceptives, long-term estrogen treatment
- Obesity, high-fat diet
BREAST CANCER - Early Detection

- 2-view mammography ± Clinical Breast Examination
  → Mortality ↓ 20-30% in 50-69 y.o. women

- In women 40-49 y.o. = no significant benefit (?)

- Yearly CBE only vs. no screening = no data.
PRESENTING SYMPTOMS

"LUMP" IN THE BREAST
(80% of cases). More than 90% of breast cancers discovered by women themselves.

PAIN IN THE BREAST

NIPPLE
- Discharge
- Erosion
- Retraction
- Enlargement
- Itching

BREAST
- Redness
- Hardness
- Enlargement
- Shrinking

RARE
- Axillary Mass
- Arm Swelling
- Bone Pain
BREAST EXAMINATION—1

PALPATE CERVICAL NODES

INSPECT BREASTS ARMS DOWN

INSPECT BREASTS ARMS-UP
BREAST EXAMINATION – 2

PALPATE BREASTS

COMPRESS NIPPLE
BREAST EXAMINATION – 3

EXAMINE AXILLAE

PALPATE BREASTS
PATIENT SUPINE
TREATMENT OF BREAST CANCER

Surgery

Radiation therapy

Hormonal therapy (anti-estrogens):
  - Tamoxifen
  - Aromatase inhibitors

Biologics:
  - Monoclonal antibodies
  - Tyrosine kinase inhibitors

Chemotherapy
Surgery of the Breast

Halsted, 1894 – Radical mastectomy (removal of breast, pectoral muscles, lymph nodes)

Handley, 1954 – Int. mammary lymph nodes involvement

Urban, 1964 – Extended radical mastectomy

Modified radical mastectomy – Preservation of pectoral muscles

Simple mastectomy – Removal of breast and axil. LN’s

“Lumpectomy”, sentinel LN’s + Radiation
State after Left Total Mastectomy
Lymphatic Spread of Breast Cancer
Frequency of internal mammary metastases in the different zones of the breast in 900 patients.
Sentinel Lymph Node Biopsy

Lymph nodes

Tumor

Radioactive substance or dye

Probe

Sentinel nodes

Tumor and sentinel nodes removed

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Treatment of Breast Cancer

Breast-conserving Surgery

Lumpectomy
- Lymph nodes
- Tumor

Partial Mastectomy
- Lymph nodes
- Tumor

Fatty tissue
- Chest wall lining

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BREAST CANCER - LIMITED DISEASE

LIMITED SURGERY WITH RADIATION THERAPY VS. RADICAL MASTECTOMY

Actuarial Disease-Free Survival

PROBABILITY

0.80

0.60

YEARS

0 1 2 3 4 5 6 7

HALSTED

QUADRANTECTOMY
BREAST CANCER
HORMONAL DEPENDENCY

- Urinary estrogen excretion
- Urinary 11-deoxy-17-oxysteroids
- Urinary 17-hydroxycorticosteroids
- Steroid hormones in breast cancer tissue
- Hormone receptors in breast tissue
ESTROGEN RECEPTORS

ESTROGEN

ESTROGEN RECEPTOR

AFFECTS DNA SYNTHESIS

NUCLEUS

CYTOPLASM

BREAST CELL
## Estrogen and Progesterone Receptors in Breast Cancer Tissue

<table>
<thead>
<tr>
<th>Progesterone Receptor</th>
<th>Responsive to Endocrine Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER−</td>
<td>0%</td>
</tr>
<tr>
<td>ER+</td>
<td>54%</td>
</tr>
<tr>
<td></td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>55%</td>
</tr>
</tbody>
</table>
HERCEPTIN

• Recombinant DNA-derived monoclonal antibody.
• **Binds selectively to Human Epidermal Growth Factor Receptor 2 protein (HER2).**
• Effective mostly in tumors **overexpressing the HER2 protein.**
• Cardiac toxicity (cardiomyopathy).
BREAST CANCER
ADJUVANT SYSTEMIC TREATMENT

NODE POSITIVE

PREMONO/PERSONAL - CHEMOTHERAPY
POSTMENO/PERSONAL - HORMONAL THERAPY (TAMOXIFEN)
BREAST CANCER
ADJUVANT SYSTEMIC TREATMENT

NODE NEGATIVE

CHEMOTHERAPY - HIGH RISK PATIENTS (?)
- T > 3 cm.
- Grade 3
- Neg. steroid receptors
- High proliferative activity

TAMOXIFEN - HIGH E.R. LEVEL
BREAST CANCER

INDICATIONS FOR IRRADIATION

• Breast mass < 5 cm
• Fixation of tumor to pectoral fascia
• Skin fixation, edema
• Multiple foci of invasive tumor
• Vascular or lymphatic invasion
• 20% or more positive axillary nodes
Various combinations of drugs.

The duration depends on extent of tumor and response.

1. **Neoadjuvant ChemoRx:** To shrink the tumor for easier surgical removal.

2. **Adjuvant ChemoRx:** To remove any cancer not seen but thought of remaining after surgery.

3. **For Advanced Cancer:** To treat metastases.
Prostate Cancer Warning Signs

- Difficulty to urinate
- Blood in the urine
- Impotence
- Bone pain in hips, spine, ribs
- Nerve pain in legs

Urinary difficulties are similar with those of BPH
Digital Rectal Examination (DRE)
Prostate Needle Biopsy/ies
## PROSTATE CANCER
### OCCULT LYMPHNODE METASTASES VS. TUMOR STAGE AND GRADE

<table>
<thead>
<tr>
<th>Clinical Stage</th>
<th>Tumor Grade (Gleason)</th>
<th>Well</th>
<th>Intermediate</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Localized Dis.)</td>
<td>(2-4)</td>
<td>(5-7)</td>
<td>(8-10)</td>
<td></td>
</tr>
<tr>
<td>T1, N0, M0</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>T2, N0, M0</td>
<td>5</td>
<td>23</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>T3, N0, M0</td>
<td>5-28</td>
<td>20-27</td>
<td>27-38</td>
<td></td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>42</td>
<td>68</td>
<td></td>
</tr>
</tbody>
</table>
Prostate Cancer Metastases

Prostate cancer that has metastasized to the lymph nodes

Prostate cancer that has metastasized to the bone
Metastatic Prostate Cancer to the Bones
PROSTATE CANCER

TREATMENT

Surgery
Radiation
Watchful Waiting
Hormone
Chemotherapy
SURGERY

What should we know?
• Disease control - rates?
• Side effects?
• Indicated for the particular patient?
• Quality of life?

Radical prostatectomy with removal of seminal vesicles
• Retropubic prostatectomy
• Perineal prostatectomy
• Laparoscopic/robotic prostatectomy

(Nerve-sparing technique and pelvic lymph node sampling are necessary)
Complications of Radical Prostatectomy

Estimated Overall Incidence

- Impotence: 30–70%
- Bladder neck contracture: 10–40%
- Incontinence: 0–7%
- Mortality: 0–3%

Smith, unpublished data
PROSTATE CANCER

RADIATION THERAPY

External beam ± hormones

3-D Conformal radiation therapy (3D – CRT)

Conformal proton beam radiation therapy

Intensity modulated radiation therapy (IMRT)

Interstitial (brachytherapy) – seeds or needles

Strontium-89 (Metastron®) for bone mets.
Clinically Localized Prostate Cancer

Prostate cancer Intervention Versus Observation Trial (PIVOT) Study

Prostatectomy vs. Observation

1994 – 2002 - 731 men, mean age 67 y.o.

Localized prostate cancer;

PSA median 7.8 ng/ml;

Any Gleason score;

Follow-up 8 yrs.

Conclusion: Prostatectomy did not reduce mortality rate
Prostate Cancer: Management of Advanced Disease
Androgen Deprivation

- Standard treatment since the work of Huggins and Hodges (1941)
- Subjective response in 80% of patients
- Objective tumor regression measurable by bone scan, x-ray, and PSA
- Median duration of response: approximately 18 months
HORMONAL CONTROL OF PROSTATE CANCER

HYPOTHALAMUS

LHRH

LH (anterior pituitary)

Leydig cells - testosterone

Converted to DHT (5α-reductase)

Androgen Receptors

CRH

ACTH

Adrenal - DHEA-S

DHEA

Androstenedione

Androstenediol
Androgen Deprivation Therapy

LHRH agonists – Turn off the testicle production of male hormone. Shots given q. 3 – 12 months (Lupron™, Zoladex™)

Combined Androgen Blockade – LHRH agonist + antiandrogen (Flutamide™)

Side effects:

• Decreased libido
• Hot flashes
• Breasts enlargement
• Loss of muscle and increase in body fat
• Osteoporosis
• Risk of coronary heart disease and of Type 2 diabetes
UPPER GI CANCER
Limit Alcohol and Tobacco

Combination of Alcohol and Cigarettes Increases Risk for **Cancer of the Esophagus**

<table>
<thead>
<tr>
<th>Risk Increase</th>
<th>Alcoholic Drinks Consumed per Day</th>
<th>Packs of Cigarettes Consumed per Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>0x</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10x</td>
<td>4+</td>
<td>2+</td>
</tr>
<tr>
<td>20x</td>
<td>0</td>
<td>2+</td>
</tr>
<tr>
<td>30x</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>40x</td>
<td>4+</td>
<td>4+</td>
</tr>
</tbody>
</table>

N. C. I.
CANCER of the ESOPHAGUS
Symptoms

Difficulty swallowing solid foods
Later difficulty and pain swallowing fluids
Weight loss
Change in taste
Endoscopy – Esophageal cancer
STOMACH CANCER

Symptoms

Lack of appetite and Unexplained weight loss is a common sign of cancer.

Nausea & vomiting: Sometimes the vomit may have blood in it.

Stomach pain in the upper abdomen.

Early satiety (Feeling full after a small meal).

Heartburn.

In general, the symptoms occur when the cancer is advanced.
STOMACH
STOMACH CANCER
Treatment

Surgery with dissection and removal of the satellite lymph nodes.
Adjuvant chemotherapy.
5-year survival rates: 18% - 94%, depending on the stage
COLORECTAL CANCER
Risk Factors for Colorectal Cancer

- Age > 50 years
- High fat; low fiber and vegetables
- Tobacco
- Alcohol, obesity
- Personal history of adenomas or cancer
- Family history of adenomas or cancer
Colon Cancer

• Obesity increases risk of colon cancer

• Physical exercise decreases the risk

• Red meat increases the risk. Heterocycle amines?

• Other dietary fat does not increase the risk
Stages in colon cancer development
<table>
<thead>
<tr>
<th>Tumor status</th>
<th>Node status</th>
<th>Systemic status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited to mucosa and submucosa ($T_1$)</td>
<td>Lymph nodes normal ($N_0$)</td>
<td>No distant metastasis ($M_0$)</td>
</tr>
<tr>
<td>Invasion into, but not beyond, muscularis propria ($T_2$)</td>
<td>Lymph node metastasis ($N_1$)</td>
<td></td>
</tr>
<tr>
<td>Penetration of full thickness of bowel wall ($T_3$)</td>
<td></td>
<td>Distant metastasis ($M_1$)</td>
</tr>
</tbody>
</table>

Tumor staging assesses depth of invasion (T) into or through bowel wall, presence or absence of lymph node (N) and distant organ metastasis (M)
COLONOSCOPY
COLONOSCOPY – COLON POLYPS

Multiple pedunculated polyps

Sessile polyp (may be multheaded)

Polyp with area of malignant transformation

Carcinoma in situ

Invasive carcinoma
Treatment of Colon Cancer

Surgery:
- Surgical removal of the area involved
- Careful dissection of satellite lymph nodes (N1-N3 sites)
- Examination of the liver

Chemotherapy
- If N+ (Stage 2) adjuvant
- If distant mets. (Stage 4)
RECTAL CARCINOMA
RADIATION THERAPY

PREOPERATIVE
REDUCES LOCAL RECURRENCE
IMPROVES RESECTABILITY RATE
REDUCES NODE METASTASES
IMPROVES SURVIVAL

POSTOPERATIVE
EXCLUDES LOW RISK PATIENTS

PALLIATIVE
RELIEVES: PAIN
TENESMUS
MUCOUS DISCHARGE
TREATMENT of TESTICULAR CANCER
TESTICULAR CANCER

Presentation

• **Symptoms:**
  • Painless swelling in one testicle
  • Scrotal pain (rare)
  • Occasional: symptoms related to mets.

• **Signs:**
  • Firm testicular nodule or mass
  • Epididymis involvement
  • Hydrocele
TESTICULAR CANCER
Management

Staging: Is the disease limited to the testicle?
Chest X-ray and abdominal CT scan

Biomarkers: Alpha-Fetoprotein (AFP)
β subunit of human chorionic gonadotropin (beta-hCG)
Lactic dehydrogenase (LDH)

All biomarkers must become normal after orchiectomy
TESTICULAR CANCER
Tumor Markers

• After orchiectomy, *markers should become normal*

• Persistent elevation = residual disease

• Useful in dx. of relapse (clinical f/u)
TESTICULAR CANCER
Treatment

RADICAL ORCHIECTOMY (Removal of the testicle and of the spermatic cord = “the only acceptable diagnostic and therapeutic procedure”)

- Retroperitoneal lymph node dissection
- Radiation therapy for pure seminoma
- Chemotherapy for extra-testicular disease
CANCER of the UTERUS
CANCER OF THE UTERUS
Risk Factors

• Menstruating at an early age.
• Starting menopause at a later age.
• Never giving birth.
• Taking estrogen only (HRT) after menopause.
• Taking tamoxifen to prevent or treat breast cancer.
• Obesity and Metabolic syndrome.
• Having type 2 diabetes.
• Having polycystic ovarian syndrome.
• Having a family history of endometrial cancer in a first-degree relative (mother, sister, or daughter).
• Having certain genetic conditions, such as Lynch syndrome.
• Having endometrial hyperplasia.
Cancer of the Uterus - Symptoms

Irregular periods
Menorrhagia
Abundant blood discharge – Metrorrhagia
Pelvic pain
Endometrial Cancer - Ultrasound
Cancer of the Uterus - Treatment
CANCER OF THE UTERINE CERVIX
Normal Uterine Cervix
Cervical Cancer (Invasive Carcinoma)
CERVICAL CANCER SCREENING
RECOMMENDATIONS

• All women who are or have been sexually active

• Papanicolaou (Pap.) test 3 yrs. after first vaginal intercourse and no later than 21 y.o.

• Pap. q. yr. in hi-risk cases

• After 30 y.o., if Pap. negative (x 3), screening with Pap. and HPV DNA testing q. 3 yrs.

• Pap. may be discontinued at 70 y.o. if previously normal
CANCER of the URINARY BLADDER
Cancer of the Urinary Bladder. Symptoms are not specific

Blood in the urine
Having to urinate more often than usual
Pain or burning during urination
Urgency = feeling that one needs to go right away, although the bladder is not full
Having trouble urinating or having a weak urine stream

Late symptoms:
Being unable to urinate
Loss of appetite and weight loss
Feeling tired or weak
Bone pain
BLADDER CANCER STAGES
SKIN CANCER
SKIN CANCER SCREENING
Burden of Suffering

2017 - >5 million new cases in U.S.
>95% are basal cell or squamous cell carcinoma
Organ transplant patients x 100 times more likely
90% of non-melanoma are associated with exposure to UV radiation

**Actinic keratosis** most common precancer
2017 – 87,000 malignant melanoma cases
2017 – 9,700 deaths
SKIN CANCER SCREENING
Risk Factors

- Atypical moles (dysplastic nevi)
- Congenital moles
- Large number of common moles
- Immunosuppression
- Family/personal history of skin cancer
- Fair skin, poor tanning ability
- Intense sun exposure
- Severe sun burns in childhood
Malignant melanoma vs. Benign nevi (moles)

- Asymmetry
- Borders
- Color
- Diameter changing
SKIN CANCER SCREENING

Recommendations

• Public education

• Avoidance of skin exposure
  (protective clothing, sun screens)

• Biopsy of suspicious lesions
STAGES OF MELANOMA
Malignant melanoma – Stage and Survival

Five-Year Survival Rates for Patients with Melanoma (by stage)

100%

50%

100%

Stage at Time of Initial Diagnosis

I

II

III

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END OF LECTURE #5
END OF THIS CLASS
THANK YOU 😊