The role of Tumor Biomarkers in Management of Cancer in Women

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Objectives

1. List the current immunoassay tumor markers for breast, ovarian, and thyroid cancer and explain their utilization.

2. Understand the potential hematologic complications of cancer.

3. Describe the clinical utilization of HER-2/neu in metastatic breast cancer
Agenda

Overview of Cancer in Women

Thyroid Cancer

Ovarian Cancer

Breast Cancer
Tumor markers and cancer

Tumor markers are most commonly used to:

- Guide treatment decisions
- Predict the chance of recovery.
- Predict or watch for recurrence.

Important considerations:

- Results and reference ranges may differ from manufacturer to manufacturer
- Continued monitoring must be performed using the same test and platform
Thyroid Cancer

Cancer...
Inappropriate cell growth
Thyroid Cancer

The American Cancer Society’s most recent estimates for thyroid cancer in the United States for 2016 are:

- About 62,450 new cases of thyroid cancer (49,350 in women, and 19,950 in men)
- About 1,980 deaths from thyroid cancer (1,070 women and 910 men)

Thyroid Cancer Risk Factors

- Age (25–65)
- Gender
- Exposure to radiation
- Family history
- Goiter
- Genetic factors
- Iodine deficiency

http://www.cancer.gov/cancertopics/pdq/treatment/thyroid/Patient/page1#Keypoint2
http://my.clevelandclinic.org/disorders/thyroid_cancer/hic_thyroid_cancer.aspx
### Thyroid Cancer Symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
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<tbody>
<tr>
<td>Swelling</td>
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<td>Lump in the neck</td>
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<td>Difficulty breathing</td>
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<td>Difficulty swallowing</td>
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<td>Hoarseness</td>
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Sources: http://www.cancer.gov/cancertopics/pdq/treatment/thyroid/Patient/page1#Keypoint2
http://my.clevelandclinic.org/disorders/thyroid_cancer/hic_thyroid_cancer.aspx
# Thyroid Cancer

<table>
<thead>
<tr>
<th></th>
<th>Third-generation TSH</th>
<th>FT3</th>
<th>FT4</th>
<th>Imaging Modalities</th>
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<td>Leukocytes</td>
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Thyroid Cancer

Four types of cancer
- Papillary (70-80%)
- Follicular (10%)
- Medullary (3%)
- Anaplastic (2%)

Thyroglobulin is synthesized/secreted by
- Thyroid follicular cells
- Differentiated thyroid cancer cells
- Papillary
- Follicular

Calcitonin is synthesized/secreted by
- Thyroid cancer C-cells
- Medullary thyroid cancer cells

Differentiated Thyroid Cancer and Thyroglobulin

Differentiated thyroid cancer:
- Follicular
- Papillary
- Prognosis is excellent if found early

Treatment:
- Surgical
- Radioactive iodine ablation

Thyroglobulin utilization:
- Monitoring after treatment
  - Presence indicative of relapse or inadequate treatment

References:
Well-Differentiated Thyroid Cancer

Tests for remaining thyroid tissue are particularly important for monitoring thyroid cancer patients for residual, metastasized, and recurring thyroid tissue after the thyroid has been completely removed. Historically, the only procedure available to monitor residual thyroid removal has been the total body scan.

An appropriately sensitive Tg assay offers a powerful complementary procedure that may reduce reliance on the far more invasive total body scans.

Anti-Tg antibodies interfere in the Tg assay, and Tg results may therefore not be reported for serum samples that are positive for these antibodies.
Well-Differentiated Thyroid Cancer

Thyroglobulin (Tg) and Anti-TG (antibodies to Tg) tests are used:

Tg for monitoring thyroid cancer patients post thyroidectomy

Synthesized in thyroid gland as precursor to thyroid hormones $T_4$, $T_3$

Not detected in the absence of thyroid tissue

Increased in physical damage to the thyroid or in thyroid cancer

Used primarily as ‘tumor marker’ for detecting return of thyroid cancer

Anti-Tg screening of thyroglobulin samples for interference
Medullary Thyroid Cancer and Calcitonin

Calcitonin is the best marker for medullary thyroid cancer

Diagnosis

- Baseline measurement
- Positive correlation between levels and tumor mass

Monitoring therapy

- Regular measurement during follow-up post-operatively
- Elevated/rising levels should trigger further investigation

Thyroid Cancer Case Study

47-year-old presents with painless lump and fatigue.

TSH: normal; free $T_4$: normal; total $T_4$: normal; anti-TPO: present

Biopsy determines follicular cancer. Patient has surgery and takes levothyroxine. Returns 2 months later.

TSH: normal; free $T_4$: normal; thyroglobulin: undetectable;
anti-thyroglobulin: undetectable

Diagnosis is euthyroid, with no biochemical evidence of tumor.
Ovarian Cancer
Ovarian Cancer

Among women in the United States, ovarian cancer is the eighth most common cancer and the fifth leading cause of cancer death. Accounts for only about 3% of all cancers in women, but causes more deaths than any other cancer of the female reproductive system.
Ovarian Cancer

- **240,000** diagnoses
- **120,000** deaths

Survival rates

Consequences

Symptoms of Ovarian Cancer

Most common symptoms:
- Bloating
- Pelvic or abdominal pain
- Trouble eating or feeling full quickly
- Urinary symptoms such as urgency

Other Symptoms:
- Fatigue
- Upset stomach
- Back pain
- Pain during sex
- Constipation
- Menstrual changes
- Abdominal swelling with weight loss
Ovarian Cancer Risk and Protective Factors

**Risk Factors**
- Age
- Family history
- Genetic factors (BRCA 1/2)
- Fertility drugs
- HRT
- Obesity

**Protective Factors**
- Oral contraceptives
- Pregnancy/breastfeeding
- Tubal ligation/hysterectomy
- Oophorectomy

Source: Ovarian Cancer Prevention (PDQ®). National Cancer Institute at the National Institutes of Health.
www.cancer.gov/cancertopics/pdq/prevention/ovarian/Patient/
How Is Ovarian Cancer Detected?

1. Signs and symptoms
2. Pelvic exam
3. Transvaginal/pelvic ultrasound
4. Blood tests

CA-125

- Also known as mucin 16 or MUC16

- 90% of women with advanced ovarian cancer have elevated levels of CA-125

- Monitoring CA-125 blood serum levels is also useful for determining how ovarian cancer is responding to treatment

  - Preoperative value >65 U/mL suggests a poor prognosis

  - Persistent elevations following chemotherapy indicate a poor prognosis.

  - The half-life of CA-125 after chemotherapy correlates with prognosis

Screening

- Lack of sensitivity, particularly for detecting early stages of ovarian cancer

  - Lack of specificity

  - May be elevated in the presence of any inflammatory condition in the abdominal area, both cancerous and benign
Caring for Women with Ovarian Cancer

<table>
<thead>
<tr>
<th>CA 125</th>
<th>CEA</th>
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<tbody>
<tr>
<td>CRP</td>
<td>Chloride</td>
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<tr>
<td>Leukocytes</td>
<td>Thrombocytes</td>
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</tbody>
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Imaging Modalities
Breast Cancer
Breast Cancer Statistics

2nd leading cause of cancer deaths in women
2.8 million survivors

- Most commonly diagnosed cancer in women
- 1 in 8 women will be diagnosed in the U.S.
- 5-year survival with early detection is 90%
- Accounts for 26% of all cancers in women
- 1,000,000 new global cases diagnosed annually

Source: American Cancer Society
Breast Cancer Risk Factors

- Age
- Family History
- Reproductive history

Risk Factors
Breast Cancer Rates

Age at Diagnosis

Rate per 100,000

Source: American Cancer Society
Elements of Staging Cancer

- Location of primary tumor
- Metastasis
- Size
- Number
- Lymph node involvement

Source: http://www.cancer.gov/cancertopics/diagnosis-staging/staging
How Is Breast Cancer Detected?

Self exam
Clinical breast exam
Mammography
Ultrasound

Breast Cancer: Five-year Survival Rates by Disease Stage

![Bar chart showing survival rates by disease stage.](chart.png)

- **Stage IV**: 20%
- **Stage III**: 40%
- **Stage II**: 65%
- **Stage I**: 90%
- **in Situ**: 100%

Source: American Cancer Society
How Is Breast Cancer Treated?

Depends on the type, stage, and aggressiveness.

Treatment:
- Surgery
- Chemotherapy
- Radiation
- Targeted therapy
- Hormone therapy
<table>
<thead>
<tr>
<th>Assay</th>
<th>Intended Use</th>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage III</th>
<th>Stage IV</th>
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<tr>
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<tr>
<td>BR</td>
<td>Treatment monitoring and follow-up</td>
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<tr>
<td>Serum HER-2/neu</td>
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Breast Cancer Tumor Markers: Diagnostic Performance

CA 15-3

MUC-1 gene product

CA 27-29

BR-MA
Serum HER-2/neu Clinical Utility in Metastatic Breast Cancer
Intended use:

- HER-2/neu ECD is associated with higher tumor stage and more aggressive form of breast cancer.
- Values obtained may be used in the follow-up and monitoring of patients with metastatic breast cancer whose initial serum HER-2/neu level is greater than 15 ng/mL.
- Elevated level of HER-2/neu ECD correlates with worst prognosis.
- Should be used in conjunction with other clinical and diagnostic procedures.
Impact of Breast Cancer

Cases (thousands)

New Cases

Deaths

Primary Breast Cancer

Breast Cancer

Triplet -

HER2 +

ER/PR +

Impact of Breast Cancer

New Cases

Deaths

Breast Cancer

Metastatic Breast Cancer

Cases (thousands)

30–90% HER-2/neu positive

HER-2/neu Signaling Pathway: What Is the HER-2/neu Oncoprotein?

Growth factor

Breast cancer cell

Breast cell

HER-2/neu protein
Structure of HER-2/neu Receptor

Extracellular domain
(ECD-p97-115Kd ligand-binding site)

Transmembrane domain

Intracellular domain
(Tyrosine kinase activity)

## Comparison of Lab Methods for HER-2/neu Testing

<table>
<thead>
<tr>
<th>Specimen type</th>
<th>IHC</th>
<th>FISH</th>
<th>Immunoassay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Technical complexity</td>
<td>Moderate</td>
<td>High</td>
<td>Low</td>
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<tr>
<td>Target</td>
<td>p185</td>
<td>DNA</td>
<td>Extracellular domain, p105</td>
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<tr>
<td>Interpretation</td>
<td>Subjective</td>
<td>Quantitative</td>
<td>Quantitative</td>
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<tr>
<td>FDA-approved clinical application</td>
<td>Candidacy for Herceptin and Tykerb</td>
<td>Candidacy for Herceptin and Tykerb</td>
<td>Monitoring of MBC patients</td>
</tr>
</tbody>
</table>

HER-2/neu Serum Assay Measures the ECD by Double MAb-based Test (Sandwich)

**Acridinium Ester**

- Anti-HER-2/neu MoAb(TA1)-AE: the light reagent

**HER-2/neu (p105)**

- Solid phase = PMP + antifluorescein MoAb

**ReACTIVE Isothiocyanate form**

- Anti-HER-2/neu MoAb(NB-3)-FITC: FL conjugate reagent

**Paramagnetic particles**

- + Fluorescein

**PMP**
Tissue Determination of HER-2/neu Status

Normal 0
Normal 1+
Abnormal 2+
Abnormal 3+

Normal
Normal
Abnormal low amplification
Abnormal high amplification
HER-2/neu Monitoring

Concentration (ng/mL)

- Serum HER-2/neu
- Disease Progression
  - “Only FDA-cleared test to monitor changes in HER-2/neu status for MBC”
- Therapy Response
  - 15 ng/mL
Serum HER-2/neu Monitoring

<table>
<thead>
<tr>
<th>Time</th>
<th>Concentration (ng/mL)</th>
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<tbody>
<tr>
<td>10</td>
<td>5</td>
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<td>30</td>
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Disease Progression

Therapy Response

Typical Use of Serum HER-2 Testing Algorithm for Metastatic Breast Cancer Complimentary to Tissue Testing

~10–30% of breast cancer patients diagnosed HER-2-negative on the primary tumor have an elevated serum HER-2 value (>15 ng/mL) in MBC.\(^1\,^2\)

Baseline Serum HER-2/neu Levels and Overall Survival

![Graph showing survival probability](#)

- **Probability of survival**
- **Months**
- **Serum HER-2/neu <15 µg/L**
- **Serum HER-2/neu >15 µg/L**

Treated with cyclophosphamide and methotrexate

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Unrestricted © Siemens Healthcare Diagnostics Inc. 2015 All rights reserved.

Summary of HER-2/neu

- HER-2/neu is overexpressed in a subset of breast cancer patients. (PBC 20–30% and 30–90% in MBC)
- Detects the circulating form of the HER-2/neu oncoprotein extracellular domain.
- May be used in the follow-up and monitoring of patients with metastatic breast cancer regardless of Tx modality.
- Is a biomarker for HER-2/neu-positive breast cancer.
- HER-2/neu-positive tumors are indicative of more aggressive forms of breast cancer.
- Is not intended to replace IHC or FISH.
- Is FDA-cleared for stage 4 metastatic breast cancer.
- Serum HER-2/neu greater than 20% decrease from baseline or <15 ng/mL indicates disease regression regardless of treatment modality
Hematologic Complications of Cancer
Hematology: The Case of an Increased Risk of Clotting in Cancer

- Second-leading cause of death
- Most common complication
- 4- to 6-fold increased risk
- Reduced survival

Francis C. J Clin Oncol. 27:4874-80.
Symptoms of DVT

Nonspecific

Pain/tenderness

Swelling

Redness/discholoration

Symptoms of PE

- Chest pain
- Coughing
- Shortness of breath
- Anxiety
- Diaphoresis
- Rapid pulse
- Wheezing
- Fainting
- Hypotension
- Heart failure

Sudden death

What Is D-Dimer?

D-dimer is a fibrin degradation product (FDP), a small protein fragment present in the blood after a blood clot is degraded by fibrinolysis.

It is so named because it contains two cross-linked D fragments of the fibrinogen protein.

D-dimer concentration may be used to help diagnose thrombosis.
Contact

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