Validity of Serum Tumor Markers in Oncology

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What are serum tumor markers (STMs)?

- STMs are serum antigens associated with (specific) malignancies.
  - Can be detected by specific monoclonal antibodies.
- Laboratory-base tests that are potentially useful in:
  - Screening for premalignant or early stage malignancy/early diagnosis
  - Aiding cancer diagnosis:
    - Differentiation between malignant and benign
    - Differentiation between types of malignancy
  - Determining prognosis
  - Surveillance following curative treatment of cancer
    - Detection of asymptomatic recurrence
  - Up-front predicting drug response/resistance
  - Monitoring treatment efficacy/response to therapy

STMs: Serum Tumor Markers

Do we have ideal STM?

100% sensitive : Always positive in patients with the disease

100% specific : Always negative in individuals who do not have the disease

- **The "ideal" STM does not exist (yet).**
- Despite this, several STMs:
  - are indispensable in the management of pts with cancer.
  - are widely accepted and highly appreciated by patients and physicians.
- Advantages of STMs:
  - Easily accessible, convenient to the pts (blood withdrawal).
  - Widely available, the result is available in a reasonable time period.
  - The assay is, at least for the majority of traditional STMs, cheap.

The aims of presentation

- To review the most widely measured STMs in clinical practice
- To summarize guidelines for the use of STMs in clinical practice

Use of STMs in Screening of Cancer (1)

- Screening:
  - Detection of malignancy in early stage
  - Detection od premalignant lesions

  } in person w/o signs or symptoms of disease.

- Advantages of STMs for the screening purpose:
  - Body fluids are easily accessible, with minimal inconvenience to the individuals undergoing screening.
  - For many STMs automated assays are widely available, allowing testing of large number of samples in a reasonable period of time.
  - The result is quantitative, with objective reference values.
  - Assays are relatively cheap in comparison to some other diagnostic procedures (imaging, endoscopy, etc.)

Use of STMs in Screening of Cancer (2)

- Limitations/weakness of STMs for screening purpose:
  - **Lack of sensitivity**:
    - If STM is elevated, the person has cancer. If it is not elevated, the person is without cancer.
  - **Lack of specificity**:
    - If a certain STM is elevated, it is associated with certain tumor type.
  - **Low prevalence of most cancers in general population**.
- STMs, if used alone, have low positive predictive values in screening asymptomatic populations.
- PSA and CA 125 are the most widely investigated (also used, although in majority of cases unjustified) for the screening purpose.
- **To date, use of STMs alone has not demonstrated a survival benefit in RCTs of screening in the general population.**

RTC: randomized controlled trial

Use of STMs as Diagnostic Aids for Cancer

- STMs can play an important role in the diagnostic procedure of malignancy, especially in differentiation between malignant and benign lesions in selected groups of pts.
- Limitations preclude the use of STMs for diagnostic of cancer:
  - **Limited sensitivity,**
  - **Limited specificity.**
- In limited number of situations STMs may help in cancer diagnosis:
  - Measurement of AFP in detection of HCC,
  - Measurement of AFP and beta-HCG in detection of GCTs.

HCC: Hepatocellular Carcinoma,
GCT: Germ Cell Tumor

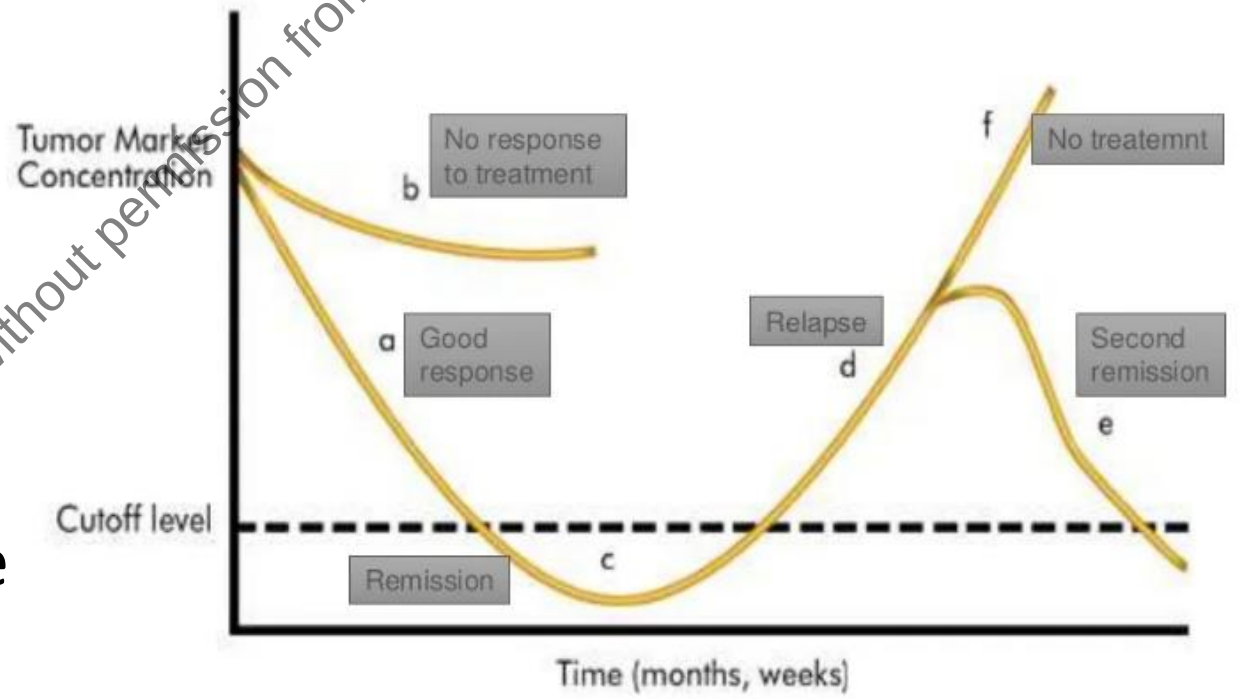
Use of STMs in Assessing Prognosis and Predicting Therapy Efficacy

- Prognostic markers:
  - Provide information on the likely outcome of malignancy.
  - Help avoiding undertreatment or overtreatment.
  - Are most important in cancers that vary widely in outcome.
- There are limited cancer types in which level of STMs is associated with prognosis:
  - For example: level of beta-HCG and outcome of GCTs
- Predictive markers:
  - Provide information on the likely response to certain therapy.
  - Traditional STMs have no proven role in predicting response to therapy.

GCTs: Germ Cell Tumors

Monitoring Efficacy of Systemic Treatment (1)

- The most frequent use of STMs is monitoring efficacy of systemic therapy.
- Decreasing levels of STMs following the initiation of therapy correlate with tumor regression and, vice versa, increasing levels predict disease progression.



Monitoring Efficacy of Systemic Treatment (2)

- Following STMs response is particularly useful when other evidence of disease is not readily accessible.
- STMs should not be used alone in assessing response to therapy:
  - Transient increase/spike can be noticed within the first few weeks of treatment, due to tumor cell necrosis/apoptosis (e.g. PSA increase in mCRPC)
  - In many pts values of STMs are in normal range despite huge burden of malignant disease/normal values do not exclude persistence of malignant disease.

mCRPC - Metastatic Castration-Resistant Prostate Cancer

Use of STMs in Surveillance Following Initial Treatment

- Pts free of detectable disease after curative/adjuvant therapy might be monitored to detect “occult” recurrence prior to classic clinical signs and symptoms of metastases develop.
  - Several STMs have been evaluated for this use in a variety of malignancies.
  - Only justified measurement of: CEA, PSA, beta-HCG, AFP, LDH.
- **The most common use of serial measurements of STMs is to monitor pts with established metastatic disease and initially elevated level of certain STM to determine if the pt should remain on his/her current regimen or the clinician should consider an alternative therapeutic strategy.**

Utility of Most Frequently Measured STMs in Everyday Clinical Practice

Cancer Antigen (CA) 15-3

- STM for breast cancer.
- It is rarely elevated in early stage of disease and is elevated in more than 2/3 of pts with stage IV disease.
- Recommended for:
  - Monitoring treatment efficacy in stage IV disease.
  - Assist in the early detection of recurrence in pts previously treated and clinically free of disease
    - Disagreement about the ability of CA 15-3 to detect asymptomatic recurrence after curative treatment
    - FDA approved.
- Not recommended:
  - For screening,
  - For diagnosing breast cancer.

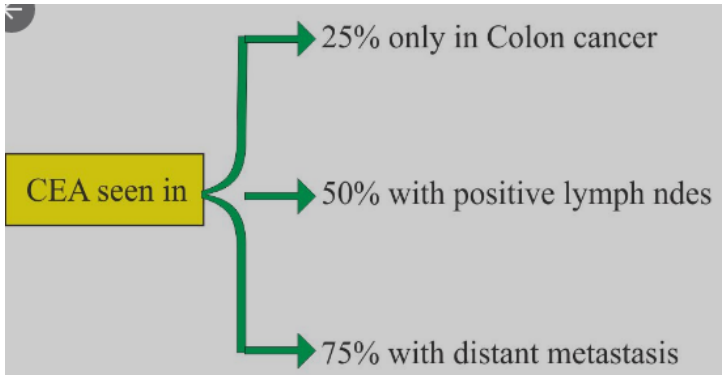
- ASCO guidelines support combined role of CA 15-3 and CEA in pts with stage IV disease for monitoring treatment response.
  - Rising level with 20-30% chance indicate treatment failure in pts with clinical/radiological undetected disease.
- May be elevated also in several benign situations:
  - Benign liver and breast diseases, pts with ovarian cysts, etc.
  - In some other cancers: pancreatic, lung, ovarian, colorectal, liver
    - not sensitive enough for early detection

Carcinoembryonic antigen (CEA) (1)

- The first reported tumor associated Ag in found in the serum.
- Reliable STM in pts with colorectal cancer.
  - CEA concentrations correlate with the stage of disease.
    - Sensitivity increases with tumor burden, elevated in 75% of pts with distant metastasis.
    - Poorly differentiated tumors are less likely to produce CEA.
- Serial measurements are recommended:
  - For pts who have been rendered disease free after primary therapy:
    - Levels typically return to normal within 4-6 weeks after successful surgical resection.
    - Looking for early relapse (every 3 months for at least 3 years).
      - Resection of isolated hepatic metastasis (oligometastatic disease) appears to improve survival.
  - Can also be helpful to monitor pts with established metastases:
    - Monitoring efficacy of current therapy/response to therapy.
    - Therapeutic reconsideration when level is not decreasing after treatment initiation.

CEA (2)

- May be elevated also in several other situations:
  - In several non-malignant situations: cirrhosis, emphysema, inflammatory bowel disease, peptic ulcer disease, benign breast diseases, in smokers, etc.
  - In many other locally advanced or stage IV cancers: breast, pancreatic, lung, ovarian, colorectal, liver, etc.
  - Is elevated in the majority of pts with metastatic liver disease.
- CEA is not recommended to be used as a screening test for colorectal cancer:
  - It is elevated in less than 25% of pts with disease confined to colon.



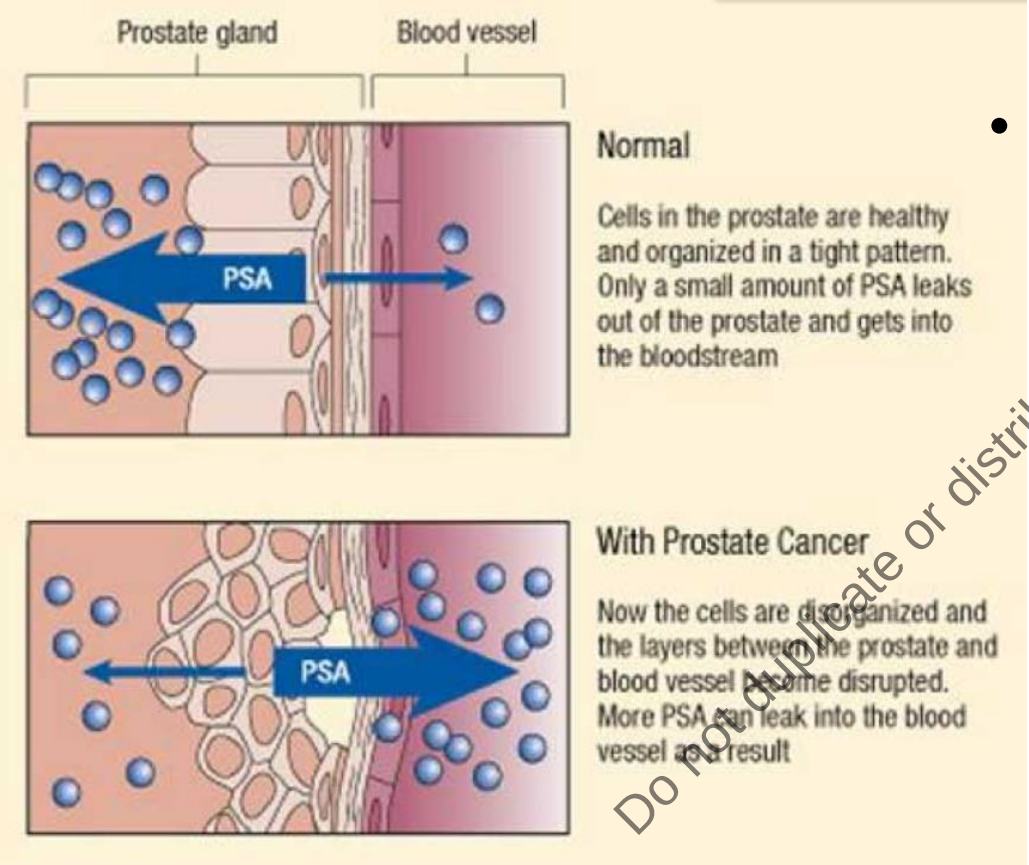
CA 19-9

- STM for pancreatic cancer and cholangiocarcinoma.
- Approximately 10% of patients are unable to synthesize CA 19-9 (Lewis-negative blood group)
- Serial measurements are recommended for:
  - Monitoring treatment efficacy.
  - It should be measured at the start of treatment for locally advanced or metastatic disease and periodically (every 1-3 month) during active treatment.
- Not recommended for:
  - Screening
    - positive predictive value less than 1% in general population,
  - Staging
  - Looking for early recurrence
    - Increasing levels with associated suspicious clinical/radiological presentation are highly predictive for local relapse or distant disease.
- Increased levels have been observed:
  - In several advanced stage cancers: ovarian, endometrial, lung cancer, etc.
  - In certain benign situations: mainly associated with GI diseases (pancreatitis, cholangitis, cirrhosis).
- Present data are insufficient to recommend use of CA 19-9 for management of patients with colon cancer.

Prostate-specific antigen (PSA) (1)

- STM for prostate cancer. It is produced by prostate epithelium.
- Serial measurements are indicated/recommended:
  - In pts with established metastases to monitor response to treatment.
  - In pts after definitive therapy (radical surgery or radiotherapy) who are free of clinically detectable disease:
    - Following radical prostatectomy the level should drop to undetectable (if not, there is some residual),
    - To look for early relapse, if a rise is detected during follow-up (biochemical relapse – 0.2 ng/mL).
    - In men with positive family history (at age 45).
- Not recommended:
  - Monitoring men (general population) with the screening intend as results are controversial:
    - EU study: PSA screening reduces disease-related death, results in overdiagnosis, overtreatment with potential associated morbidity and mortality (year 2012).
    - US Study: There is more harm than benefit from testing (2012).
    - Update in 2018: guidelines recommend against screening in men aged 70+, screening may offer small potential benefit in men aged 55-69.

PSA (2)



- There were many attempts how to increase the specificity of PSA:
  - Age or race specific reference ranges, PSA velocity
  - Different algorithms/nomograms (combining lab. data with some demographic information)
  - Calculation of ratio free/total PSA – most promising (included in NCCN guidelines):
    - In men with prostate cancer there is a higher percentage of protein-bound PSA
    - Measurement of free and total PSA level is advised to men with borderline elevated PSA (4-10 ng/mL), negative digital rectal examination to spare biopsies in men with benign disease.
      - If percentage of free PSA is > 25%: the likelihood of prostate cancer is less than 10%,
      - If percentage of free PSA is < 10%: the likelihood of prostate cancer is grater than 50%.

PSA (3)

- May be elevated also in some benign situations: benign prostate hyperplasia, prostatitis, prostatic trauma as well as after ejaculation.
  - Waiting 48 hours after ejaculation to measure the level has been recommended.
  - Digital rectal examination does not elevate the level above normal.
- In pts with known prostate cancer level of PSA correlates with tumor volume: higher level is associated with more advanced stage.
- About 20% of men with prostate cancer have PSA levels within normal ranges.
- Measurement of PSA level should be included in the surveillance of pts after radical treatment:
  - Every 6 months at least 5 years and annually thereafter.
  - After radical prostatectomy any detectable PSA is significant.
  - After radical prostate radiotherapy 3 consecutive elevations of the PSA level indicate biochemical relapse.

CA 125 and human epididymis protein 4 (HE 4) (1)

- STMs for epithelial ovarian and endometrial cancer.
  - The same indications as for CA 125 apply for HE4. It should be measured in women that lack CA 125 expression.
- Elevated in 85% of pts with ovarian cancer, level is associated with disease burden
- Serial measurements are recommended:
  - In pts with metastatic disease to monitor treatment response.
  - In pts after definitive therapy who are free of clinically detectable disease to look for early relapse and plan postsurgical treatment.
  - Annual US examination and measurement of CA 125 is recommended for women with confirmed hereditary syndromes (e.g. BRCA1/2 mutation).
- Not recommended:
  - For screening of healthy women/general population
    - Low sensitivity in early-disease stage
    - Low prevalence of disease.

CA 125 and HE 4 (2)

- It can help in differential diagnosis of tumor mass in postmenopausal women with pelvic masses:
  - Levels higher of 65 IU/mL are often associated with ovarian cancer/less likely benign lesion.
  - Less applicable for premenopausal women/several benign causes of elevated levels.
- It can be elevated in several other situations:
  - In some other cancers: pancreatic, breast, GI cancers
  - Several non-malignant situations, presumably where serosal surfaces are affected: endometriosis, hepatitis, pelvic inflammatory disease, etc.
  - It is also elevated during pregnancy.

Alpha-fetoprotein (AFP) (1)

- STM for hepatocellular (HCC) and germ cell (non-seminomatous) carcinoma.
- It is produced by fetal liver and yolk sac with a peak in concentration in 13-14 weeks of gestation. The level declines to normal adults by 18 months after birth.
- It is normally elevated during pregnancy.
- It is usually elevated in some other, non-malignant situations:
  - Benign liver diseases: cirrhosis, hepatitis.
    - Usually levels < 500 ng/mL
- Majority of individuals with HCC have cirrhosis w/o hepatitis (different etiology).
- Increasing values or concentrations greater than 1000 ng/mL suggest presence of cancer.

AFP (2)

- Serial measurements in combination with US are recommended in pts with cirrhosis.
  - No firm data on OS benefit with combined modality.
- In pts with HCC, measurements of AFP assist in:
  - Establishing prognosis.
  - Monitoring response to treatment.

AFP and beta-human chorionic gonadotropin (HCG) (1)

- STMs for men with germ cell tumors (GCT):
  - Non-seminomatous testicular cancers and extragonadal GCTs.
  - High levels are reliable marker of disease in men with midline tumor mases even if histology is inconclusive.
  - Are useful in staging (greater concentrations are associated with more advanced stage).
    - AFP, beta-HCG and LDH should be determined in every the patient with testicular GCTs as:
      - they have prognostic significance
        - AFP > 10 000 ng/mL or beta-HCG > 50 000 IU/mL are associated with poor prognosis
      - are needed for proper staging before orchiectomy
        - concentration of TMs is included in TNM staging, as S0-3,
  - One or both are elevated in 80-85% of men with non-seminomatous GCTs.
    - Measurement of beta-HCG and AFP is an essential part of management of pts with GCTs.
    - In seminomas, AFP is not elevated, beta-HCG is elevated in < 25% of cases.

AFP and beta-HCG (2)

- Serial measurements are recommended:
  - In pts with metastatic disease to monitor treatment response,
    - Reconsider treatment regimen if appropriate decline in STMs is not detected (in poor risk disease treatment with ChT can be itensified in the case of insufficient decline).
  - In pts after definitive therapy who are free of clinically detectable disease to look for early relapse.
    - Very important: even on relapse, in many cases the disease is still curable if diagnosed early enough and properly treated. Confirmed elevation direct prompt additional diagnostics and reinstitution of therapy.
- Not recommended:
  - For screening of healthy men.
- Beta-HCG is normally produced in placenta.
  - Levels are normally elevated during pregnancy.
  - Elevated levels are seen in pts with rare gestational trophoblastic disease.
  - False positive values occur in hypogonadal states and marijuana use.

Role of STMs in Cancer of Unknown Primary

- Value of STMs in diagnostics of CUP is poorly defined.
- Usually, the panel of STMs is done.
  - Rarely helps in establishing the origin od the disease.
  - Many STMs are non-specifically elevated in aggressive, metastatic disease (the most common presentation of CUP).
- Some exceptions:
  - Man with adenocarcinoma and significantly elevated PSA level → prostate cancer.
  - Pts with poorly differentiated tumors and elevated AFP and beta-HCG levels → extragonadal germ cell tumor.
  - Woman with peritoneal carcinomatosis w/o ascites and significantly elevated CA 125 level → ovarian cancer.

CUP: Cancer of Unknown Primary

Future perspectives (1)

- Traditional STMs: proteins, detected by monoclonal antibodies.
- Recent past researches: measurement of levels of intact circulating tumor cells ("liquid biopsy"):
  - To detect early/occult relapse.
  - To determine the efficacy of current treatment regimen.
- Many studies are still ongoing, although is seems that (at least for the solid tumors) this is not optimal strategy:
    - Low sensitivity/specificity (frequent false positive results).
- Current researches: measurement of cell free tumor DNA (cfDNA):
  - Studies are ongoing.

Future perspectives (2)

- Current researches:
  - Measurement of circulating free tumor DNA (cfDNA) is the most promising (give an example: ctDNA in bladder cancer after cystectomy[1)].
- It may enable us:
    - The detection of molecular residual disease or molecular relapse in pts treated for early-stage cancers,
    - The identification of pts not responding to current therapy,
    - The identification of actionable mutations to direct target therapy.
  - Multiple clinical trials are underway that may provide evidence for utility of cfDNA as additional tool for decision making in different cancer types.

[1]Powles et al, Nature 2021

Conclusions

- Measurement of STMs is part of daily clinical practice/mandatory in the management of pts with certain cancer types:
  - The elevated levels should always be interpreted within clinical, pathological and radiological findings.
- The main constrains of STMs are:
  - Low sensitivity,
  - Low specificity.
- STMs can rarely be used as a sole criteria for clinical decision making:
  - Some rare exceptions: high levels of beta-HCG and AFP are highly indicative for GCTs (even in inconclusive histology).
- In general the validity of majority of STMs is limited or less clear:
  - None of STMs is recommended for screening purpose.
  - The main role of majority of STMs is in monitoring response to treatment in pts with advanced disease and initially elevated levels of STMs:
    - Declining levels predict effectiveness of the treatment.
  - Some STMs are recommended in surveillance of pts after curative treatment to detect early relapse.
    - Validity of majority of STMs for the purpose of early relapse detection is controversial.
- There are some new STMs under evaluation:
  - Currently the most promising is the measurement of cfDNA.

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