CLINICAL CORRELATION RENDERED: A REVIEW FOR RADIOLOGISTS OF THE MORE COMMONLY USED SERUM TUMOR MARKERS IN ONCOLOGY

Costello JE, Reiter MJ, Schwope RB, Lisanti CJ, Osswald MB

San Antonio Military Medical Center, San Antonio, Texas

The views expressed in this material are those of the authors, and do not reflect the official policy or position of the U.S. Government, the Department of Defense or the Department of the Army.
Neither the authors nor their immediate family members have a financial relationship with a commercial organization that may have a direct or indirect interest in the content.
The target audience for this exhibit is general radiologists

PURPOSE

Review the most frequently utilized serum tumor markers, with a focus on strengths and limitations of each marker

Discuss how serum tumor markers may assist radiologists in image interpretation

Introduce newer tumor markers and novel uses of existing markers
Tumor Markers

- Defined as any molecule which may be elevated in the presence of cancer
- Marker levels elevate either as a reaction of the host to the tumor or as a product of the tumor itself
- Tumor markers can be measured from the fluid of various tissues
- Only serum markers are discussed in this presentation
No “gold standard” tumor marker exists for any specific type of malignancy

Tumor markers, similar to radiologic examinations, should only be utilized if they will assist in diagnosis, alter management, or assess prognosis

Several markers are recommended by various cancer societies

Radiologists should be aware of recommended guidelines for tumor markers

- Can prevent unnecessary procedures
- Can be useful when interpreting an imaging study
Hepatocellular Carcinoma

3rd most common cause of cancer death worldwide; increasing incidence in the US

Invariably occurs in setting of chronic liver disease: 0.5% and 1-6% annual risk for HCC with chronic hepatitis and cirrhosis, respectively

Alpha-fetoprotein (AFP) is the marker associated with HCC

AFP levels and ultrasound (US) previously recommended every 6 months for high risk patients

Now only biannual screening US per current AASLD guidelines

60-year-old male with cirrhosis and hepatitis C found to have an ill defined hyperechoic liver lesion (arrow) on screening abdominal ultrasound. Serum AFP was 113 ng/mL (0.6-8.1 ng/mL is normal range). Follow up MRI and surgical resection confirmed HCC.
Limitations of AFP for HCC Screening

Screening for HCC with serum AFP is not currently recommended due to its low sensitivity.

Overall sensitivity of 60% using cutoff value of 20 ng/mL.

The sensitivity for potentially resectable tumors (those less than 3 cm in size) is 25%.

Also low specificity, as cirrhosis and hepatitis can elevate AFP without malignancy.

If surveillance US is abnormal, dynamic liver CT or MRI performed.

Large centrally necrotic right hepatic lobe mass (arrow) in a 60-year-old male with hepatitis B. Serum AFP was not elevated at 6.4 ng/mL, but imaging characteristics on CT were suggestive of HCC. Biopsy of mass confirmed HCC.
HCC Diagnosis is Imaging Based

Originally, lesions > 2 cm in size with hypervascularity on arterial phase imaging coupled with AFP > 400 ng/mL were diagnostic of HCC.

Most recent update of AASLD (American Association for the Study of Liver Diseases) requires one dynamic imaging technique (CT or MRI) showing arterial enhancement with venous washout to diagnose HCC in lesions > 1 cm. AFP is now non-contributory.

Nodular liver morphology in a 75-year-old woman with cirrhosis and centrally necrotic mass in the right lobe (arrows). Smaller 1 cm adjacent hyperenhancing (arrowhead) mass with rapid washout is also present. MR findings are characteristic of multifocal HCC without need for histologic verification.
AFP Still Augments Imaging Interpretation of Hepatic Masses

Despite being dropped as diagnostic criterion, AFP level > 300 ng/mL prompts increased scrutiny of all liver lesions in cirrhotic patients as 60% will have HCC.

Lesions < 2 cm in size with arterial enhancement but no washout, or those without hypervascularity but with other features such as washout and presence of a “capsule” are variably managed (grouped as LI-RADS 3 lesions). If serum AFP is > 300 ng/mL, short interval follow-up is necessary if tissue sampling is not performed.

61-year-old man with alcoholic cirrhosis presents with 2 cm mass in the caudate lobe. Mass is not hyperenhancing (arrows), has mild hyperintense T2 signal relative to the hepatic parenchyma (arrowhead), and no “capsule” (not shown). Findings are not diagnostic of HCC. Serum AFP was 321 ng/mL which is suspicious and warranted biopsy in this case instead of follow-up imaging. Histologically confirmed HCC.
Higher concentrations of AFP prior to treatment indicates a poorer prognosis (as does increased size and number of tumors and higher histologic grade)

AFP > 400 ng/mL portends portal vein tumor thrombus; distal thrombus difficult to detect on imaging as it does not result in expansion, unlike thrombi in main portal vein

If AFP was elevated prior to treatment and returned to normal after therapy, a subsequent rise heralds recurrence. AFP monitoring does not replace imaging surveillance

Large infiltrative HCC within the right and left hepatic lobes (arrow) in a 56-year-old male with cirrhosis. There is involvement of the hepatic hilum, where there is portal vein thrombus extending to the portal vein confluence (arrowhead). AFP was elevated at 5304 ng/mL.
Most common cancer in men and 2\textsuperscript{nd} leading cause of cancer related death in the United States

Prostate specific antigen (PSA) is not specific for cancer as it is also elevated in BPH and prostatitis

Guidelines for screening with PSA +/- rectal exam are not uniform

Serum PSA level > 4 ng/mL most common threshold used

If screening PSA is abnormal, US-guided transrectal biopsy required; PSA has limited role in diagnosis

Nuclear medicine bone scan demonstrates diffuse osteoblastic metastatic throughout the axial and appendicular skeleton (superscan appearance given diminished renal and soft tissue activity). Patient was newly diagnosed with prostate cancer and PSA was 1409 ng/mL. See subsequent slide for bone scan recommendations based on PSA values.
Although considered the gold standard for cancer detection, sextant US-guided prostate biopsy is imperfect.

For biopsy negative patients with persistent PSA > 4 ng/mL or rising PSA, repeat biopsy has been classic next step in management.

MR imaging-guided biopsy of suspicious areas has proven to be reliable alternative to repeat US-guided biopsy.

Awareness of this specific role of prostate MRI is vital for radiologists. ACR appropriateness criteria rates this indication as 7 (usually appropriate).

45-year-old male with several negative US-guided prostate biopsies but rising PSA levels. MRI performed to aid targeted biopsy and shows low T2 signal lesion (arrow) with restricted diffusion (open arrows) in the central gland (central gland not routinely sampled during sextant prostate biopsy). Repeat biopsy confirmed adenocarcinoma.
Bone scan, CT and/or MRI may be employed in staging.

Bone scans only necessary for patients with PSA levels > 10 ng/mL (or Gleason score > 7 on biopsy). There are similar guidelines for CT given low likelihood of positive findings in patients with lower values.

Prostate MRI aids risk stratification and predicts organ-confined disease.

Following radical retropubic prostatectomy (RRP), PSA levels should be undetectable. Persistent/rising PSA is evidence of residual or recurrent disease.

81-year-old male with tumor in the left peripheral zone (open arrow) extending from the apex to the base on prostate MRI. Extracapsular extension evident as bulging of the capsule and obliteration of the rectoprostatic angle.
Detection of Prostate Cancer Recurrence

65-year-old male with suspected recurrence of prostate cancer given PSA level of 1.1 ng/mL (range of 0.2-0.4 ng/mL used to define biochemical recurrence which differs from normal threshold). RRP performed several years prior. MRI with mild T2 hyperintense and isointense T1 signal in left surgical bed (arrows), the most common appearance of recurrence.

63-year-old male with prior RRP and uptrending PSA to 2.3 ng/mL. Ovoid lesion (arrowheads) with mild T2 hyperintensity and isointense T1 signal in surgical bed on right posterior to urethra (open arrow) suggests recurrence. Rising PSA often predates imaging findings but MRI can ascertain if disease is local or widespread which affects treatment.
Colorectal Cancer (CRC)

3rd most common malignancy worldwide

Carcinoembryonic antigen (CEA) is tumor marker associated with CRC

Nonspecific; elevated levels seen with other malignancies (pancreatic and gastric cancer) and other entities (cirrhosis, gastritis, IBD, diverticulitis)

No role for CEA in CRC screening or diagnosis

Screening colonoscopy recommended at age 50. CT colonoscopy is an alternative option for CRC screening

50-year-old woman with non-specific systemic symptoms and elevated serum CEA of 15.2 ng/mL (0-4 ng/mL is normal range). PET imaging reveals focal intense FDG avidity within the gastric antrum (arrows), consistent with gastritis or gastric neoplasm. Biopsy confirmed adenocarcinoma.
Increased preoperative CEA level (>5 ng/mL) correlates with decreased survival.

New chemotherapies have improved survival in metastatic CRC but are potentially toxic and expensive.

Therefore, it is prudent to discontinue ineffective treatments quickly.

CEA increase (two successive elevated levels above baseline) suggests progressive disease, even in absence of radiologic findings.

Patient with known metastatic colon cancer and uptrending CEA >50% baseline value. CT abdomen pelvis shows progression of metastatic liver disease (arrows), new mesenteric lesions (not shown), and a new vertebral body metastasis (arrowhead).
CEA should be measured every 3 months in patients with stage II or III CRC for 3 years following diagnosis and treatment.

Elevated postoperative CEA level has a higher likelihood of representing metastatic disease as opposed to isolated local recurrence.

Normal CEA concentrations do not exclude disease progression.

PET/CT is useful in detecting CRC recurrence, particularly in patients who do not present with elevated serum CEA levels.

40-year-old female with history of stage IIIb colon cancer and uptrending CEA 2 years after diagnosis. PET imaging reveals a new FDG avid lesion within the right mesorectal fat (arrows) consistent with early disease recurrence.
Pancreatic Cancer

4th leading cause of cancer death in the United States

Precise role of serum carbohydrate antigen 19.9 (CA 19-9) is not defined. It is the most validated tumor marker but with several limitations

CA 19-9 can be elevated with non-pancreas cancers as well as with pancreatitis and cirrhosis. False negatives for pancreatic cancer occur in 5-10% of population

No role for CA 19-9 in pancreatic cancer screening

Double duct sign evident as both common duct (arrow) and pancreatic duct (arrowhead) are dilated. Obstructing pancreatic head mass (not shown) confirmed to be adenocarcinoma. Patient had normal serum CA 19-9 level of 8 U/mL (0-36 U/mL is normal range) at time of diagnosis, highlighting case of false negative tumor marker for pancreatic cancer.
Normal blood levels of CA 19-9 are below 37 U/mL

Not accurate enough to detect cancer in isolation

In conjunction with imaging, elevated CA 19-9 helps differentiate pancreatic cancer from focal pancreatitis

Reported specificity of CA19-9 for pancreatic cancer when > 100 U/mL is 98%

Addition of CEA level increases specificity for pancreatic carcinoma if both markers are elevated

Ill-defined pancreatic head mass (arrow) in a 69-year-old male with epigastric pain. Findings initially favored to represent focal pancreatitis, given adjacent fat stranding (arrowhead) and elevated lipase. However, CA 19-9 was markedly elevated at 524 U/mL and CEA was 87 ng/mL, highly suggestive of malignancy. Surgical biopsy confirmed pancreatic adenocarcinoma.
CA 19-9 Useful for Prognosis and Monitoring Treatment Response

Higher preoperative CA 19-9 level (>37 U/mL) associated with lower median survival.

CA 19-9 level > 1000 U/mL suggests unresectable or metastatic disease. This augments imaging which can underestimate vascular invasion or metastasis in up to 15% of patients.

Monitoring response of therapy with CT or MRI for nonsurgical patients is difficult as these lesions often have obscure margins.

Therefore, trending of CA 19-9 serves as a complimentary test.

61-year-old woman with unresectable pancreatic cancer. 3.6 cm hypodense pancreatic head mass (open arrow) with ill-defined borders and obstruction of the common bile duct (arrow). Increasing CA 19-9 during chemotherapy indicates progression. Definitive change in size of the mass is difficult to evaluate on follow-up CT 3 weeks later due to the obscure margins but new hepatic metastases (arrowheads) confirm disease progression despite treatment.
76-year-old male found to have a 4.7 cm hypoenhancing pancreatic head mass (arrow), consistent with adenocarcinoma. CT is without evidence of vascular invasion or metastatic disease. However, based on tumor size and CA 19-9 >500 U/mL, neoadjuvant chemotherapy was pursued in lieu of surgery.

Follow up CT 6 weeks later reveals disease progression with enlargement of pancreatic head mass (open arrow) and multiple new liver metastases (arrowheads). Initial serum CA 19-9 > 500 U/mL suggested presence of radiographically occult metastatic disease which made Whipple procedure a poor treatment option despite no contraindication on CT.
Testicular Cancer

Most common in men age 15-35

AFP, lactate dehydrogenase (LDH), and human chorionic gonadotropin (hCG) are established tumor markers

No role in screening

Work-up of testicular mass includes physical exam, US, and serum tumor markers

Lower levels of hCG (<500 mIU/mL) suggest seminoma. Non-seminoma germ cell tumors (NSGCTs) are associated with levels >1000 mIU/mL

Pure seminomas do not produce AFP

Left testicular NSGCT (arrows). A tumor histologically classified as a seminoma will be reclassified as NSGCT if serum AFP is elevated, indicating the importance of tumor markers as treatment varies significantly between the two. Seminomas are also typically homogenous in appearance on US.
Tumor marker measurement is mandatory in staging of testicular cancer

Degree of AFP, hCG, and LDH elevation is proportional to tumor burden and therefore reflects prognosis

In TNMS staging system, S refers to serum tumor markers. These markers are used to risk stratify patients. These markers are used to risk stratify patients

Treatment selection based on prognostic group

<table>
<thead>
<tr>
<th>Stage</th>
<th>LDH (U/liter)</th>
<th>hCG (mIU/mL)</th>
<th>AFP (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S0</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>S1</td>
<td>&lt;1.5 x nml</td>
<td>&lt;5000</td>
<td>&lt;1000</td>
</tr>
<tr>
<td>S2</td>
<td>1.5 – 10x nml</td>
<td>5000-50000</td>
<td>1000-10000</td>
</tr>
<tr>
<td>S3</td>
<td>&gt;10x nml</td>
<td>&gt;50000</td>
<td>&gt;10000</td>
</tr>
</tbody>
</table>

S portion of “TNMS” staging for testicular cancer (chart to left).
If AFP or hCG elevated prior to therapy, the rate of marker decline reflects response to treatment. Failure of marker levels to normalize suggests residual disease and requires chemotherapy.

After successful primary therapy, markers are monitored weekly for 6 months and then less sporadic for 5 years.

Even if not raised before therapy, serial tumor marker monitoring is recommended as marker expression can change after treatment.

Homogeneous left testicular mass (arrows). CT abdomen shows enlarged retroperitoneal lymph nodes (arrowhead). Gross path specimen (bottom) determined to be seminoma. LDH 2x greater than normal. Patient staged T1N1M0S2 and received adjuvant chemoradiation therapy. LDH subsequently normalized.
Ovarian Cancer

Highest mortality of gynecologic tumors

CA 125 most reliable tumor marker, but is effective for epithelial ovarian malignancy only

Not recommended for screening due to lack of sensitivity and specificity

CA 125 elevated in only 50%-60% of patients with stage I ovarian cancer

Pelvic inflammatory disease, endometriosis, and pregnancy can falsely elevate CA 125

Left ovarian mass with homogeneous low level echos (arrows) and no internal flow on US, suggestive of an endometrioma. Patient had elevated CA 125 of 87 U/mL (normal range is 0.6-35 U/mL) and endometrioma was confirmed at surgery.
Threshold CA 125 value is 35 U/mL

CA 125 used as an adjunct in distinguishing benign from malignant ovarian masses

Risk of malignancy index (RMI) incorporates CA 125 levels in addition to sonographic features of an adnexal mass and menopausal status of patient

A single CA 125 measurement is not as effective as trends. Benign masses have stable levels, and progressively increasing levels indicate ovarian cancer

Risk of Malignancy Index

Ultrasound Components (>1 = higher risk):
1. Multilocular
2. Solid component
3. Evidence for metastasis
4. Ascites
5. Bilateral ovarian lesions

US score (maximum of 3) is multiplied by menopausal status (expressed as 1 if premenopausal and 3 if postmenopausal) and CA 125 level to derive a RMI value. RMI greater than 200 indicates malignancy.

If there is suspicion for a germ cell tumor (more common in women younger than 40), AFP and hCG are important adjunct tumor markers
Discrimination of Pelvic Masses

Cystic left ovarian mass with irregular solid component (arrow) in a 32-year-old woman. There was no ascites and the serum CA 125 was 20 U/mL. RMI calculated to be 20 which favors a benign entity. A mature cystic teratoma was confirmed.

Purely solid right adnexal mass (arrow) with moderate pelvic free fluid (arrowheads) and a serum CA 125 of 256 U/mL in a 63-year-old woman. RMI calculated to be 2304 which suggests a malignant lesion. A serous cystadenocarcinoma was confirmed.
Ovarian Disease Recurrence

Declining CA 125 levels correlate with response to chemotherapy.

Rising CA 125 values after definitive treatment predict relapse. Normal levels, however, do not exclude presence of disease.

CA 125 is monitored every 2-4 months for at least 2 years.

Human epididymal protein 4 (HE4) is new marker that aids in distinguishing ovarian cancer from benign disease.

50-year-old woman previously treated for ovarian serous cystadenocarcinoma with increasing CA 125 levels. CT confirms recurrent disease, evident as peritoneal implants/studding (arrows) and large volume ascites (arrowheads).
The radiologist often interprets oncologic imaging examinations with only a portion of the complete clinical picture which can yield indeterminate reports.

Knowledge of serum tumor markers at the time of imaging interpretation can increase diagnostic accuracy and improve the quality of radiology reports by highlighting information that is germane to the referring clinician.

Serum tumor markers are particularly useful in diagnosing pancreatic and ovarian cancer, staging testicular cancer, and predicting advanced disease in numerous cancers.

**Conclusion**
Michael Reiter
mikereiter13@yahoo.com
San Antonio Military Medical Center
3851 Roger Brooke Drive
San Antonio, TX 78234