Hepatocellular Carcinoma Surveillance and Treatment

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Disclosures

- Consultant
  - Gilead
- Speakers’ Bureau
  - Gilead
HCC: Epidemiology

- HCC is the most common primary liver malignancy
- Worldwide incidence >600,000 cases per year
- >25,000 new cases and >20,000 deaths in 2014 in
- HCC develops in a cirrhotic liver in 80% of cases
- More common in men than women (4:1)
- The overall HCC 5-year relative survival rate for 1996-2004 was 11.7%

Who is at risk?

- Cirrhosis from any cause
  - HCV: 3-5% per year
  - HBV: 5-8% per year
  - Heavy alcohol consumption
  - Non-alcoholic fatty liver disease
  - Autoimmune hepatitis
  - Hemochromatosis
  - PBC
- HBV without cirrhosis: 0.5% per year
SCREENING AND SURVEILLANCE
Practice Guidelines on Screening & Surveillance for HCC

- **At-risk patient groups:**
  - Hepatitis B carriers
    - Asian males >40 years
    - Asian females >50 years
    - All cirrhotic hepatitis B carriers
    - Family history of HCC
    - Africans/North American Blacks
    - (Non-cirrhotic hepatitis B carriers with high HBV DNA levels or more severe current/past levels of inflammatory activity)
  - Cirrhosis due to hepatitis C, alcohol, hemochromatosis, PBC, or other causes
## Surveillance Guidelines for High-Risk Patients

| Society/Institution                          | Guidelines                  |
|----------------------------------------------|----------------------------|---|
| AASLD American Association for the Study of Liver Diseases | US every 6 months          |
| EASL European Association for the Study of the Liver | US every 6 months          |
| APASL Asian-Pacific Association for the Study of the Liver | AFP + US every 6 months    |
| NCCN National Comprehensive Cancer Network   | AFP + US every 6-12 months  |
| VA United States Department of Veterans Affairs | AFP + US every 6-12 months  |
Ultrasound

- In studies reported to be ~60% sensitive for HCC
- Multiple limitations
  - Does not detect infiltrative disease
  - Sensitivity decreased in difficult patients
    - Cirrhotic nodular livers
    - Obesity
    - Abdominal gas
    - Noncompliant with breath-hold
  - Highly operator dependent
- Real life US sensitivity likely much lower than that of studies
Surveillance and Diagnostic Tests

- Serologic markers
  - Alpha-fetoprotein (AFP)
  - AFP-L3%
  - Des-gamma carboxyprothrombin (DCP)

- Imaging
  - Ultrasound
  - Computed tomography (CT)
  - Magnetic resonance imaging (MRI)

Must be multiphase with contrast
How Good is AFP for HCC?

• Depends on…
  – Who your patient is (etiology, age, ALT, etc)
  – Where you are (prevalence of HCC)
  – What you consider to be an elevated AFP
  – How often you measure AFP (one or more time points)
  – How good your other testing for HCC is
Other Causes of Elevated AFP

- Hepatoblastoma
- Neuroblastoma
- Non-seminomatous germ cell tumors including endodermal sinus tumors and teratomas
- Hepatitis
- Colitis
- Ataxia telangiectasia
- Pregnancy
- Other cancers: gastric, mixed hepatobiliary, pancreatic
The “Accuracy” of AFP

• May be influenced by
  – Patient factors
  – Test cut-off value
  – Prevalence of disease of interest in the population

• Weigh these factors when assessing the value of AFP, but before you dismiss it…

• Remember that 20% of HCCs are detected by elevated AFP alone!

Lok a et al, Gastro 2010
Improving the Accuracy of AFP

- AFP combined with other biomarkers
- Serial AFP: Assessing a trend
- AFP combined with imaging tests
AFP-L3%

- AFP-L3% is the ratio of AFP-L3 to total AFP as a percentage. The AFP-L3(%) has been reported to be highly specific for HCC compared to AFP concentration in clinical practice.

- The glycoform AFP-L3 has an additional alpha1-6 fucose residue attached at the reducing terminus of N-acetylglucosamine. The AFP-L3 protein has been shown to be elevated in patients with HCC.
Des-gamma CarboxyProthrombin

- DCP is an abnormal form of the coagulation protein, prothrombin
- The prothrombin precursor normally undergoes post-translational carboxylation in the liver
- Many HCCs lacks the appropriate carboxlase and secretes instead the unmodified precursor, DCP

**NOT accurate in patients on warfarin**
Combined Testing Identifies a Greater Number of Patients with HCC

In this study of 74 patients with known HCC, the use of AFP alone would have detected 45 positive cases and missed 29 cases of HCC.

<table>
<thead>
<tr>
<th></th>
<th>Cut-off point</th>
<th>Positive cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFP</td>
<td>≥ 20 ng/mL</td>
<td>45 (60.8%)</td>
</tr>
<tr>
<td>AFP-L3</td>
<td>≥ 10 %</td>
<td>49 (66.2%)</td>
</tr>
<tr>
<td>DCP</td>
<td>≥ 7.5 ng/mL</td>
<td>29 (39.2%)</td>
</tr>
<tr>
<td>Combination of AFP, AFP-L3, and DCP</td>
<td>Same as above</td>
<td>67 (90.5%)</td>
</tr>
</tbody>
</table>

FDA submission data for uTASWako i30 (data not published)
How Good is Imaging for HCC?

Imaging improves sensitivity compares with AFP alone

<table>
<thead>
<tr>
<th>Number of Studies</th>
<th>Ultrasound 199</th>
<th>Multiphase CT 164</th>
<th>Multiphase MRI 197</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Sensitivity</td>
<td>58%</td>
<td>69%</td>
<td>78%</td>
</tr>
<tr>
<td>Lesions &lt;2 cm</td>
<td>35%</td>
<td>59%</td>
<td>63%</td>
</tr>
<tr>
<td>Lesions &gt;2 cm</td>
<td>69%</td>
<td>73%</td>
<td>85%</td>
</tr>
</tbody>
</table>

- If the suspicion for HCC is high, choices are to do a more sensitive test or wait for the tumor to get bigger

Snowberger et al, Aliment Pharmacol Ther 2007
Stepwise Hepatocarcinogenesis and Changes of Intranodular Blood Supply

- Portal venous supply
- Hepatic arterial supply
- Abnormal arterial supply

RN  Low DN  High DN  Early HCC  Well HCC  Moderately HCC
Triple Phase Imaging
Making the diagnosis of HCC

- Biopsy is very rarely indicated
  - Risk of tracking tumor cells
    - 0.5-1.5%
  - High false negative rate
    - Up to 30% in some series
      - More with smaller lesions
      - More difficult with well differentiated tumors
TREATMENT
HCC Prognosis

- Survival has been improving over last 15 years
  - Improved survival after resection
  - More diagnosis at earlier stage (screening!)
  - More local therapy available

1 Year Survival of HCC
Management of HCC

- Liver transplantation
- Resection
- Imaging guided interventions
  - Percutaneous ethanol injection (PEI)
  - Radiofrequency thermal ablation (RFA)
  - Chemoembolization (TACE)
  - Yttrium
- Targeted molecular therapy: Sorafenib
Liver Transplant for HCC
Milan Criteria (Stage I+II)

Single, not > 5cm

Up to 3, none > 3cm

Absence of Macroscopic Vascular Invasion
Absence of Extrahepatic Spread

Liver Transplantation for HCC: Outcomes Applying Milan Criteria

<table>
<thead>
<tr>
<th>Authors</th>
<th>N</th>
<th>Selection Criteria</th>
<th>Recurrence</th>
<th>5-yr Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mazzaferro (1996)</td>
<td>48</td>
<td>Single &lt;5 cm 3 nodules &lt;3 cm</td>
<td>8%</td>
<td>74%</td>
</tr>
<tr>
<td>Bismuth (1999)</td>
<td>45</td>
<td>Single &lt;3 cm 3 nodules &lt;3 cm</td>
<td>11%</td>
<td>74%</td>
</tr>
<tr>
<td>Llovet (1999)</td>
<td>79</td>
<td>Single &lt;5 cm</td>
<td>4%</td>
<td>75%</td>
</tr>
<tr>
<td>Jonas (2001)</td>
<td>120</td>
<td>Single &lt;5 cm 3 nodules &lt;3 cm</td>
<td>16%</td>
<td>71%</td>
</tr>
</tbody>
</table>

Downstaging

• “a treatment that intends to facilitate or make possible a surgical procedure that otherwise would be too risky or unfeasible”

Key issues:
- Inclusion criteria
  - Tumor size/number, AFP, tumor grade
- Type of therapy to downstage
- Criteria for response
  - Within Milan, degree of necrosis, decline in AFP
- Mandated period of observation to determine success of downstaging procedure
  - 3 mos vs 6 mos
<table>
<thead>
<tr>
<th>Reference</th>
<th>Treatment</th>
<th>Criteria for Downstaging</th>
<th>Criteria for Response</th>
<th>Post-OLT results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graziadei 2003</td>
<td>TACE</td>
<td>&gt;UCSF</td>
<td>&gt;50% tumor reduction</td>
<td>5 yr OS 25%</td>
</tr>
<tr>
<td>Otto 2006</td>
<td>TACE</td>
<td>No upper size limit</td>
<td>RECIST</td>
<td>5 yr RFS 93% if stable, 28% with minimal progression</td>
</tr>
</tbody>
</table>
| Yao 2008       | TACE, RFA, PEI, combo, resection | 1 lesion 5-8 cm  
2 or 3 lesions: less than 5 cm, total diameter <8 cm  
4 or 5 lesions, all <3 cm, total diameter <8 | Milan T2 or complete tumor necrosis                       | 4 yr OS 94%, no recurrence                                 |
| Ravaioli 2008  | TACE, RFA, PEI     | 1 lesion <8 cm  
5 lesions <4 cm and total diameter <12 cm                                               | Milan T2 including necrotic portion, AFP <400              | 3 yr DFS 71%          |
| Chapman 2008   | TACE               | UNOS stage III/IV                                                                      | Degree of necrosis/RECIST                                  | 5 yr OS 94.1% 6% recurrence |
| Lewandowski 2009 | TACE, TARE        | T3                                                                                     | Milan, including necrotic portion                           | 1 yr DFS 73% 1 yr OS 89% |
| DeLuna 2009    | TACE               | >Milan                                                                                  | Milan                                                      | 3 yr OS 79%          |
| Baraakat 2010  | TACE+RFA, TARE     | 1 lesion <6 cm  
<3 lesions <4 cm                                                                 | Milan                                                      | 2 yr OS 75% Recurrence 14%                                   |
| Jang 2010      | TACE               | >Milan                                                                                  | Milan                                                      | 5 yr DFS 66%         |
| Toso 2010      | RFA, TACE, TARE    | <TTV <250 cm3  
(1 lesion <7.8 cm or 3 lesions up to 5.4 cm)                                           | Milan criteria NOT including necrotic portion AND AFP <400 | pending              |
Downstaging to Transplant

- Yao et al reported excellent downstaging results in 61 patients:
  - 4 yr OS 92%
  - No recurrence post OLT median F/U 25 months
- Updated report: 122 patients enrolled
  - 81 pts (66%) downstaged to Milan, mandated 3 mos waiting time
  - 68 pts (56%) OLT: 28 complete necrosis, 30 T2, 10 >T2

Failure: >3 LRT, HR 2.1; pre-treatment AFP >1000, HR 2.4

<table>
<thead>
<tr>
<th></th>
<th>Downstaging group N=122</th>
<th>Control Group N=488 T2 on presentation</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PostOLTOS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 YR</td>
<td>93.8%</td>
<td>94.3%</td>
<td>0.87</td>
</tr>
<tr>
<td>5 YR</td>
<td>80.3%</td>
<td>81%</td>
<td></td>
</tr>
<tr>
<td>RFS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 YR</td>
<td>95.3%</td>
<td>95.9%</td>
<td>0.31</td>
</tr>
<tr>
<td>5 YR</td>
<td>91.4%</td>
<td>87.6%</td>
<td></td>
</tr>
<tr>
<td>ITT OS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 YR</td>
<td>88.5%</td>
<td>After listing</td>
<td>0.11</td>
</tr>
<tr>
<td>5 YR</td>
<td>56.1%</td>
<td>85.2%</td>
<td></td>
</tr>
</tbody>
</table>

Yao et al, Hepatol 2008; Yao et al, AASLD 2012
Ablation

- Radiofrequency ablation (RFA) is the current standard
- Percutaneous ethanol injection (PEI) is for developing countries with limited resources
- Microwave is faster to full tumor ablation but resources are expensive
Radiofrequency Ablation (RFA)

- Radiofrequency thermal energy applied to the tumor (percutaneous or laparoscopically)
  - Limited by adjacent structures
- For patients who do not meet resection criteria and are Child-Pugh A or B
  - Best for tumors less than 4cm

<table>
<thead>
<tr>
<th>Diameter (cm)</th>
<th>Complete local control</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2.5</td>
<td>90%</td>
</tr>
<tr>
<td>2.5-3.5</td>
<td>70-90%</td>
</tr>
<tr>
<td>3.5-5.0</td>
<td>50-70%</td>
</tr>
<tr>
<td>&gt;5.0</td>
<td>&lt;50%</td>
</tr>
</tbody>
</table>

Recurrence of HCC after RFA

- Overall recurrence rate 70% at 3 years, 81% at 5 years
- Local recurrence (LR) 13% at 5 years
- Nonlocal recurrence (NLR) 50% at 5 years
  - Advanced nonlocal recurrence (ANLR) 19.2%
Transarterial Chemoembolization (TACE)
**TACE/TAE versus best supportive care or suboptimal therapy: A meta-analysis**

<table>
<thead>
<tr>
<th>Randomized controlled trials</th>
<th>Number of pts</th>
<th>Odds ratio (95% CI) 2-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lin et al, 1998</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>GRETCH, 1995</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td>Bruix et al, 1998</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>Pelletier et al, 1998-73</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lo et al, 2002</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>Llovet et al, 2002</td>
<td>112</td>
<td></td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td><strong>503</strong></td>
<td></td>
</tr>
</tbody>
</table>

| Odds ratio (95% CI) 2-year survival | p=0.086 | p=0.017 |

OR=0.53 [95% CI, 0.32–0.89]; p=0.017

Heterogeneity p=0.14

TACE: Evolving Techniques

Non-selective treatment of the entire liver parenchyma

Selective treatment
(segmental approaches with microcatheters)

‘Homemade’ drug-in-oil emulsions and embolic agents

Drug-eluting bead
(calibrated embolic microsphere)

HCC, hepatocellular carcinoma;
TACE, transarterial chemoembolization.

Lencioni R. Personal communication.
cTACE vs DEB TACE

- Similar outcomes for response rate and overall survival
  - Response rates 30%-73.1%
  - Overall survival
    - BCLC A 40-54.1 months
    - BCLC B 17.4-47.7 months
  - Time to progression longer with DEB-TACE
- Less chemotherapeutic side effects with DEB-TACE
- Less post-embolic syndrome with DEB-TACE
90Yttrium Microspheres

- Glass or resin available
- 10-60 microns in size
- 100% pure beta emitter
- Physical half-life of 64.2 h: gone in 2 weeks
- Average tissue penetration range of 2.5 mm
- With delivery preferentially deposits in tumor tissue due to increased blood flow
90Yttrium Microspheres

- Exposure to radiation causes irreversible cell damage to epithelial, stromal, and endothelial cells
- This leads to compromised tumor growth
- Median time to response
  - 1.2 months for necrosis
  - 6 months for shrinkage
- Progression the result of new lesions elsewhere or within the primary lesion due to nests of tumor cells that were not treated due to lack of arterialization
## Large Series of Y90

<table>
<thead>
<tr>
<th>Reference</th>
<th>Child Pugh</th>
<th>Interim Stage</th>
<th>Branch PVT</th>
<th>Main PVT</th>
<th>Branch or Main PVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hilgard et al, N=108</td>
<td></td>
<td>A/B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>51</td>
<td>16.4</td>
<td></td>
<td>33</td>
</tr>
<tr>
<td>Salem et al, N=291</td>
<td>A</td>
<td>48</td>
<td>17.3</td>
<td>19</td>
<td>16.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>35</td>
<td>13.5</td>
<td>27</td>
<td>6.5</td>
</tr>
<tr>
<td>Sangro et al, N=325</td>
<td>A</td>
<td>82</td>
<td>18.4</td>
<td>44</td>
<td>10.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5</td>
<td>3.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mazzaferro et al, N=51</td>
<td>A</td>
<td>15</td>
<td>18</td>
<td>23</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>-</td>
<td>6</td>
<td>8</td>
</tr>
</tbody>
</table>
Radioembolization-Induced Liver Disease (REILD)

- A form of sinusoidal obstructive syndrome
- Occurs 4-8 weeks after Y90
- Jaundice, ascites, increased GGT/Alk Phos
- 0-33% treated as whole liver
- 8-15% treated as partial liver
- Supportive care only as treatment
Y90 General Consensus

**Indications**
- Intermediate HCC
  - Single or multinodular, <20% of liver volume with CP A, PS 0
  - Multifocal 20-40% of liver, only if good liver function
- Advanced HCC
  - No extrahepatic disease
  - Branch or main PV invasion
  - Normal liver function
  - PS 0

**Contraindications**
- Relative
  - Renal failure
  - High risk varices
- Absolute
  - Decompensated cirrhosis
  - Bilirubin over ~2
  - Massive tumor with both lobes involved (tumor >75% of liver volume)
  - Lung or GI shunts
## TACE vs Y90

<table>
<thead>
<tr>
<th>TACE</th>
<th>Y90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embolic</td>
<td>Microembolic</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>Radiation</td>
</tr>
<tr>
<td>One procedure</td>
<td>Two procedures: planning and treatment</td>
</tr>
<tr>
<td>Overnight hospital admission</td>
<td>Same day discharge</td>
</tr>
<tr>
<td>Extensive research</td>
<td>Early research</td>
</tr>
<tr>
<td>Accepted therapy for intermediate HCC</td>
<td>Still considered investigational</td>
</tr>
<tr>
<td>$3,500 per dose</td>
<td>$12,500 per dose</td>
</tr>
</tbody>
</table>

Would need a study of over 1000 patients to detect any difference
External Beam Radiation Therapy: Where does it fit?

- Role is not well defined in HCC
- Previous radiation therapy limited by low tolerance of liver
- Newer strategies to decrease radiation exposure to normal tissues while delivering high doses to tumor
  - Optimal dose for both HCC and cirrhotic liver still not clearly defined
Factors to Consider for Safety of XRT

- **Liver Function**
  - Child Pugh A vs B vs C
  - Planned residual functional liver
    - >700 mL nontumor liver (vs <700 mL)
  - Liver dose volume constraints can be met

- **Tumor characteristics**
  - Distribution of tumors (focal vs diffuse)
  - Number of tumors (<3 vs 3-5 vs >5)

- **Target proximity to luminal GI tissues**
  - >2 cm from tumor vs 1-2 cm vs <1 cm

- **Experience with specific radiation technique**
Management of Hepatocellular Carcinoma Requires a Multidisciplinary Approach

Hepatobiliary Surgery

Hepatology

Pathology

Oncology

Radiology

Radiation Oncology
Chemotherapies
Phase III SHARP Trial: Overall Survival (Intent-to-Treat Population)

Sorafenib Median: 10.7 months (95% CI, 40.9-57.9)
Placebo Median: 7.9 months (95% CI, 29.4-39.4)

Hazard ratio (Sor/Pbo): 0.69 (95% CI, 0.55-0.87)
P = 0.00058*

Patients at risk
Sorafenib: 299 274 241 205 161 108 67 38 12 7 2
Placebo: 303 276 224 179 126 78 47 25 12 7 2

## Combination Therapy: Locoregional Therapy and Angiogenesis Inhibition

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Sorafenib + TACE</th>
<th>TACE</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Kudo et al</strong></td>
<td>N=458</td>
<td>Sorafenib + TACE</td>
<td>TACE</td>
<td>p value</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median Sorafenib 385 mg/d</td>
<td></td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median TTP (mos) 5.4</td>
<td>3.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median OS (mos) 29.7</td>
<td>Not reached</td>
<td>0.79</td>
</tr>
<tr>
<td><strong>Sansonno et al</strong></td>
<td></td>
<td>Sorafenib + TACE</td>
<td>TACE</td>
<td>p value</td>
</tr>
<tr>
<td>HCV pts only</td>
<td></td>
<td>Median TTP (mos) 9.2</td>
<td>4.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recurrence at 6 mos 22%</td>
<td>77%</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>Lencioni et al</strong></td>
<td>“SPACE”</td>
<td>Sorafenib + TACE</td>
<td>TACE</td>
<td>p value*</td>
</tr>
<tr>
<td>“SPACE”</td>
<td></td>
<td>Median Sorafenib 566 mg/d</td>
<td></td>
<td>0.072</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median TTP (d) 169</td>
<td>166</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>median TTP 25% 112</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>median TTP 75% 285</td>
<td>224</td>
<td></td>
</tr>
</tbody>
</table>

*1 sided log rank w/alpha set 0.15
Molecular Therapies Under Evaluation for HCC

<table>
<thead>
<tr>
<th>Targeted Population</th>
<th>Rationale/Setting</th>
<th>Phase 3 Comparison</th>
</tr>
</thead>
</table>
| **Adjuvant**        | Prevent recurrence| 1. Sorafenib vs placebo  
2. Retinoids vs placebo |
| Intermediate HCC    | Improve TACE      | 1. TACE ± sorafenib  
2. TACE ± brivanib |
| **Advanced HCC**    |                   | 1. Sorafenib ± erlotinib  
2. Sorafenib vs brivanib  
3. Sorafenib vs sunitinib  
4. Sorafenib vs linifanib  
5. Sorafenib ± Y90  
6. Sorafenib ± doxorubicin |
|                     | First line        | 1. Brivanib vs placebo  
2. Everolimus vs placebo  
3. Ramucirumab vs placebo  
4. ADI-PEG 20 vs placebo  
5. Tivantinib vs placebo |
|                     | Second line       |                    |

ADI = Arginine deaminase inhibitor.
Clinical Trials.gov Website. Available at: http://clinicaltrials.gov
Conclusions

- HCC is a rapidly rising cause of morbidity and mortality in the US
- Appropriate screening can save lives
- Treatment is best offered in a multidisciplinary setting
- Multiple treatment options available can improve patient survival