Research Prioritization Topic Brief

Topic 14: “Treatments for Liver Cancer”

Comparative effectiveness of medical and surgical treatment options in patients with primary or metastatic malignancies of the liver in adults.

PCORI Scientific Program Area: Assessment of Prevention, Diagnosis and Treatment Options

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The Duke Clinical Research Institute

April 16, 2013
<table>
<thead>
<tr>
<th>Criteria</th>
<th>Brief Description</th>
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<tbody>
<tr>
<td><strong>Introduction</strong></td>
<td><strong>DESCRIPTION OF CONDITION</strong></td>
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<tr>
<td>Overview/definition of topic</td>
<td>• Two different types of liver cancer: primary and secondary</td>
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<td></td>
<td>• Primary liver cancer (cancer arising from the cells of the liver)</td>
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<td></td>
<td>o Most commonly hepatocellular carcinoma (HCC)</td>
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<td>o HCC almost always arises in patients with chronic liver disease (from other causes): 1-2</td>
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<td></td>
<td>▪ Alcohol addiction/abuse/overuse</td>
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<td></td>
<td>▪ Chronic infection with Hepatitis B or C</td>
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<td>▪ Nonalcoholic fatty liver disease (associated with obesity and Type 2 diabetes)</td>
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<td>▪ Less common exposures such as arsenic, certain chemicals in plastics, abuse of anabolic steroids (testosterone derivatives), rare metabolic/genetic conditions</td>
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<td>• Secondary liver cancer (other cancer has spread to liver; called liver metastases)</td>
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<td>o Cancer cells from another organ cause tumors in the liver</td>
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<td>o Most common original cancer site is the colon 3                                                                -dismissed</td>
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<td>▪ 60-70% of colon cancer patients eventually develop liver metastases</td>
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<td>▪ 20-25% have liver metastases at time of diagnosis</td>
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<td>▪ 40-50% develop liver metastases despite colon cancer treatment</td>
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<td>o Other cancers that spread to the liver include breast, esophagus, stomach, pancreas, skin, and lung</td>
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<td>o Treatment of secondary liver cancer is based on treatment of original cancer</td>
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<td>Relevance to patient-centered outcomes</td>
<td>• Symptoms</td>
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<td></td>
<td>o Primary liver cancer (HCC)</td>
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<td></td>
<td>▪ Jaundice (skin and whites of eyes become yellow, urine darkens, color of stool becomes lighter than normal)</td>
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<td>▪ General feelings of poor health, weakness, and fatigue</td>
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<td>▪ Loss of appetite and/or weight loss</td>
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<td>▪ Abdominal bloating</td>
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<td>▪ Itching of skin</td>
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<td>▪ Abdominal pain or discomfort</td>
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<td>▪ Swelling of legs</td>
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<td></td>
<td>o Secondary liver cancer (liver metastases)</td>
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<td>▪ Similar to HCC</td>
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<td>▪ May have symptoms related to original type of cancer or from its treatment</td>
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<td>• Other outcomes</td>
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<td>o Mortality</td>
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<td>o Quality of life (affected both by underlying disease and by treatments)</td>
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<td>Burden on Society</td>
<td><strong>INCIDENCE (new cases)/PREVALENCE (proportion of population with condition)</strong></td>
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<td>Recent incidence and prevalence in populations and subpopulations</td>
<td>• Incidence approximates prevalence for both primary and secondary liver cancer due to high mortality rates</td>
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<tr>
<td></td>
<td>• Primary liver cancer (HCC)</td>
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<td>o Age-adjusted incidence 3.2 per 100,000 in the United States in 2006 and increasing due to increases in causes such as obesity and Type 2 diabetes and exposure to hepatitis B or C</td>
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to rise in rate of hepatitis B and C (present in 80% of HCC cases)

- Incidence and prevalence are much higher in other parts of the world (eg, Asia, Africa), mirroring higher rates of hepatitis B and C
- In the United States, more common in men than women and more common among Asian/Pacific Islanders, Native Americans/Alaska Natives, blacks, and Hispanic people than in whites (age-adjusted incidence per 100,000)

• Secondary liver cancer (liver metastases): Difficult to estimate overall, as multiple cancers can cause liver metastasis
  - Overall incidence of colon cancer is 46.3 per 100,000, and about 20-25% of these patients have metastases
  - Assuming 65% of all cases eventually develop liver metastases (age-adjusted incidence per 100,000)
  - By race/sex, secondary liver cancer (liver metastases) are between 1.5 to more than 10 times more likely than primary liver cancer (HCC)
  - Metastases at time of diagnosis are slightly more common in blacks than in whites

<table>
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<th>Effects on patients’ quality of life, productivity, functional capacity, mortality, use of health care services</th>
<th>QUALITY OF LIFE</th>
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<tbody>
<tr>
<td>• Both primary (HCC) and secondary liver cancer (liver metastases) have a major impact on quality of life, with impact increasing with worsened tumor cancer stage</td>
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FUNCTIONAL CAPACITY/PRODUCTIVITY

- Primary liver cancer/HCC: Functional capacity reduced; impact on functional capacity often worse among patients with advanced liver disease due to hepatitis B or C infections and/or other illnesses
- Secondary liver cancer (liver metastases): Major impact on functional capacity; patients often debilitated from their cancer treatments (which can include surgery, chemotherapy, and radiation) as well as from underlying illness

MORTALITY

- Primary liver cancer (HCC):
  - One-year survival rate remains <50%, five-year survival rate 14.4%
  - Age-adjusted death rate is estimated at 5.2 per 100,000 people per year in the United States
- Secondary liver cancer: Varies by tumor type; for colon cancer that spreads to the liver, one-year survival is ~40%, and five-year survival is ~6-8%

How strongly does this overall societal burden suggest that CER on alternative approaches to this problem should be given high priority?

- Incidence of primary liver cancer (HCC) is increasing as prevalence of hepatitis B and hepatitis C increase
  - Primary liver cancer (HCC) is a high-mortality condition
    - There is a range of available treatments, lending high priority to CER
    - However, relative burden of primary liver cancer much smaller than for secondary liver cancer
    - Other strategies available for preventing morbidity/mortality from primary liver cancer
      - Primary prevention of hepatitis B and C through vaccination (currently available only for hepatitis B), screening, measures to prevent the spread of hepatitis
infections between people, improved treatments for chronic hepatitis infection
- Prevention and treatment of other conditions (alcoholism, type 2 diabetes, and other liver diseases)
  - Secondary liver cancer (liver metastases) can result from multiple other types of cancers
    - Colon cancer with associated liver metastasis is a relatively common, high-mortality condition. This also makes colon cancer a high priority for CER.

### Options for Addressing the Issue

**Based on recent systematic reviews, what is known about the relative benefits and harms of the available management options?**

<table>
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<tr>
<th>SYSTEMATIC REVIEWS</th>
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<tr>
<td>Imaging Techniques for the Surveillance, Diagnosis, and Staging of Hepatocellular Carcinoma (HCC) (EPC Project In Process)¹¹</td>
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<tr>
<td>Local Therapies for Unresectable Primary Hepatocellular Carcinoma: Comparative Effectiveness Review (Draft 2012)¹⁴</td>
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**SCREENING/EARLY DIAGNOSIS**

- Primary liver cancer (HCC)¹¹
  - Among patients with hepatitis B or C, screening is typically done using ultrasonography (u/s), computerized tomography (CT, aka CAT scan), and magnetic resonance imaging (MRI)
  - Otherwise, primary liver cancer is most often found incidentally on imaging studies done for other reasons

- Secondary liver cancer (liver metastases)
  - Liver metastases not typically screened for, though primary cancers that lead to liver metastases often have established screening tests (eg, colon cancer and screening with a colonoscopy)

**TREATMENT**

- Primary liver cancer (HCC): In cases where HCC is detected early enough and the patient’s liver function is sufficient to allow a procedure, a variety of procedural treatments may be possible.
  - Medical treatment (most commonly a drug called sorafenib) is sometimes an option, but HCC tends to be resistant to standard drug therapy¹⁴-¹⁵
  - Surgery: If a tumor meets certain criteria for size and location, surgical removal may be an option, and may prolong survival or even be curative.
  - Liver transplantation: This is the treatment of choice for some patients with poor liver function who cannot tolerate surgery.
  - Treatment with one of the below therapies may be used as a bridge to transplant.
    - Ablation: Destruction of liver cancer tissue through chemical injury or heating.
    - Embolization: Blockage of blood vessels that supply the liver cancer.
    - Radiotherapy: Directed radiation to destroy liver cancer tissue.

- Secondary liver cancer (liver metastasis): In cases where metastases are confined to the liver, local treatment may be possible, along with treatment of the primary cancer and
Chemotherapy (focus here is on colon cancer, as this is the most common cause for liver metastases).\(^8\)

- Surgery: If a metastatic tumor in the liver meets certain criteria for size and location, surgical removal may be an option, and may prolong survival or even be curative. Pretreatment with chemotherapy may also shrink metastatic tumors so that they can be treated surgically.
- Ablation: Destruction of liver cancer tissue through chemical injury or heating.
- Embolization: Blockage of blood vessels that supply the liver cancer.
- Radiotherapy: Directed radiation to destroy liver cancer tissue.

| What could new research contribute to achieving better patient-centered outcomes? | New research could contribute to achieving better patient-centered outcomes by evaluating:\(^8,14\)
- Comparative effectiveness (regarding survival and quality of life) of the various liver-directed therapies in patients with primary or secondary liver cancer who are not otherwise candidates for surgical resection (or liver transplantation for primary liver cancer)
- Comparative harms (regarding side effects) of the various liver-directed therapies in patients with primary or secondary liver cancer who are not otherwise candidates for surgical resection (or transplantation)
- Effect of specific patient and tumor characteristics, such as age, sex, disease etiology, and liver function on comparative effectiveness of various liver-directed therapies in patients with primary or secondary liver cancer who are not otherwise candidates for surgical resection (or transplantation)
- Role of the various liver-directed therapies in patients who are candidates for liver-directed therapy as an adjunct to chemotherapy for metastases to the liver that cannot be operated on |

| Have recent innovations made research on this topic especially compelling? | Recent innovations:
- Many available procedural therapies for primary or secondary liver cancer represent recent innovations, and procedural techniques continue to evolve.
- New comparative-effectiveness research (CER) will likely be needed to establish which of the options is preferred in specific clinical situations and in specific patient subgroups. |

| How widely does care now vary? | VARIABILITY IN CARE
- While the indications for surgery for primary or secondary liver cancer are reasonably well-understood, there is likely more variability in the use of other newer procedural therapies due to variation in local expertise and access to advanced care.
- Care may be provided by different specialties (surgeons, medical oncologists, interventional radiologists, radiation therapies)
- Local practices, financial incentives/disincentives may contribute to variability in care |

| What is the pace of other research on this topic (as indicated by recent publications and ongoing trials)? | RECENT PUBLICATIONS
- MEDLINE search 1/1/08-4/16/13:
  - Total: 6,442 citations
  - Labeled as randomized controlled trial (RCT): 224
  - Labeled as meta-analysis or systematic review: 386
ONGOING TRIALS
- Clinicaltrials.gov: search term ‘liver cancer’
  - Ongoing trials: 645
<table>
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<tr>
<th>How likely is it that new CER on this topic would provide better information to guide clinical decision making?</th>
<th>KEY UNCERTAINTIES IN CLINICAL DECISION-MAKING</th>
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</table>
| • Completed trials: 414  
  Clinicaltrials.gov: search term ‘hepatocellular carcinoma’  
  • Ongoing trials: 397  
  • Completed trials: 226  
  NIH reporter: Hepatic carcinoma  
  • Projects: 662  
  • Publications: 143 | • Optimal strategy for screening/early diagnosis  
  • Comparative effectiveness of treatment options (surgery, medical therapy, ablation, or observation) on disease-free survival and overall survival, tumor recurrence, and quality of life in patients with:  
  o Primary liver cancer  
  o Secondary liver cancer  
  • Optimal treatment for primary and secondary liver cancer that cannot be operated on |

**LIKELIHOOD THAT CER WOULD BE ABLE TO REDUCE THESE UNCERTAINTIES**

- Appropriately designed studies would have a high likelihood of answering the above questions and reducing key areas of uncertainty
- Randomized trials of easily measured outcomes (like disease-free survival and overall survival) usually sponsored by National Cancer Institute or manufacturer (especially chemotherapeutic drugs)
  - Treatments based on surgical procedures (e.g., cutting off tumor blood supply with embolization) are less likely to be subjected to RCTs, because either no regulatory requirements (surgical procedures) or fewer restrictive regulatory requirements (devices) compared to drugs
- CER by PCORI focused on patient-centered outcomes, particularly quality of life, preferences for different treatments, as well as other factors, more feasible than large-scale RCTs with mortality as primary outcome

**Potential for New Information to Improve Care and Patient-Centered Outcomes**

<table>
<thead>
<tr>
<th>What are the facilitators and barriers that would affect the implementation of new findings in practice?</th>
<th>FACILITATORS</th>
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</table>
| • Acceptance of evidence-based treatment results generally better in cancer treatment than other areas of medicine  
  • Evidence of improved survival and other outcomes likely to be well accepted by both patients and health care providers | BARRIERS |
| • Treatment options may be expensive and uncovered or only partially covered by third-party payers  
  • Access to different treatments may be affected by availability of appropriately trained and experienced clinicians  
  • Different financial incentives/disincentives for treatment options, competition between different types of practitioners | EVIDENCE OF BENEFIT |
<p>| How likely is it that the results of new evidence of benefit, particularly for survival, likely to be rapidly implemented |</p>
<table>
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<tr>
<th>research on this topic would be implemented in practice right away?</th>
<th>EVIDENCE OF NO BENEFIT OR HARM</th>
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</table>
| Would new information from CER on this topic remain current for several years, or would it be rendered obsolete quickly by subsequent studies? | • Evidence of no benefit may or may not be rapidly implemented (ie, treatment with no benefit compared to other available treatments may continue to be used) based on issues of access, provider incentives, and other factors.  
• Evidence of harm may or may not be rapidly implemented depending on types of harm (decreased survival likely to be implemented, increased risk of side effects or negative impact on quality of life possibly less likely to be implemented depending on other factors) |
| • Primary Liver Cancer (HCC)  
  o Incidence attributable to chronic hepatitis likely to continue to rise even if vaccine for hepatitis C is discovered, given high prevalence in other parts of world and difficulty in establishing vaccination program  
  o Incidence related to other causes, particularly nonalcoholic fatty liver disease, also likely to continue to increase |
| • Secondary Liver Cancer (liver metastases)  
  o Given that colon cancer is the third most common cancer in the United States, high rate of metastases, and variability in cancer outcomes even for same treatment in same cancer type, CER results unlikely to become obsolete  
  ▪ CER results may be modified if genetic or other biomarkers predictive of treatment response become available |

REFERENCES:


**APPENDIX: TOPIC QUESTIONS**

*Nominated by Institute of Medicine*

1) Compare the effectiveness of surgical resection, observation, or ablative techniques on disease-free and overall survival, tumor recurrence, quality of life, and toxicity in patients with liver metastases.

*Nominated by ‘Web’*

1) Treatments for Unresectable Liver Cancer - This is a Center for Medical Technology Policy (CMTP)-identified CER priority