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Executive Summary

There are a growing number of newly emerging focal tumour ablation innovations that are minimally invasive and offer additional treatment options for patients with a variety of cancers, including lung, liver, and kidney tumours. These include thermal ablation (which encompasses radiofrequency ablation [RFA] and microwave ablation) and transcatheter arterial chemoembolization (TACE). Cancer Care Ontario (CCO) developed the Focal Tumour Ablation Advisory Committee to create recommendations for the organization and delivery of selected focal tumour ablation services for cancer in Ontario with a focus on access, quality and funding.

The following recommendations lay out the framework for serving the focal tumour ablation needs of patients in Ontario. These recommendations were formed by consensus of the Advisory Committee and are based on best available evidence, the current practice in Ontario, and guidance from other jurisdictions and experts in the field.

Clinical Criteria

#1 – The Advisory Committee recommends that patients must meet specific clinical criteria to be considered eligible for treatment. (Specific criteria for decision making are described in Recommendations two through five)

#2 – For liver tumour patients, the Advisory Committee recommends thermal ablation according to the following criteria:

   A) Radiofrequency ablation (RFA) is recommended for diagnosed hepatocellular carcinoma (HCC) in the following cases:
      o For primary liver cancer, “very early stage” or “early stage” disease, according to the Barcelona Clinic Liver Cancer (BCLC) classification, and
      o Where the patient is not a surgical candidate, and
      o The size of the tumour is up to and including four centimetres, and
      o The maximum number of tumours is three per presentation.
   B) RFA alone is not recommended when surgical resection is recommended.
   C) RFA is recommended for liver metastases of colorectal cancer in the following cases:
      o Unresectable metastases, and
      o The size of the tumour is up to and including four centimetres, and
      o The maximum number of tumours is three per presentation, and
      o No evidence of vascular invasion or unresectable extrahepatic spread.
      o Intraoperative RFA for metastases of colorectal cancer may be used to treat a greater number of tumours if combined with surgical resection.
#3 – For kidney tumour patients, the Advisory Committee recommends thermal ablation of the kidney according to the following criteria:

A) RFA is recommended for renal cell carcinoma (RCC) in the following cases:
   o Biopsy proven stage T1a N0 M0 RCC, in whom surgery or active surveillance is not recommended, and
   o The size of the tumour is up to and including four centimetres, and
   o The maximum number of tumours is three per presentation.

#4 – For lung tumour patients, the Advisory Committee recommends thermal ablation under the following criteria:

A) RFA is recommended for lung tumours in the following cases:
   o Early-stage primary lung cancers, or
   o Metastases, where surgery is contraindicated, and
   o Unresectable tumour, and
   o The size of the tumour is up to and including four centimetres, and
   o The maximum number of tumours is three in both lungs, per presentation.

B) RFA alone is not recommended for patients eligible for surgical resection.

#5 – The Advisory Committee recommends TACE of the liver under the following criteria:

A) TACE is recommended for HCC in the following cases:
   o Diagnosed “intermediate” stage HCC, using BCLC classification, and
   o Unresectable/untransplantable HCC, and
   o No major vascular invasion or extrahepatic spread.

B) Follow-up imaging with contrast-enhanced CT or MRI is recommended at appropriate intervals, with consideration for repeat procedures as needed.

C) TACE is not recommended where surgical resection or RFA is recommended.

#6 – The Advisory Committee does not recommend microwave ablation for liver, kidney, and lung tumours at this time. Further evidence is needed.

Service Providers

#7 – The Advisory Committee recommends that patients being considered for treatment with focal tumour ablation services should receive care under the oversight of a multidisciplinary care team and have their case reviewed at a multidisciplinary cancer conference (MCC), which includes a liver, kidney or thoracic surgeon as relevant to the case.

* TACE refers to both conventional transcatheter chemoembolization and drug eluting beads.
#8 – The Advisory Committee recommends that centres providing focal tumour ablation services must meet, at a minimum, the following criteria for delivering services to ensure high quality care:

A) Have the necessary infrastructure
   o MCC in place to review cases (onsite or offsite), and
   o Multidisciplinary care team, and
   o Necessary capital equipment (e.g. CT scanner, ultrasound machine, etc.), and
   o Space to support the treatment and recovery of patients.
B) Perform sufficient volumes of treatment to maintain expertise.

System

#9 – The Advisory Committee recommends provincial oversight be established by CCO for the delivery of focal tumour ablation services in Ontario.

#10 – The Advisory Committee recommends that centres providing focal tumour ablation services work together as part of a provincial program to ensure equitable and appropriate access to services for all patients in Ontario.

#11 – The Advisory Committee recommends that appropriate funding be made available to support the delivery of equitable, accessible, and high quality services for all eligible patients in Ontario.

#12 – The Advisory Committee recommends that hospitals report ambulatory focal tumour ablation services as part of the National Ambulatory Cancer Reporting System (NACRS).

#13 – The Advisory Committee recommends that appropriate program quality indicators be developed.
Introduction

There are a growing number of newly emerging focal tumour ablation innovations that are minimally invasive and offer additional treatment options for patients with a variety of cancers, including lung, liver, and kidney tumours. These include thermal ablation (which encompasses radiofrequency ablation [RFA] and microwave ablation) and transcatheter arterial chemoembolization (TACE). These procedures may be an appropriate option for selected patients in certain clinical circumstances and be delivered at a lower cost.¹

“**The option of having a lung removed was scary. I thought, isn’t there anything else that can be done?**”  
(Patient)

Emerging therapies, such as these, can provide improved patient care, but can also be resource-intensive (e.g., use of imaging equipment, supplies such as catheters or probes, staffing, and space [recovery]). As their use increases, pressures are being felt on the system. The cost of this work has stressed hospital global budgets, with no direct source of consistent funding. Patient services must often be supported by alternate funds available through research or philanthropic sources. In addition, some service caps have been implemented by hospital administrators to manage available resources where dedicated funds are unavailable. Programs in Toronto, Hamilton, and other regions, have articulated the need for additional resources to meet the growing demand in these areas.

“There wasn’t a lot of information out there. I didn’t know this was available in Ontario. It seemed like a secret.”  
(Patient)

Better access for all patients in Ontario is needed. The issue is not limited to local funding constraints. There is an opportunity to:

- identify the appropriate patient populations, ensuring optimal patient care provincially while optimizing value for money, and
- provide guidance regarding the standard of care to ensure consistency in approach and across the province.

In 2014, CCO developed the Focal Tumour Ablation Advisory Committee to create recommendations for the organization and delivery of thermal ablation (including both RFA and microwave ablation) and TACE services for cancer in Ontario with a focus on access, quality and funding (see Appendix B and C). With patients, clinicians and administrators at the table, the

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Committee was tasked with developing recommendations based on the following principles:

- provide appropriate access to high quality cancer treatment services, and
- optimize care and resource utilization across the province.

The scope of these recommendations includes thermal ablation for lung, liver and renal tumours and TACE for liver cancers. Other emerging minimally invasive technologies (e.g. cryoablation) and disease sites will be considered for future discussions.
Background

The Clinical Perspective

An estimated 173,800 new cases of cancer were diagnosed in 2010 in Canada with lung, colorectal, prostate and breast cancers accounting for 54.4 percent of the total. In Ontario in 2010, 65,100 new cases of cancer were diagnosed, accounting for approximately 37.5 percent of the total disease burden in Canada.\(^b\)

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third leading cause of cancer death worldwide. The liver is a common site for primary metastases to develop from other primary cancers, such as colorectal carcinoma. Hepatic resection (surgery) is currently considered a first line treatment for many patients with HCC or liver metastases. Fewer than 20 percent of these patients, however, are surgical candidates due to poor hepatic reserve, tumour location or tumour burden. Focal tumour ablation provides the opportunity for cure or control of malignant disease and can improve survival when surgery is no longer an option.\(^a\)

The word ablation originates from the Latin word “ablatio” and means “a taking away”. In clinical medicine, “tumour ablation” is defined as the direct application of thermal or chemical therapies to a specific focal tumour (tumours) in order to achieve either eradication or substantial tumour destruction. The term “direct” is combined with tumor ablation to distinguish these therapies from other therapies that are applied orally or via an intravascular or a peripheral venous route. Most focal tumour ablation therapies are performed percutaneously using image guidance modalities such as ultrasound and/or other computed tomography (CT).

Ablation can be achieved in a number of ways. The destruction of the tumour using thermal sources, either cold or hot, is called thermal ablation. The destruction of tumour using low temperatures or freezing is called cryoablation. The destruction of tumour using heat generated by radiofrequency energy is called radiofrequency ablation (RFA). Thermal tumour destruction can also be achieved using microwave and laser energy sources. Chemical ablation is defined as the destruction of tumour through the percutaneous delivery of chemicals such as ethanol or acetic acid or via the trans-catheter delivery of chemotherapy known as chemoembolization.

\(^b\) Canadian Cancer Statistics 2010; Produced by: Canadian Cancer Society, Statistics Canada, Provincial/Territorial Cancer Registries, Public Health Agency of Canada. www.cancer.ca
In building the clinical criteria for focal tumour ablation for liver, lung and kidney tumours, the Advisory Committee considered data available from multiple sources.

**Literature Review**

The Program in Evidence-Based Care (PEBC) at CCO conducted a systematic search of the literature. A complete summary of the evidence is provided in Appendix F. As a first step this literature review looked to answer the following questions related to thermal ablation for liver tumours.

- What is the effectiveness of liver lesion thermal ablation using radiofrequency, microwaves, alone or in combination with other strategies for the treatment of patients with HCC or liver metastases (e.g., from colorectal cancer)?
- What are the subgroups of patients most likely to benefit from thermal ablation interventions?
- What are the potential adverse events with thermal ablation techniques?

**Jurisdictional Review**

In addition to the review of the clinical literature, information was sought to understand the context for focal tumour ablation in Ontario. Information sources included clinical recommendations from other jurisdictions, service delivery plans, infrastructure models, and current practice in other hospitals, organizations and governmental bodies. Much can be learned from what works well in other jurisdictions and systems. 30 guidance documents were considered by the Committee (see Appendix E for list of documents). In addition, targeted outreach to key opinion and clinical leaders around the world provided guidance to the recommendations development.

“The other countries are doing this.” (Patient)

The jurisdictional review identified variability in practice in various international institutions (i.e., size and number of lesions treated). The Advisory Committee’s recommendations, however (although less aggressive than these institutions) are based on available evidence, consensus of the group and the current practice in Ontario.

**Current State of Focal Tumour Ablation in Ontario**

Focal tumour ablation has become an important part of care in the patient cancer pathway. Like many complex treatments, focal tumour ablation requires a multidisciplinary team approach. Care must be taken in the planning, delivery and follow-up for these procedures.
Focal Tumour Ablation in Ontario: Recommendation Report, 2015

(see Figure 1). RFA of tumours is being increasingly utilized in academic centers and community hospitals in Ontario. Over the last several years, the number of patients undergoing focal tumour ablation in Ontario has risen significantly, placing pressures on the public health care system. The need for a systems approach that incorporates quality elements and ensures value for money is paramount.

**Figure 1: Care Path for RFA and TACE**

<table>
<thead>
<tr>
<th>Components of Care Path</th>
<th>Prior to day of Procedure</th>
<th>Pre-Procedural</th>
<th>Procedure</th>
<th>Post-Procedural Monitoring</th>
<th>Post-procedural Follow-Up</th>
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<tr>
<td></td>
<td></td>
<td>Patient arrives at Hospital and registers</td>
<td>Patient safety checklist and safety pause</td>
<td>Clinical assessment and observation</td>
<td>Patient follow-up, including appropriate imaging</td>
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<tr>
<td></td>
<td></td>
<td>Clinical assessment of patient (nursing assessment and consent)</td>
<td>Conscious/IV sedation administered</td>
<td>Patient discharged</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Preparation of patient for procedure (change into gown and IV)</td>
<td>Perform focal tumour ablation procedure with intermittent or continuous imaging throughout procedure</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>For TACE:</td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td>Chemotherapeutic medication is prescribed and prepared by pharmacy</td>
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<td></td>
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<td>Patient admission, where clinically appropriate</td>
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<td></td>
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<td>For TACE:</td>
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In December 2013, CCO conducted a survey of Regional Cancer Programs to identify the current state of focal tumour ablation services being offered in Ontario (Appendix D). RFA and TACE were, by a large margin, identified as the most frequently provided services. Liver and renal cancers were the diseases most often treated with these interventions. There was significant regional variation with highest treatment volumes seen in Toronto and the Southwest regions of the province (see Figure 2).

“This should be available to everyone in the province, not just people who live in the right places.” (Patient)
Using incidence of disease and clinical recommendations for intervention, forecast models were developed to estimate provincial demand for in-scope services and disease sites. Expert opinion and consensus contributed where data were limited. Upper and lower volume estimates were developed. Using the mid-range of these estimates, the demand in 2015/16 is expected to be 2093, 380, 276, and 504 treatments with RFA for liver, TACE for liver, RFA for kidney and RFA for lung, respectively. These estimates will be revised as more information becomes available, but the need is expected to grow over time.

Some hospitals have established baseline RFA and TACE volumes to appropriately reflect the limited funding available through global budgets. Growth in RFA and TACE have now far exceeded these baselines and there has been no additional funding provided to address this. Programs are in competition with other hospital priorities, and many are not successful in securing the necessary funding to provide this type of care. Following the care pathway, defined by the Advisory Committee (see Figure 1), various data sources were examined to help identify cost drivers. Limitations to service provisions may also include space (e.g., beds for post-procedure recovery) and supporting infrastructure (e.g., booking clerks, access to CT scanners). Research funding opportunities, while helpful, are not a sustainable mechanism to provide ongoing access to care.
A survey of cancer programs in Ontario revealed that although many physicians are trained and ready to provide this care, they do not have the support within the system to do so. A System Capacity Survey of Ontario hospitals and cancer centres was conducted in April 2014 to examine availability of infrastructure and trained clinicians, and interest to provide focal tumour ablation services. Self-reported data revealed that a significant number of centres would be willing to provide these services if appropriate funding was provided. Therefore, capacity estimates indicate that, outside of financial constraints, hospitals have potential to meet the needs in the years to come (see Figures 4 through 7). While it is encouraging to see some capacity in the system for increased services, it is important to note that quality criteria for service delivery, and wait times and other access measures did not factor into this analysis. Once appropriate funding mechanisms, referral networks, and quality assurance measures are in place, capacity can be better defined. Mechanisms to ensure access at the provincial level will need to be developed to support ongoing capacity needs following a ramp-up period.
Figure 4: Projected Demand and Capacity for RFA for Liver

![Projections for RFA for Neoplasms in the Liver](image)

**Report Date:** February 2014  
**Data Source:** Ontario Cancer Registry and the 2014 Current State Survey for RFA/TACE in Ontario  
**Prepared by:** Cancer Care Ontario, Surveillance Unit and Planning and Regional Program

Figure 5: Projected Demand and Capacity for TACE for Liver

![Projections for TACE for Neoplasms in the Liver](image)

**Report Date:** February 2014  
**Data Source:** Ontario Cancer Registry and the 2014 Current State Survey for RFA/TACE in Ontario  
**Prepared by:** Cancer Care Ontario, Surveillance Unit and Planning and Regional Programs
Figure 6: Projected Demand and Capacity for RFA for Kidney

Projections for RFA for Neoplasms in the Kidney

Report Date: February 2014
Data Source: Ontario Cancer Registry and the 2014 Current State Survey for RFA/TACE in Ontario
Prepared by: Cancer Care Ontario, Surveillance Unit and Planning and Regional Programs

Figure 7: Projected Demand and Capacity for RFA for Lung

Projections for RFA for Neoplasms in the Lung

Report Date: February 2014
Data Source: Ontario Cancer Registry and the 2014 Current State Survey for RFA/TACE in Ontario
Prepared by: Cancer Care Ontario, Surveillance Unit and Planning and Regional Programs
Recommendations

The following recommendations lay out the framework for serving the focal tumour ablation needs of patients in Ontario. These recommendations were formed by consensus of the Advisory Committee and are based on best available evidence, current practice and organization of health care services in Ontario, and guidance from other jurisdictions and experts in the field. Recommendations have been grouped into Clinical Criteria, recommendations for Service Providers and recommendations for the System.

Clinical Criteria

#1 – The Advisory Committee recommends that patients must meet specific clinical criteria to be considered eligible for treatment. (Specific criteria for decision making are described in Recommendations two through five)

Appropriate patient selection is key. Stage of disease, size and number of nodules to be treated, co-morbidities and other factors which may preclude surgical or other interventions must be considered when making the decision for focal tumour ablation.

“I didn’t know this was an option. There is not a lot of information out there.” (Patient)

The Evidence Summary, Focal Tumour Ablation 1: Thermal Ablation of Hepatocellular Carcinoma and Metastases from Colorectal Carcinoma (see Appendix F), comprehensive jurisdictional review (see Appendix E), consultation with key stakeholders and analysis of additional publications brought forward by the Committee informed the specific clinical criteria. While it was the consensus of the Advisory Committee that sufficient information was available to make these recommendations, further study and analysis are needed to support evolving clinical practice.

“Focal tumour ablation is a very important, even critical, option for a patient who isn’t suited to other therapies, like surgery.” (Patient)
#2 – For liver tumour patients, the Advisory Committee recommends thermal ablation under the following criteria:

A) Radiofrequency ablation (RFA) is recommended for diagnosed hepatocellular carcinoma (HCC) in the following cases:
   o For primary liver cancer, “very early stage” or “early stage” disease, according to the Barcelona Clinic Liver Cancer (BCLC) classification, and
   o Where the patient is not a surgical candidate, and
   o The size of the tumour is up to and including four centimetres, and
   o The maximum number of tumours is three tumours per presentation.

B) RFA alone is not recommended when surgical resection is recommended

C) RFA is recommended for liver metastases of colorectal cancer in the following cases:
   o Unresectable metastases, and
   o The size of the tumour is up to and including four centimetres, and
   o The maximum number of tumours is three per presentation, and
   o No evidence of vascular invasion or unresectable extrahepatic spread.
   o Intraoperative RFA for metastases of colorectal cancer may be used to treat a greater number of tumours if combined with surgical resection.

#3 – For kidney tumour patients, the Advisory Committee recommends thermal ablation of the kidney under the following criteria:

A) RFA is recommended for renal cell carcinoma (RCC) in the following cases:
   o Biopsy proven stage T1a N0 M0 RCC, in whom surgery or active surveillance is not recommended, and
   o The size of the tumour is up to and including four centimetres, and
   o The maximum number of tumours is three per presentation.

#4 – For lung tumour patients, the Advisory Committee recommends thermal ablation of the lung under the following criteria:

A) RFA is recommended for lung tumours in the following cases:
   o Early-stage primary lung cancers, or
   o Metastases, where surgery is contraindicated, and
   o Unresectable tumour, and
   o The size of the tumour is up to and including four centimetres, and
   o The maximum number of tumours is three in both lungs, per presentation.

B) RFA alone is not recommended for patients eligible for surgical resection.
#5 – The Advisory Committee recommends transcatheter arterial chemoembolization (TACE*) of the liver under the following criteria:

A) TACE is recommended for HCC in the following cases:
  o Diagnosed “intermediate” stage HCC, using BCLC classification, and
  o Unresectable/untransplantable HCC, and
  o No major vascular invasion or extrahepatic spread.
B) Follow-up imaging with contrast-enhanced CT or MRI is recommended at appropriate intervals, with consideration for repeat procedures as needed,
C) TACE is not recommended where surgical resection or RFA is recommended.

#6 – The Advisory Committee does not recommend microwave ablation for liver, kidney, and lung tumours at this time. Further evidence is needed.

Service Providers

#7 – The Advisory Committee recommends that patients being considered for treatment with focal tumour ablation services should receive care under the oversight of a multidisciplinary care team and have their case reviewed at a MCC, which includes a liver, kidney or thoracic surgeon as relevant to the case.

“My husband had a rare form of cancer. It gave me tremendous peace of mind when I found out that our surgeon discussed (his) case at a Multidisciplinary Cancer Conference and worked with a team to ensure that the way he was planning to treat the tumour was the best way. It made me confident that the treatment he was getting was the best.” (Family member)

MCCs are regularly scheduled meetings where healthcare providers discuss the diagnosis and treatment of individual cancer patients. There is increasing evidence that clinical evaluation and patient selection by a multidisciplinary clinical team contribute to improved patient outcomes. CCO has developed standards, tools and a performance measurement strategy to support the broad implementation of MCCs. This includes disease-site specific criteria for organization, attendees and types of cases to be brought forward.

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* TACE refers to both conventional transcatheter chemoembolization and drug eluting beads.
Designated Hepato-Pancreatic Biliary (HPB) centres in Ontario are hospitals that meet certain safety and quality standards. For patients with liver disease, it is important to ensure the surgical expertise from the HPB centre is incorporated into the MCC decision making process.

**#8 – The Advisory Committee recommends that centres providing focal tumour ablation services must meet, at a minimum, the following criteria for delivering services to ensure high quality care:**

A) **Have the necessary infrastructure**
   - MCC in place to review cases (onsite or offsite), and
   - Multidisciplinary care team, and
   - Necessary capital equipment (e.g., CT scanner, ultrasound machine, etc.), and
   - Space to support the treatment and recovery of patients.

B) **Perform sufficient volumes of treatment to maintain expertise.**

Multidisciplinary support for decision making and case management are essential. As discussed, the MCC is an established mechanism to support this. In addition, proper patient selection, expert service delivery and management of potential complications demands health care providers who have competencies which can only be achieved with ongoing clinical practice.

Evidence to support a minimal service volume is not available. However, consensus is strong in this area. When making this recommendation the Advisory Committee considered the importance of clinical expertise achieved through ongoing practice and avoiding infrequent interventions by providers not skilled in this area of care. As the evidence builds, future data collection and analysis can inform this recommendation further.

**System**

“My greatest hope is that we get RFA as much a part of care as we have chemotherapy and radiation.” (Patient)

**#9 – The Advisory Committee recommends provincial oversight be established by Cancer Care Ontario for the delivery of focal tumour ablation services in Ontario.**

The role of provincial oversight would be to:

- provide a provincial forum (e.g., Steering Committee) for program development, implementation, and monitoring,
• leverage existing and establish new data collection and reporting mechanisms to enable system monitoring, funding, and quality assurance,
• implement a performance management structure, and
• review changing evidence base to further develop scope of program.

It is a strategic priority of the 2011-2015 Ontario Cancer Plan (OCP) to provide oversight (including planning and quality management) of specialized services. Oversight programs are currently in place at CCO for several specialized cancer services. These specialized services are low volume, high complexity, high cost, not available in every region of the province and involve a rapidly evolving knowledge base and high degree of specialization. Oversight can include the development of clinical guidelines, quality standards, data standards, system planning, and the introduction of new techniques and technology. The goal of these programs is to ensure consistent quality and access for eligible patients when they need it. This promotes care as close to home as possible and helps to avoid inappropriate use of costly services and out-of-country referrals.

As an example, CCO currently oversees the Evidence-Based Positron Emission Tomography (PET) Program (PET Scans Ontario) through a collaboration with the Ministry of Health and Long-Term Care and the Cardiac Care Network. Key elements of this program include:

• a committee of experts to advise on issues affecting access to PET in Ontario, including indications to be funded and the geographic location of services,
• evaluation of emerging indications in Ontario through the PET registry,
• selected clinical trials guided by the PET Steering Committee,
• a case-by-case review program (PET Access Program),
• continuous evidence review to ensure alignment with emerging evidence on the clinical utility of PET, and
• ongoing communications to promote equitable access to PET for Ontario patients.

CCO also provides oversight for other specialized cancer services, including Stem Cell Transplant and Sarcoma. Each program is built on a foundation of expert clinical guidance and system-level planning, funding and performance management.

This type of oversight is particularly well-suited to the needs of providing focal tumour ablation services for the people of Ontario.

#10 – The Advisory Committee recommends that Centres providing focal tumour ablation services work together as part of a provincial program to ensure equitable and appropriate access to services for all patients in Ontario.

It is important to ensure stakeholders at all levels are involved in provincial planning, implementation, monitoring and performance improvement activities for specialized services such as these. As an example, the Sarcoma Services Provincial Plan provides an overview of
how adult sarcoma services are organized in Ontario. It was developed collaboratively by regional, clinical and patient representatives through a Steering Committee facilitated by CCO. This type of system level planning and service delivery cannot successfully occur without the active participation of providers.

**#11 – The Advisory Committee recommends that appropriate funding be made available to support the delivery of equitable, accessible, and high quality services for all eligible patients in Ontario.**

Hospitals are often stressed to provide needed services within budgetary constraints. An assessment of the cost of focal tumour ablation services, current funding mechanisms and new system pressures is needed. Appropriate funding mechanisms to address incremental pressures are required to support access and optimize the use of resources.

**#12 – The Advisory Committee recommends that hospitals report ambulatory focal tumour ablation services as part of the National Ambulatory Cancer Reporting System (NACRS).**

Having high quality data, consistently reported across all treatment hospitals is essential to accurate system planning, funding and performance management. NACRS, maintained by the Canadian Institute for Health Information, contains data for all hospital-based and community-based ambulatory care and is the standard for reporting across Canada. A number of data sources were examined to aid in the development of these recommendations and the Advisory Committee used the best available information. Unfortunately, focal tumour ablation is not currently a mandated entry field in NACRS and therefore, the data at this time is unreliable for decision making purposes. As this area of clinical practice evolves, there is an opportunity to gather a more robust data set that serves these needs (e.g., managing volumes and forecasts, establishing appropriate funding rates and assessing access and quality measures).

**#13 – The Advisory Committee recommends that appropriate program quality indicators be developed.**

One aim of the OCP is to improve the performance of Ontario’s cancer system. Various quality service delivery components, including equitable access and safety, are measured and published. Progress can be tracked as quality improvement strategies are implemented. For example, CCO regularly reports on the quality in the cancer system through the Cancer System Quality Index (CSQI). The CSQI tracks Ontario’s progress against cancer and shows where quality and performance improvements are needed. In 2014, the CSQI reported 33 evidence-based quality measures covering every aspect of cancer control, from cancer prevention to survivorship and end-of-life care.

As an emerging technology, it is important to support the development of high quality focal tumour ablation programs across the province with the use of appropriate metrics and a
performance management approach. In addition to the CSQI, regular data analysis informs system gaps and drives quality improvement.

Relevant indicators should be developed for focal tumour ablation services. These may include:

- clinical and safety indicators: MCC implementation, complication rates,
- patient access indicators: wait times, regional referral patterns, and
- system impact indicators: cost/benefit analysis.

Conclusions

“I have had cancer three times, and undergone chemotherapy, radiation and surgery. Two and a half years ago I had RFAs on both kidneys and there is no indication of further kidney cancer. Thanks to expert clinical care, I am alive today and cancer free.” (Patient)

Focal tumour ablation can be an appropriate treatment for select patients. These recommendations provide the basis for the development of a provincial program in Ontario which would deliver equitable access to high quality focal tumour ablation services for appropriate patients.
## Appendices

### Appendix A: Glossary of Terms

<table>
<thead>
<tr>
<th>Terms</th>
<th>Definition</th>
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<tr>
<td>ablation</td>
<td>The process of removing or destroying part of a biological tissue, while preserving as much of the surrounding tissue as possible.</td>
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<td>active surveillance</td>
<td>Also referred to as watchful waiting. Refers to the careful monitoring for signs and symptoms of disease progression that indicate the cancer is growing and treatment might be needed.</td>
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<tr>
<td>ambulatory services</td>
<td>Medical care provided on an outpatient basis, including diagnosis, observation, treatment and rehabilitation services.</td>
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<td>Barcelona Clinic Liver Cancer (BCLC) Staging System</td>
<td>System used by clinicians and researchers to stage and guide the treatment of hepatocellular carcinoma (HCC).</td>
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<td>biopsy</td>
<td>A biopsy involves removing a sample of tissue or tumour from the body and examining it under a microscope for cancer cells. Biopsies are used to diagnose a cancer and to determine the extent of disease during the staging process.</td>
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<td>chemoembolization</td>
<td>A procedure to reduce or block the main blood supply to a tumour and deliver chemotherapy drugs directly to the tumour.</td>
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<tr>
<td>chemotherapy</td>
<td>The use of anti-cancer cytotoxic drugs to destroy cancer cells.</td>
</tr>
<tr>
<td>co-morbidity</td>
<td>When two or more disorders or illnesses occur in the same person, simultaneously or sequentially.</td>
</tr>
<tr>
<td>computed tomography (CT)</td>
<td>A computed tomography (CT) scan is an imaging test that uses a computer to put a series of special x-ray images together to create detailed 3-dimensional images of organs and tissues.</td>
</tr>
<tr>
<td>contraindicated</td>
<td>The suggestion or indication that a particular drug or other treatment should not be used in the case in question.</td>
</tr>
<tr>
<td>contrast-enhanced</td>
<td>Method of enhancing an image to make it easier to see a structure (e.g., tumour, blood vessels).</td>
</tr>
<tr>
<td>cryoablation</td>
<td>Procedure that uses extremely cold or freezing temperatures to destroy abnormal cells or tissue.</td>
</tr>
<tr>
<td>cytotoxic</td>
<td>Toxic to living cells.</td>
</tr>
<tr>
<td>destruction</td>
<td>The act or process of damaging a tissue or tumour so that it no longer exists or cannot be repaired.</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>drug-eluting beads</td>
<td>Beads that have been impregnated (infused) with a chemotherapy agent. The drug eluting beads are given via catheter directly to the tumour.</td>
</tr>
<tr>
<td>eradication</td>
<td>To remove a tumour completely.</td>
</tr>
<tr>
<td>extrahepatic spread</td>
<td>Spread of cancer beyond the liver.</td>
</tr>
<tr>
<td>hepatic resection</td>
<td>Surgical removal of part of the liver.</td>
</tr>
<tr>
<td>hepatic reserve</td>
<td>Portion of functional liver that has not been affected by tumour or disease.</td>
</tr>
<tr>
<td>hepatocellular carcinoma (HCC)</td>
<td>Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer. It starts in the cells that make up the parenchyma of the liver (hepatocytes).</td>
</tr>
<tr>
<td>Hepato-Pancreatic Biliary (HPB) Centres</td>
<td>Designated centres (hospitals) in Ontario that meet certain safety and quality standards for the delivery of HPB cancer treatment.</td>
</tr>
<tr>
<td>intervention</td>
<td>The act or method of interfering with the outcome or course of a condition (as to prevent harm or improve function).</td>
</tr>
<tr>
<td>central venous route</td>
<td>Use of a central vein, for example for the administration of medications.</td>
</tr>
<tr>
<td>jurisdictional</td>
<td>Proceedings within a defined area.</td>
</tr>
<tr>
<td>metastases</td>
<td>Spread of cancer from its primary site to other locations in the body.</td>
</tr>
<tr>
<td>microwave ablation</td>
<td>Ablation by use of microwaves to produce heat.</td>
</tr>
<tr>
<td>modality</td>
<td>The way in which something is done.</td>
</tr>
<tr>
<td>multidisciplinary care team</td>
<td>A group of health care workers who are members of different disciplines, each providing specific services to a patient.</td>
</tr>
<tr>
<td>nodule</td>
<td>A small mass of rounded or irregular shape, such as a tumourous growth.</td>
</tr>
<tr>
<td>percutaneously</td>
<td>Through the skin and musculature directly into the targeted tissue (e.g., a liver tumour).</td>
</tr>
<tr>
<td>perioperative mortality</td>
<td>Death related to a surgical procedure.</td>
</tr>
<tr>
<td>peripheral venous route</td>
<td>Use of a peripheral vein, for example for the administration of medications.</td>
</tr>
<tr>
<td>radiofrequency ablation (RFA)</td>
<td>Ablation by use of high frequency alternating electrical current to produce heat.</td>
</tr>
<tr>
<td>radiofrequency energy</td>
<td>High-frequency electrical current that creates heat.</td>
</tr>
<tr>
<td>renal cell carcinoma (RCC)</td>
<td>The most common type of primary kidney cancer. These tumours start in the lining of the tubules of the kidney and are mostly found in the cortex of the kidney.</td>
</tr>
<tr>
<td>surgical resection</td>
<td>Surgical removal of part of an organ or structure.</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
</tr>
<tr>
<td>------</td>
<td>------------</td>
</tr>
<tr>
<td>thermal ablation</td>
<td>Ablation by use of extreme temperatures (either cold or hot).</td>
</tr>
<tr>
<td>transcatheter</td>
<td>The delivery of treatment via insertion and navigation of a catheter within blood vessels.</td>
</tr>
<tr>
<td>transcatheter arterial chemoembolization (TACE)</td>
<td>Chemoembolization delivered through the insertion of a catheter into a blood vessel.</td>
</tr>
<tr>
<td>tumour burden</td>
<td>The total mass of tumour tissue carried by a patient with cancer.</td>
</tr>
<tr>
<td>ultrasound</td>
<td>An imaging test that uses high-frequency sound waves to produce images of structures in the body. Ultrasound works by bouncing sound waves off solid parts of the body.</td>
</tr>
<tr>
<td>vascular invasion</td>
<td>Growth of a tumour into the veins or arteries.</td>
</tr>
</tbody>
</table>
## Appendix B: Advisory Committee Membership List

<table>
<thead>
<tr>
<th></th>
<th>Name</th>
<th>Title</th>
<th>Institution/Program/Department</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Dr. Julian Dobranowski</td>
<td>Co-Chair</td>
<td>Provincial Head, Cancer Imaging Program, Cancer Care Ontario</td>
</tr>
<tr>
<td>2</td>
<td>Dr. John Kachura</td>
<td>Co-Chair</td>
<td>Vascular and Interventional Radiologist, University Health Network and Mount Sinai Hospital</td>
</tr>
<tr>
<td>3</td>
<td>Dr. Sriharsha Athreya</td>
<td></td>
<td>Interventional Radiologist, St. Joseph’s Health Centre</td>
</tr>
<tr>
<td>4</td>
<td>Dr. Mark Baerlocher</td>
<td></td>
<td>Interventional and Diagnostic Radiologist, Royal Victoria Hospital</td>
</tr>
<tr>
<td>5</td>
<td>Dr. Robert Beecroft</td>
<td></td>
<td>Staff Radiologist, University Health Network and Mount Sinai Hospital</td>
</tr>
<tr>
<td>6</td>
<td>Ms. Brigitta Boekers</td>
<td></td>
<td>Patient and Family Advisor</td>
</tr>
<tr>
<td>7</td>
<td>Dr. Elizabeth David</td>
<td></td>
<td>Radiologist, Sunnybrook Health Sciences Centre</td>
</tr>
<tr>
<td>8</td>
<td>Dr. Laura Dawson</td>
<td></td>
<td>Radiation Oncologist, University Health Network</td>
</tr>
<tr>
<td>9</td>
<td>Mr. David Gast</td>
<td></td>
<td>Patient and Family Advisor</td>
</tr>
<tr>
<td>10</td>
<td>Dr. Ania Kielar</td>
<td></td>
<td>Director of the Division of Abdominal and Pelvic Imaging, Radiologist, The Ottawa Hospital</td>
</tr>
<tr>
<td>11</td>
<td>Dr. Darren Knibutat</td>
<td></td>
<td>Vascular and Interventional Radiologist, Chief and Medical Director, Grand River, St. Mary's and Cambridge Memorial Hospitals</td>
</tr>
<tr>
<td>12</td>
<td>Dr. Calvin Law</td>
<td></td>
<td>Regional Vice President, Toronto Central, Odette Cancer Centre</td>
</tr>
<tr>
<td>13</td>
<td>Dr. Richard Malthaner</td>
<td></td>
<td>Surgeon, London Health Sciences Centre</td>
</tr>
<tr>
<td>14</td>
<td>Dr. George Markose</td>
<td></td>
<td>Staff Radiologist, Juravinski Cancer Centre</td>
</tr>
<tr>
<td>15</td>
<td>Dr. Guillaume Martel</td>
<td></td>
<td>Surgeon, The Ottawa Hospital</td>
</tr>
<tr>
<td>16</td>
<td>Dr. Alexandre Ménard</td>
<td></td>
<td>Vascular and Interventional Radiologist, Kingston General Hospital</td>
</tr>
<tr>
<td>17</td>
<td>Dr. Mehran Midia</td>
<td></td>
<td>Staff Radiologist, Hamilton Health Science Centre</td>
</tr>
<tr>
<td>18</td>
<td>Dr. Amol Mujoomdar</td>
<td></td>
<td>Vascular and Interventional Radiologist, London Health Sciences Centre</td>
</tr>
<tr>
<td>19</td>
<td>Dr. Wael Shabana</td>
<td></td>
<td>Radiologist, The Ottawa Hospital</td>
</tr>
<tr>
<td>20</td>
<td>Ms. Catherine Wang</td>
<td></td>
<td>Executive Director, Joint Department of Medical Imaging, Mount Sinai Hospital, University Health Network and Women’s College Hospital</td>
</tr>
</tbody>
</table>

---
The Advisory Committee also wishes to thank all those that contributed to the development of these recommendations, including subject matter experts.

**Dr. Sean P. Cleary**
BScH, MD, MSc, MPH, FRCSC
Associate Professor, University of Toronto
General Surgery, Pancreatic and Hepatobiliary Surgery
Research Associate, Samuel Lunenfeld Research Institute

**Dr. Antonio Finelli**, MD, MSc, FRCSC
Disease Site Lead, Genitourinary, Cancer Care Ontario
Associate Professor, Department of Surgical Oncology, University of Toronto
Division of Urology, Departments of Surgery and Surgical Oncology, Princess Margaret Cancer Centre

**Dr. Anil Kapoor**, MD, FRCSC
Professor of Surgery (Urology), McMaster University
Chair, Genitourinary Oncology Program, Juravinski Cancer Centre
Program Director, McMaster University Urology Residency Program
Surgical Director, SJH Transplant Program
Appendix C: Focal Tumour Ablation Advisory Committee – Terms of Reference

Focal Tumour Ablation Advisory Committee
Cancer Care Ontario
Terms of Reference

Background
There are a growing number of newly emerging ablation innovations, including Radiofrequency Ablation (RFA) and Transcatheter Arterial Chemoembolization (TACE), which are minimally invasive and offer additional treatment options for patients with a variety of cancers, including lung, liver, prostate and kidney cancer. Cancer Care Ontario (CCO) is convening a Focal Tumour Ablation Advisory Committee to better understand the current state, and make recommendations for optimizing the use of these procedures in Ontario.

In alignment with CCO’s specialized services oversight programs structure, the Focal Tumour Ablation Advisory Committee will address issues of quality, access, funding, planning and performance management. The Advisory Committee will guide the development of recommendations that addresses partnership development, sustainability and resource allocation, ensuring alignment with the Ontario Cancer Plan.

Deliverables
The Advisory Committee will develop recommendations for the organization and delivery of RFA and TACE services for liver and renal cancer in Ontario with a focus on access, quality and funding. This work will include the following:

Literature Review:
- Direct appropriate literature/evidence gathering and analysis to inform recommendations;
- Direct the development of additional clinical guidance for the indications and effectiveness of RFA and TACE treatment for liver and renal tumours.

Capacity and Access:
- Lead a jurisdictional review of the service availability within and outside of Ontario;
- Oversee a review of the current availability, organization and capacity for RFA and TACE treatments in the Ontario;
- Oversee forecasting of future demand for service in Ontario.

Recommendations Development:
- Identify system gaps and make recommendations for improvement;
- Develop recommendations for the organization and delivery of RFA and TACE services for cancer patients in Ontario with a focus on access, quality and funding.
Meetings

- The committee is expected to meet at least monthly for 6 to 8 months from the time of commencement, or more frequently as required. The work of the committee may be extended beyond this time, if necessary.
- Minutes and agenda for each meeting will be circulated. The Co-Chairs can be approached with questions regarding the meeting and program content at any time. Members unable to attend meetings are encouraged to review meeting notes, materials and connect with other Committee members. The nature of ongoing program discussions is not appropriate for delegates to attend meetings if members are unable to attend.
- Members may also have the opportunity to participate on smaller working groups, as needed.
- Meetings will be one to two hours in length and will be held primarily via teleconference.
- One or two face-to-face, half or full day meetings may be scheduled as the group determines necessary.

Term

- This Terms of Reference will be finalized early in the term of the Advisory Committee and continue until August 31, 2014, after which they will be reviewed and updated as appropriate. At this point in time, the membership of the Advisory Committee will also be reviewed.

Membership (approx. 18-21)

- Co-Chair (Regional) (1)
- Co-Chair (Clinical Lead - CCO Provincial Program Head, Cancer Imaging) (1)
- Intervention Radiologist and Disease Site Specialists (6-8)
- Medical Oncologist (2)
- Radiation Oncologist (1)
- Medical Physicist (1)
- Surgeons (2)
- Referring Physicians (1-2)
- Hospital Administrator/RVP (2)
- Patient/Caregiver Representatives (2)
- CCO Director, Clinical Programs, Diagnosis and Treatment (1)
- CCO Director, Planning and Regional Programs (1)
- CCO Director, Funding Unit (1)
- CCO Director, Program in Evidence Based Care

The above membership will be selected to ensure representation as follows:

- Regional representation from across the province
- Representation for all aspects of the patients care
- Patient perspective
CCO will support the project through:

- Clinical Programs Division for alignment with strategic direction and for project management: Policy Research Analyst, Specialized Services Oversight; Program Manager, Specialized Services Oversight
- Informatics to provide data and analysis about focal tumour ablation services demand and capacity: CIO Manager/Team Lead; Analyst; Funding Methodologist
- Planning & Regional Programs and Performance Management to advise on performance management mechanisms and issues regarding implementation of committee recommendations within the regional cancer programs: Program Manager; Planning Analyst
- Public Affairs to assist with formulation and delivery of final advice, as well as partnership and patient communication plans: Communications Advisor

**Accountability**

The Co-Chairs are accountable to the Executive Team of Cancer Care Ontario via the Vice President of Clinical Programs and Quality Initiatives and the Vice President of Planning and Regional Programs.

**Meeting Minutes**

Minutes will be kept of all meetings and will be distributed to members.
Appendix D: Current State Survey

Request for Information

Focal Tumour Ablation Services in Ontario

Health care institutions are indicating increasing pressures in the delivery of image guided focal tumour ablation services for cancer. As part of a larger initiative to identify appropriate practice, current resources and potential pressures, Cancer Care Ontario would like your assistance in learning more about what services are currently available.

Your input, through the brief survey attached, is appreciated. Please note that at this time we are looking at current services, versus previous and/or potential. In the future, additional surveys may be administered to gather additional information.

Please complete the survey by Monday, December 16, 2013 and return by email to Cassandra Howse, Project Coordinator, Specialized Services Oversight at Cassandra.Howse@cancercare.on.ca.

Should you have any questions, please contact:

Sherrie Hertz, Program Manager, Specialized Services Oversight at Sherrie.Hertz@cancercare.on.ca

or Peter Bevan, Program Manager, Cancer Imaging at Peter.Bevan@cancercare.on.ca.

Center Name: ________________________________

Contact Information

Name: ________________________________

Email: ________________________________
1) Does your centre offer image guided tumour ablation services as a form of cancer treatment?
- YES
- NO (Thank you for your time, please submit the survey).

2) If yes, please indicate what image guided tumour ablation services for cancer are available at your centre and indicate the relevant tumour disease sites.  

*Please note that if any information is left blank, we will assume these services are not available at your centre.*

<table>
<thead>
<tr>
<th>Service</th>
<th>Availability?</th>
<th>Disease Location</th>
<th>Treatment of this location?</th>
<th>If yes, approximately how many are cases treated/month? (e.g. 5, 10, 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiofrequency Ablation (RFA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>O YES</td>
<td>Liver</td>
<td>○ YES</td>
<td></td>
</tr>
<tr>
<td></td>
<td>O NO</td>
<td></td>
<td>○ NO</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Kidney</td>
<td>○ YES</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>○ NO</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lung</td>
<td>○ YES</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>○ NO</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Breast</td>
<td>○ YES</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>○ NO</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prostate</td>
<td>○ YES</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>○ NO</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other – Specify:</td>
<td>○ YES</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>○ NO</td>
<td></td>
</tr>
<tr>
<td>Microwave Ablation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>O YES</td>
<td>Liver</td>
<td>○ YES</td>
<td></td>
</tr>
<tr>
<td></td>
<td>O NO</td>
<td></td>
<td>○ NO</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Kidney</td>
<td>○ YES</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>○ NO</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lung</td>
<td>○ YES</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>○ NO</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Breast</td>
<td>○ YES</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>○ NO</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prostate</td>
<td>○ YES</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>○ NO</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other – Specify:</td>
<td>○ YES</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>○ NO</td>
<td></td>
</tr>
<tr>
<td>Procedure</td>
<td>Uterus</td>
<td>Prostate</td>
<td>Other – Specify:</td>
<td></td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>--------</td>
<td>----------</td>
<td>------------------</td>
<td></td>
</tr>
<tr>
<td><strong>High Intensity Focused Ultrasound</strong></td>
<td>![YES/NO]</td>
<td>![YES/NO]</td>
<td>![YES/NO]</td>
<td></td>
</tr>
<tr>
<td><strong>Laser Ablation</strong></td>
<td>![YES/NO]</td>
<td>![YES/NO]</td>
<td>![YES/NO]</td>
<td></td>
</tr>
<tr>
<td><strong>Bland Embolization</strong></td>
<td>![YES/NO]</td>
<td>![YES/NO]</td>
<td>![YES/NO]</td>
<td></td>
</tr>
<tr>
<td><strong>Radioembolization (Y-90)</strong></td>
<td>![YES/NO]</td>
<td>![YES/NO]</td>
<td>![YES/NO]</td>
<td></td>
</tr>
<tr>
<td><strong>Thermal Balloon Ablation</strong></td>
<td>![YES/NO]</td>
<td>![YES/NO]</td>
<td>![YES/NO]</td>
<td></td>
</tr>
<tr>
<td><strong>Cryoablation</strong></td>
<td>![YES/NO]</td>
<td>![YES/NO]</td>
<td>![YES/NO]</td>
<td></td>
</tr>
</tbody>
</table>
Focal Tumour Ablation in Ontario: Recommendation Report, 2015

| Chemical Ablation Techniques (including TACE) | | | | |
|---------------------------------------------|------------------|------------------|------------------|
| Prostate                                   | YES ( ) NO ( )   | YES ( ) NO ( )   |
| Other – Specify:                           | YES ( ) NO ( )   |
|                                            | YES ( ) NO ( )   |

| Irreversible Electroporation (IRE) | | | | |
|-----------------------------------|------------------|------------------|------------------|
| Liver                             | YES ( ) NO ( )   | YES ( ) NO ( )   |
| Other – Specify:                 | YES ( ) NO ( )   |
|                                   | YES ( ) NO ( )   |

3) Are there any other image guided tumour ablation services provided at your centre that are used to treat cancer (e.g. rollerball ablation, portal vein embolization, etc.)? Please fill in the chart below indicating the tumour ablation service, the treatment location(s) and volumes of patients treated monthly.

<table>
<thead>
<tr>
<th>Other Focal Ablation Service</th>
<th>Treatment Location</th>
<th>Number of Patients Treated Monthly</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
4) Please provide us with any additional comments you may have about services currently available at your centre:

_____________________________________________________________________________________

_____________________________________________________________________________________

_____________________________________________________________________________________

_____________________________________________________________________________________

_____________________________________________________________________________________

_____________________________________________________________________________________

_____________________________________________________________________________________

Thank you for your time.
## Appendix E: Guidance Documents from other Jurisdictions

<table>
<thead>
<tr>
<th>No.</th>
<th>Source</th>
<th>Details</th>
<th>URL</th>
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<tbody>
<tr>
<td></td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>-----------</td>
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</tr>
</tbody>
</table>
Appendix F: PEBC Evidence Summary

Evidence Summary Focal Ablation 1: Thermal Ablation for Liver Cancer

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Focal Tumour Ablation 1: Thermal Ablation of Hepatocellular Carcinoma and Metastases from Colorectal Carcinoma

Fulvia G. Baldassarre, Mark Baerlocher, Robert Beecroft, Laura A. Dawson and John Kachura

Report Date: July 28, 2014

The full Evidence Summary is available on the CCO website (http://www.cancercare.on.ca)

For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:

Phone: 905-527-4322, ext. 42842
Fax: 905-526-6775
E-mail: ccopgi@mcmaster.ca

Evidence Summary Citation:

Evidence Summary (ES) Focal Ablation 1: Thermal Ablation for Liver Cancer

QUESTIONS

1. What is the effectiveness of liver lesion thermal ablation using radiofrequency ablation or microwave ablation, alone or in combination with other strategies for the treatment of patients with hepatocellular carcinoma (HCC) or liver metastases (e.g., from colorectal cancer)?
2. What are the subgroups of patients most likely to benefit from thermal ablation interventions?
3. What are the potential adverse events associated with thermal ablation techniques?

Target Population

Patients with HCC or colorectal liver metastases (CLM).

Target Users

Interventional radiologists, radiation oncologists, hepatobiliary surgeons, medical oncologists, healthcare professionals caring for patients with HCC or CLM.

INTRODUCTION

This report summarizes the peer-reviewed evidence regarding the use of radiofrequency ablation (RFA) and microwave ablation (MA) in the treatment of HCC and CLM.

Both RFA and MA are thermal ablative techniques that use heat to destroy cancerous cells. Permanent tissue destruction occurs once the temperature reaches 45°C, and irreversible cellular damage occurs at temperatures between 45°C and 60°C (1). Once the temperature rises above 60°C, protein coagulates almost instantly, with permanent damage occurring at the mitochondrial and enzymatic level. With thermal ablation, the goal is to heat the target tissues to a temperature between 50°C and 100°C and maintain that temperature until irreversible cellular destruction has occurred.

RFA refers to the destruction of cells by inducing coagulation with any electromagnetic energy source with a frequency less than 30 MHz, with most RFA generators working within a range of 375 to 500 kHz (2,3). There are various types of RFA applicators currently available, including single- and multi-tined applicators, internally cooled electrodes, and perfusion electrodes. Various algorithms of energy deposition are used, including ramped energy and impedance regulated.

Microwave ablation is similar to RFA; however, cellular destruction is achieved by inducing coagulation with an electromagnetic energy source of a frequency between 30 MHz and 30 GHz.

There are ablative therapies other than RFA and MA that can be used to treat liver cancers by using either heating or cooling to destroy the tumour. External beam conformal radiation therapy or stereotactic body radiation therapy (SBRT; also known as stereotactic ablative radiotherapy, SABR) can also be used to treat liver cancers. This current review does not cover all ablative therapies or all liver cancer presentations. It focuses specifically on the use of RFA and MA in the treatment of HCC and CRC liver metastases.
METHODS

This evidence-based report was developed by the Focal Thermal Ablation Working Group in collaboration with the Program in Evidence-Based Care (PEBC). For this project, a systematic review was used to develop the evidentiary base. A review of systematic reviews was conducted by the methodologist (FGB). The evidence from the systematic reviews was complemented by a search of primary randomized controlled trials (RCTs), which was also conducted by the methodologist.

Evidence was selected and reviewed by the methodologist (FGB). The final document was independently reviewed by the other authors (MB, RB, and LD).

Search Strategy

A literature search was performed using MEDLINE, EMBASE (Ovid interface), and the Cochrane Library (to Issue 4, 2014), first for systematic reviews published from 2009 to March 7, 2014 and then for RCTs published from January 1, 2012 to April 25, 2014. The search strategies are reported in Appendices 1 and 2. The citations of the RCTs referenced by the systematic reviews retrieved were also pulled and added to the RCTs retrieved from the database searches.

Additionally, the following resources were checked for systematic reviews, practice guidelines or relevant RCTs: the National Guideline Clearing House, the National Institute for Health and Clinical Excellence, the Scottish Intercollegiate Guideline Network, the Focal Ablation Advisory Committee members’ own files, and the Clinicaltrials.gov registry of ongoing trials. All databases were searched on March 7, 2014.

Study Selection Criteria

Systematic Reviews

Inclusion Criteria

Systematic reviews were eligible for inclusion if they met all the following criteria:

- Included studies with a population of patients with HCC or CLM.
- Had a research question pertaining to ablative treatments with radiofrequency and/or microwave.
- Reported on any outcomes (e.g., survival, disease control, adverse events, quality of life).
- Had a search strategy with a cut-off date of 2009 or later.
- Included RCTs and/or non-RCTs.

Exclusion Criteria

Systematic reviews were excluded if they:

- Had a focus different from the treatments of interest (e.g., cryoablation).
- Were published in languages other than English.
- Examined thermal ablation used solely with palliative intent.
- Examined thermal ablation to treat metastatic disease to the liver from sources other than colorectal cancer.
Examine thermal ablation used intraoperatively.
Examine thermal ablation used for the ablation of biliary obstructions.

The RCTs were sought to cover areas not already discussed by the systematic reviews. The time lag between the date of the most recent cut-off date for the included systematic reviews and the date of search was identified as a gap. Therefore, a search for RCTs was performed to cover the years 2012 to 2014.

**Study Selection Criteria: Randomized Controlled Trials**

**Inclusion criteria**
RCTs were included if they:
- Included a population of patients with HCC or CLM.
- Had a research question pertaining to RFA and/or MA compared to alternative strategies.
- Reported on any outcomes (e.g., survival, disease control, adverse events, quality of life).
- Were published in 2012 or later.

**Exclusion criteria**
RCTs were excluded if they:
- Had a focus different from the treatments of interest (RFA and MA).
- Focused on cryoablation.
- Were published in languages other than English.
- Examined thermal ablation used solely with palliative intent.
- Examined thermal ablation to treat metastatic disease to the liver from sources other than colorectal cancer.
- Examined thermal ablation used intraoperatively
- Examined thermal ablation used for the ablation of biliary obstructions

**Study Selection, Data Abstraction and Analysis**

The methodologist (FGB) reviewed the titles and abstracts of retrieved citations to identify potentially relevant articles which were then retrieved for full-text review. The methodologist reviewed the full text of the systematic reviews and of the RCTs. The methodologist evaluated the quality of the reviews with A Measurement Tool to Assess Systematic Reviews (AMSTAR) instrument (4) and the Cochrane Risk of Bias Tool for the RCTs (5). The AMSTAR tool is an 11-item checklist that evaluates the likelihood of bias in a systematic review by asking questions such as whether the literature search was comprehensive, the study selection was done in duplicate, the methods for combining the results were appropriate, and the quality of the included studies were assessed. The Cochrane Risk of Bias Tool is a domain-based evaluation tool, that critically assesses seven different domains representing selection bias, performance bias, detection bias, attrition bias, and reporting bias.

The data from the included systematic reviews and included RCTs and their quality assessments were summarized in tables. The results of the highest quality systematic reviews and those most relevant to the questions asked by the Panel are reported in detail in the Results section. The initial plan was to pool in a meta-analysis the RCTs if they were sufficiently clinically homogeneous, and to follow a narrative approach if the RCTs were heterogeneous.
RESULTS

Literature Search

The search for systematic reviews resulted in 75 citations from the Cochrane Library, 108 citations from EMBASE, 72 from MEDLINE, 36 from the Panel’s own files, and 13 from the guidelines search. We reviewed 304 citations at the title and abstract level, and 82 articles were selected and reviewed at the full-text level. We were unable to locate the full publication of one study. A total of 21 systematic reviews met eligibility criteria and were included. Reasons for exclusion included: duplicate publication (n = 3), abstract of systematic review (n = 4), not the intervention of interest (n = 21), not in English (n = 3), search was before than 2009 (n = 14), no outcomes of interest reported (n = 4), and not a systematic review (n = 12) (see study flow chart in Appendix 3A, and list of excluded systematic reviews in Appendix 4A).

The search for RCTs resulted in 41 citations from Cochrane (CENTRAL), 14 citations from MEDLINE, 197 from EMBASE, and one from the Panel’s files. We reviewed 253 citations at the title and abstract level; 13 publications were considered of potential interest and the full text was retrieved. Two RCTs were included after full-text review. Reasons for exclusion included: an abstract of an interim analysis (n = 1), already included in systematic reviews (n = 2), duplicate publication (n = 2), not written in English (n = 1), not an intervention of interest (n = 2), and not a RCT (n =3) (see study flow chart in Appendix 3B and list of excluded RCTs in Appendix 4B).

Tables 1A and 1B present the general characteristics and the summary results of the included systematic reviews. Tables 2A and 2B present the quality characteristics of the included systematic reviews. Tables 3A and 3B present the general characteristics and summary results of the included RCTs and Table 4 presents the quality of the included RCTs.
Table 1A. Focal ablation: summary table of included systematic reviews of thermal ablation – HCC.

<table>
<thead>
<tr>
<th>Author, date, funding source</th>
<th>Search cut-off date</th>
<th># of studies included</th>
<th>Review objectives/Design</th>
<th>Study designs included</th>
<th>Population</th>
<th>Intervention/comparison(s)</th>
<th>Outcomes</th>
<th>Summary results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang, 2014 (6)</td>
<td>Nov 2012</td>
<td>28: 3 RCTs and 25 non-RCTs</td>
<td>To evaluate the efficacy and safety of RFA versus hepatic resection for early HCC meeting the Milan criteria</td>
<td>RCTs, non-RCTs, retrospective clinical, or cohort studies</td>
<td>N = 11,873 meeting the Milan criteria</td>
<td>RFA vs. SR</td>
<td>OS (at 1-, 3-, and 5 y), RFS (at 1-, 3-, and 5 y), DFS (at 1-, 3-, and 5 y), Safety (at 1-, 3-, and 5 y)</td>
<td>Meta-analysis of RCTs</td>
</tr>
<tr>
<td>Weiss, 2013 (7)</td>
<td>Sept 2012</td>
<td>11 RCTs</td>
<td>To assess the beneficial and harmful effects of RFA versus placebo, no intervention, or any other therapeutic approach in patients with HCC.</td>
<td>RCTs</td>
<td>N = 578 pts with HCC without contraindications for RFA (e.g., too many or too large tumours)</td>
<td>RFA vs SR OS vs SR RFA vs PEI</td>
<td>OS EFS (recurrence and death)</td>
<td>Meta-analysis of non-RCTs</td>
</tr>
</tbody>
</table>

AE: (Time intervals NR)
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<thead>
<tr>
<th>Author, date, funding source</th>
<th>Search cut-off date</th>
<th># of studies included</th>
<th>Review objectives/Design</th>
<th>Study designs included</th>
<th>Population</th>
<th>Intervention/comparison(s)</th>
<th>Outcomes</th>
<th>Summary results</th>
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<tbody>
<tr>
<td>Belinson, 2013 (8)</td>
<td>Jul 2012</td>
<td>48: 6 RCTs, 4 non-RCTs, 35 case series, and 3 case reports</td>
<td>To examine the comparative effectiveness of local interventions for HCC. Systematic review and meta-analysis (only RCTs)</td>
<td>3 RCTs, 1 non-RCT, 6 case series and 1 case report.</td>
<td>N = 483 (RCTs only) with unresectable HCC. Pts with unresectable primary HCC who meet all of the following criteria: • No extrahepatic spread • No portal invasion • Child-Pugh class A or B disease • Eastern Cooperative Oncology Group (ECOG) status ≤1 and/or • BCLC stage A or B, or equivalent</td>
<td>RFA vs. PEI/PAI (3 trials) RFA vs. TACE</td>
<td>OS Progression Length of stay AE</td>
<td>Local recurrence favoured RFA (HR 2.44; 95% CI 1.71-3.49). However, no significant difference was found if only the result from the 4 trials with low risk of bias were meta-analyzed (OS: HR 1.19; 95% CI 0.79-1.77). RFA vs. MA (1 trial): AE for all comparisons: p = NS</td>
</tr>
<tr>
<td>Qi, 2013 (9)</td>
<td>Dec 2012</td>
<td>3 RCTs</td>
<td>To test the efficacy of RFA compared with SR</td>
<td>RCTs</td>
<td>N = 559 with HCC who met the Milan</td>
<td>RFA vs SR</td>
<td>OS RFS</td>
<td>OS: SR superior to RFA (p=0.02) RFS: SR superior to RFA (p=0.001)</td>
</tr>
<tr>
<td>Author, date, funding source</td>
<td>Search cut-off date</td>
<td># of studies included</td>
<td>Review objectives/Design</td>
<td>Study designs included</td>
<td>Population</td>
<td>Intervention/comparison(s)</td>
<td>Outcomes</td>
<td>Summary results</td>
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<tr>
<td><strong>5</strong> Duan, 2013 (10)</td>
<td>Jun 2013</td>
<td>12: 2 RCTs and 10 non-RCTs</td>
<td>To compare the effectiveness of RFA with SR</td>
<td>Meta-analysis</td>
<td>N = 8,612 with early stage HCC</td>
<td>RFA vs SR</td>
<td>OS (at 1, 3, and 5 y) DFS (1, 3 and 5 y) Complications Length of hospital stay</td>
<td>OS at 3 and 5 y: RFA shorter than SR</td>
</tr>
<tr>
<td><strong>Funding</strong>: National Science Foundation of China</td>
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<td></td>
<td>AE: SR had higher incidence of treatment-related AE than pts treated with RFA (p=0.002) Hospitalization: SR pts had longer hospitalizations than pts treated with RFA (p&lt;0.00001)</td>
</tr>
<tr>
<td><strong>6</strong> Cucchetti, 2013 (11)</td>
<td>Dec 2012</td>
<td>19: 3 RCTs and 16 retrospective observational studies</td>
<td>To examine the available literature directly comparing surgical resection with RFA</td>
<td>Systematic review</td>
<td>N = 12,703 with HCC</td>
<td>RFA vs SR</td>
<td>OS Complications</td>
<td>Unable to draw conclusions from the evidence. Includes 3 RCTs of which 2 state NS difference in OS and one favours SR. Good discussion of non-RCTs, and separate analysis because RFA is offered as an alternative not competitive strategy (i.e., prognostic factors are different in patients allocated to RFA and to SR in favour of SR)</td>
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<tr>
<td><strong>Funding</strong>: Siemens, Esaote, Bayer</td>
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<td><strong>7</strong> Shen, 2013 (12)</td>
<td>Mar 2012</td>
<td>4 RCTs</td>
<td>To perform a systematic review and meta-analysis of RCTs to compare RFA with PEI</td>
<td>Meta-analysis</td>
<td>N = 766 with HCC &lt;3 centimetres</td>
<td>RFA vs. PEI</td>
<td>OS Complete tumour necrosis Recurrence Metastases Complications Cost Hospital stay</td>
<td>OS: RFA better than PEI (HR = 0.66, 95% CI 0.48–0.90, p = 0.009) Recurrence: RFA had lower risk of local recurrence (HR = 0.38, 95% CI 0.15–0.96, p = 0.04), but for distant hepatic recurrence NS. Complete tumour necrosis: RFA was better Complications: RFA caused more major complications Cost: RFA cost more</td>
</tr>
<tr>
<td><strong>Funding</strong>: National Natural Science Foundation of China and Chongqing Natural Science Foundation of China</td>
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<td><strong>8</strong> Xu, 2012 (13)</td>
<td>Dec 2011</td>
<td>13: 2 RCTs and 11 non-RCTs</td>
<td>To perform a meta-analysis of SR vs RFA</td>
<td>All comparative</td>
<td>N = 2,535 with HCC</td>
<td>RFA vs SR</td>
<td>OS Recurrence</td>
<td>OS: SR better at 1, 3 and 5 y (respectively: OR, 0.60, 95% CI, 0.42 to 0.86; OR, 0.49, 95% CI, 0.36 to 0.65; OR,</td>
</tr>
<tr>
<td>Author, date, funding source</td>
<td>Search cut-off date</td>
<td># of studies included</td>
<td>Review objectives/Design</td>
<td>Study designs included</td>
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<td>Intervention/comparison(s)</td>
<td>Outcomes</td>
<td>Summary results</td>
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<td>9 Li, 2012 (14)</td>
<td>Mar 2011</td>
<td>6: 2 RCTs and 4 non-RCTs</td>
<td>To retrospectively evaluate the long term effects of RFA and SR</td>
<td>All comparative N = 877 with HCC</td>
<td>RFA vs SR</td>
<td>OS</td>
<td>RFS</td>
<td>Local recurrence</td>
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<tr>
<td>Funding: ND</td>
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<tr>
<td>10 Tiong, 2011 (15)</td>
<td>Nov 2010</td>
<td>43: 12 RCTs, and 31 non-RCTs</td>
<td>To test the effect of RFA</td>
<td>RCTs, quasi-RCT, and non-RCTs N = 1,558 with resectable and unresectable HCC</td>
<td>RFA vs SR</td>
<td>OS (at 1,3 and 5 y) Disease recurrence</td>
<td>RFA vs SR</td>
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<tr>
<td>Funding: University of Adelaide, Discipline of Surgery (Australia)</td>
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<tr>
<td>11 Cho, 2011 (16)</td>
<td>Feb 2011</td>
<td>8: 2 RCTs and 6 retrospective analyses</td>
<td>To compare SR with RFA as a primary treatment for HCC.</td>
<td>All comparative N = 1,100 meeting the Milan criteria*</td>
<td>RFA vs. SR</td>
<td>OS Safety (perioperative mortality) Local recurrence</td>
<td>Cannot reach a conclusion from available evidence.</td>
<td></td>
</tr>
<tr>
<td>Funding: ND</td>
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<tr>
<td>12 Salhab, 2011 (17)</td>
<td>Dec 2010</td>
<td>17 of which 5 of percutaneous treatment and 4 included in meta-analysis</td>
<td>To identify survival benefit for medical modalities in HCC</td>
<td>RCTs N = 628 with HCC (included in meta-analysis)</td>
<td>RFA vs. PEI</td>
<td>OS (at 1, 2, and 3 yrs) Cumulative probability of no recurrence</td>
<td>OS at 3 y RFA superior to PEI (p=0.002) AE NS</td>
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<td>Author, date, funding source</td>
<td>Search cut-off date</td>
<td># of studies included</td>
<td>Review objectives/Design</td>
<td>Study designs included</td>
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<td>Intervention/comparison(s)</td>
<td>Outcomes</td>
<td>Summary results</td>
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<tr>
<td>13 Xie, 2009, 2010 (18,19)</td>
<td>Jan 2009</td>
<td>6: 1 RCT and 5 comparative studies</td>
<td>To compare effectiveness and cost of RFA and SR for HCC</td>
<td>RCTs, non-randomized comparative cohort studies, and cohort studies. (For cohort studies the min sample size was N = 50).</td>
<td>N = 1,014 with either primary HCC or CLM</td>
<td>RFA vs. SR</td>
<td>OS DFS Recurrence AE Cost</td>
<td>RFA vs SR: OS NS DFS SR is superior to RFA Recurrence: Either comparable or SR is superior to RFA AE RFA has less complications than SR</td>
</tr>
<tr>
<td>14 Zhou, (20)</td>
<td>Nov 2009</td>
<td>10: 1 RCT and 9 non-RCTs</td>
<td>To test whether RFA is superior to SR</td>
<td>RCTs and non-RCTs</td>
<td>N = 1411 Pts with a small HCC eligible for SR</td>
<td>RFA vs SR 2 of the studies included laparoscopic RFA and the others included percutaneous RFA</td>
<td>OS Recurrence DFS Safety</td>
<td>OS 1 y (all trials): p =NS OS 2 y (4 trials): p = NS OS 3 y (9 trials) OR: 0.56, 95% CI: 0.44-0.71 p&lt;0.001 favours SR Local recurrence (5 trials): OR: 4.50, 95% CI: 2.45-8.27 p&lt;0.001 favours SR Distant recurrence: NS DFS: at 1, 2, 3, 5 y: significantly better for HR (p&lt;0.006, p&lt;0.001, p&lt;0.001, p&lt;0.05 respectively) Morbidity: OR: 0.29, 95% CI: 0.13-0.65 p= 0.003 favours RFA Mortality: p = NS</td>
</tr>
</tbody>
</table>

AE = adverse events; BSC = best supportive care; CI = confidence interval; CLMs = colorectal liver metastases; DFS = disease free survival; EFS = event-free survival; HCC = hepatocellular carcinoma; HR = hazard ratio; LA = laser ablation; LITT = laser induced thermal therapy; MA = microwave ablation; min = minimum; ND = not declared; NNH = number needed to harm; NS = not significant; OR = odds ratio; OS = overall survival; PAI = percutaneous acetic acid injection; PEI = percutaneous ethanol injection; PRFA = percutaneous radiofrequency ablation; Pts = patients; QOL = quality of life; RCTs = randomized controlled trials; RFA = radio frequency ablation; RFS = recurrence-free survival; RR = relative risk; SR = surgical resection; Sys Revs = systematic reviews; TACE = transarterial chemoembolization; TTP = time to progression; vs = versus; y = years.

* Milan criteria: single HCC<5 centimetres or 3 nodules <3 centimetres
Table 1B. Focal ablation: Summary table of included systematic reviews of thermal ablation - CLM

<table>
<thead>
<tr>
<th>Author, date, Funding source, Search cut-off date, # of studies included, Review objectives/Design</th>
<th>Study designs included</th>
<th>Population</th>
<th>Intervention/Comparison(s)</th>
<th>Outcomes</th>
<th>Summary Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loveman, 2014 (21)</td>
<td>RCTs, Prospective non-RCTs, Prospective case series (sample &gt;100), Economic evaluations</td>
<td>N = 2,618 with liver metastases</td>
<td>RFA, MA cryoaulation, PEI, LA, focused ultrasound, electrolytic ablation, TACE and radioembolization vs. SR, chemotherapy and BSC</td>
<td>Effectiveness and cost</td>
<td>Narrative synthesis: low quality evidence does not permit conclusions or pooling.</td>
</tr>
<tr>
<td>Funding: Health Technology Assessment Programme, UK</td>
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<td>MA</td>
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<td>OS: from RCT: p = NS</td>
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<td>DFS: p = NS</td>
<td>Surgical invasiveness: in favor of MA (p=0.0027)</td>
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<td>AE: p = NS</td>
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<td>RFA</td>
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<td>OS from 1 non-RCT + 5 case series: contrasting results</td>
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<td>DFS: p = NS</td>
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<td>AE: low</td>
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<tr>
<td>Baia, 2013 (22)</td>
<td>RCTs, Quasi-RCTs, Other controlled studies</td>
<td>N = 30 with liver metastases regardless of the location of the primary tumour.</td>
<td>MA vs. SR</td>
<td>All-cause mortality, Survival at 1, 3-y DFS, AE, QOL, Cancer mortality, Failure to clear liver metastases, TTP, Tumour response</td>
<td>Insufficient evidence to draw conclusions.</td>
</tr>
<tr>
<td>Cochrane review (sub group of a larger review by Riemsma 2009)</td>
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<td>Body of the evidence of moderate risk of bias</td>
<td>Mortality: p = NS</td>
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<td>DFS: p = NS</td>
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<td>AE: p = NS</td>
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<tr>
<td>Author, date, Funding source, Search cut-off date</td>
<td># of studies included</td>
<td>Review objectives/ Design</td>
<td>Study designs included</td>
<td>Population</td>
<td>Intervention/ Comparison(s)</td>
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<tr>
<td>Cirocchi, 2012 (23) Jan 2, 2012</td>
<td>18: 1 RCT (abs), 7 CCTs, and 10 observational studies</td>
<td>To systematically review the role of RFA in the treatment of CLMs</td>
<td>RCTs; Quasi-RCTs; Observational designs</td>
<td>N = 2,709 with CLMs and pts with unresectable extrahepatic disease</td>
<td>RFA alone or in combination compared with any other intervention</td>
</tr>
<tr>
<td>Belinson, 2012 (24) Jun 2012</td>
<td>30: 1 RCT, and 29 case series</td>
<td>To characterize the comparative effectiveness and harms of various local hepatic therapies for metastases to the liver from unresectable colorectal cancer (CRC)</td>
<td>Comparative studies</td>
<td>N = NR 1. Pts with liver-dominant metastases not eligible for systemic chemotherapy because of refractory disease. 2. Pts candidate for local liver therapies as an adjunct to systemic chemotherapy.</td>
<td>Ablation, embolization, and radiotherapy approaches.</td>
</tr>
<tr>
<td>Wu, 2011 (25) 2010 (month ND)</td>
<td>7 non-RCTs</td>
<td>To compare the efficacy of RFA with SR</td>
<td>Comparative studies</td>
<td>N = 847 with solitary colorectal cancer liver metastasis</td>
<td>RFA vs SR</td>
</tr>
<tr>
<td>Author, date, Funding source, # of studies included</td>
<td>Review objectives/ Design</td>
<td>Study designs included</td>
<td>Population</td>
<td>Intervention/ Comparison(s)</td>
<td>Outcomes</td>
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</tr>
<tr>
<td>Pathak, 2011 (26) 75: 13 MA, 36 RFA, and 26 cryo</td>
<td>To systematically review the literature on ablative strategies.</td>
<td>RCTs, case series</td>
<td>N = 4,248 with CLM</td>
<td>RFA, Cryoablation, and MA vs. palliative chemotherapy</td>
<td>OS (at 1, 2, 3, 4, and 5 y) Recurrence (at 1, 2, 3, 4, and 5 y) Complications (at 1, 2, 3, 4, and 5 y)</td>
</tr>
<tr>
<td>NICE, 2009 (27) 1 sys rev</td>
<td>To produce an evidence base for recommendations</td>
<td>1 systematic reviews, 2 non-RCTs, 3 case series, and 2 case reports</td>
<td>N = 1,570 with CLM</td>
<td>RFA alone or in combination with SR</td>
<td>Efficacy AE</td>
</tr>
</tbody>
</table>

Abs = abstract; AE = adverse events; BSC = best supportive care; CI = confidence interval; CCT = clinical controlled trials; CLMs = colorectal liver metastases; DFS = disease-free survival; HCC = hepatocellular carcinoma; LA = laser ablation; LITT = laser induced thermal therapy; LR = liver resection; MA = microwave ablation; ND = not declared; NNH = number needed to harm; NS = not significant; OS = overall survival; PAI = percutaneous acetic acid injection; PEI = percutaneous ethanol injection; PFs = progression-free survival; PRFA = percutaneous radiofrequency ablation; Pts = patients; QOL = quality of life; RCTs = randomized controlled trials; RFA = radiofrequency ablation; RFS = recurrence free survival; RR = relative risk; SR = surgical resection; Sys Revs = systematic reviews; TACE = transarterial chemoembolization; TTP = time to progression; vs = versus; yrs = years.
Table 2A. Quality assessment of included systematic reviews with AMSTAR - HCC

<table>
<thead>
<tr>
<th>Study</th>
<th>An a priori design provided</th>
<th>Duplicate study selection and data extraction</th>
<th>Comprehensive literature search performed</th>
<th>Status of publication used for inclusion criterion</th>
<th>List of studies (included and excluded) provided</th>
<th>Characteristics of included studies provided</th>
<th>Quality of included studies assessed and documented</th>
<th>Quality of included studies used appropriately in formulating conclusions</th>
<th>Methods used to combine the findings of studies</th>
<th>Likelihood of publication bias assessed</th>
<th>Conflict of Interest included</th>
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<tr>
<td>Wang 2014 (6)</td>
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<td>Y</td>
<td>N</td>
<td>Y*</td>
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<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N*</td>
<td>Y</td>
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<tr>
<td>Weiss, 2013 (7)</td>
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<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Belinson, 2013 (8)</td>
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<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
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</tr>
<tr>
<td>Qi, 2013 (9)</td>
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<td>Y</td>
<td>N</td>
<td>Y</td>
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<td>Y</td>
<td>N</td>
<td>N*</td>
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<td>Duan, 2013 (10)</td>
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<td>Can’t determine</td>
<td>N (only MEDLINE)</td>
<td>N</td>
<td>Y*</td>
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<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N*</td>
<td>Y</td>
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<tr>
<td>Cucchetti, 2013 (11)</td>
<td>Can’t determine</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N*</td>
<td>Y</td>
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<tr>
<td>Shen, 2013 (12)</td>
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<td>N</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N*</td>
<td>Y</td>
</tr>
<tr>
<td>Xu, 2012 (13)</td>
<td>Can’t determine</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
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<td>Y</td>
</tr>
<tr>
<td>Li, 2012 (14)</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Y*</td>
<td>Y</td>
<td>Y</td>
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<td>N</td>
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<tr>
<td>Tiong, 2011 (15)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
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<td>Y</td>
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<td>N</td>
<td>N</td>
<td>Y</td>
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<td>N*</td>
</tr>
<tr>
<td>Salhab, 2011 (17)</td>
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<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>N</td>
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<tr>
<td>Xie, 2009, 2010 (18,19)</td>
<td>Can’t tell</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
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<tr>
<td>Zhou, (20)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
</tbody>
</table>

* Only included studies listed
* The authors combined observational & RCT studies in meta-analysis.
* Does not report source of funding for the included studies, although it does report authors’ conflict of interests and funding source for the review.

HCC = hepatocellular carcinoma
Table 2B. Quality assessment of included systematic reviews with AMSTAR - CLM

<table>
<thead>
<tr>
<th>Study</th>
<th>An a priori design provided</th>
<th>Duplicate study selection and data extraction</th>
<th>Comprehensive literature search performed</th>
<th>Status of publication used as an inclusion criterion</th>
<th>List of studies (included and excluded) provided</th>
<th>Characteristics of included studies provided</th>
<th>Quality of included studies assessed and documented</th>
<th>Quality of included studies used appropriately in formulating conclusions</th>
<th>Methods used to combine the findings of studies appropriate</th>
<th>Likelihood of publication bias assessed</th>
<th>Conflict of Interest included</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loveman, 2014 (21)</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y*</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Bala, 2013 (22)</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y*</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
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<td>Y</td>
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<tr>
<td>Cirocchi, 2012 (23)</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Belinson, 2012 (24)</td>
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<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>Wu, 2011 (25)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Pathak, 2011 (26)</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>NICE, 2009 (27)</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Can’t determine</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N*</td>
</tr>
</tbody>
</table>

* Only included studies listed

Does not report source of funding for the included studies, although it does report authors’ conflict of interests and funding source for the review.

CLM = colorectal liver metastases
### Table 3A. General characteristics and summary results of included RCTs - HCC

<table>
<thead>
<tr>
<th>Study, year, funding</th>
<th>Objectives</th>
<th>Population</th>
<th>Intervention/comparison</th>
<th>Outcomes</th>
<th>Summary results</th>
</tr>
</thead>
</table>
| Di Costanzo (abs) 2013 (28) | To prospectively evaluate tumour response after RFA or LA of small HCC | N = 140 with cirrhosis and total 157 HCC nodules | RFA (n = 70 with total 77 nodules) LA (n = 70 with total 80 nodules) | CTA TTR OS | AT median follow-up 18.5 mo: 

**CTA:** 97.2% vs. 95.8% 

**TTR:** 16 mo (95% CI, 11-21) vs. 21 months (95% CI, 18-24) (p=0.08) 

**OS:** 93% vs. 93% |

CI = confidence interval; CTA = complete tumour ablation; HCC = hepatocellular carcinoma; LA = laser ablation; mo = months; OS = overall survival; ND = not declared; PFS = progression-free survival; RFA = radiofrequency ablation; TTR = time to recurrence; vs = versus.
### Table 3B. General characteristics and summary results of included RCTs – CLM.

<table>
<thead>
<tr>
<th>Study, year, Funding</th>
<th>Objectives</th>
<th>Population</th>
<th>Intervention/Comparison</th>
<th>Outcomes</th>
<th>Summary results</th>
</tr>
</thead>
</table>
| Ruers, 2012 (29)*    | To compare the efficacy of RFA + systemic treatment vs. systemic treatment alone | N = 119 with nonresectable liver metastases from colorectal adenocarcinoma without detectable extrahepatic disease | RFA + systemic treatment (n = 60) Systemic treatment alone (n = 59) | OS, PFS, HRQoL, Toxicity | OS: 45.3 (95% CI 33.1–NA) mo vs. 40.5 (95% CI 29.5–50.1); HR = 0.74, 95% CI 0.46–1.19, p = 0.22  
PFS: 16.8 mo (95% CI 11.7–22.1) vs. 9.9 mo (95% CI 9.3–13.7); HR = 0.63 (95% CI 0.42–0.95, p = 0.025)  
HRQoL: HRQoL scores were similar in both treatment groups.  
Toxicity: There was one postoperative death due to sepsis in the combined treatment arm. Toxicity from systemic treatment was comparable in both arms. |

*The Ruers’ study was included in one of the included systematic reviews as an abstract of an ongoing study, we identified the full text publication.

CI = confidence interval; HR = hazard ratio; HRQoL = health-related quality of life; mo = months; OS = overall survival; PFS = progression free survival; RFA = radiofrequency ablation;
Table 4. Quality of the included RCTs

<table>
<thead>
<tr>
<th>Risk of Bias Tool</th>
<th>Di Costanzo, 2013 (28)</th>
<th>Ruers, 2012 (29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Low risk(^a)</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Unclear risk</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Unclear risk</td>
<td>High risk</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>High risk</td>
</tr>
<tr>
<td>Incomplete outcome data addressed (attrition bias)</td>
<td>Unclear risk</td>
<td>Low risk(^b)</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

\(^a\)The authors performed central randomization  
\(^b\)The authors performed an intention-to-treat analysis

Question 1: Effectiveness of Thermal Ablation

A. Hepatocellular Carcinoma

Two high-quality systematic reviews compared RFA with surgical resection, percutaneous ethanol injection (PEI), transarterial chemoembolization (TACE) and MA in patients with primary hepatocellular carcinoma who were (7) or were not (8) candidates for surgical resection. Both systematic reviews included RCTs and non-RCTs.

Radiofrequency Ablation versus Surgical Resection.

Weis et al. (7) included three RCTs, and they rated their quality according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system (30). According to this system, the quality of the studies is rated with the Cochrane Risk of Bias tool (5) and the evidence for each outcome considered critical, across multiple studies, is evaluated individually. Evidence begins with a high ratings for RCTs and a low rating for observational studies. It may be then “graded down” according to evaluation of five factors: risk of bias, inconsistency, indirectness, imprecision, and publication bias. It may be “graded up” according to three factors: large magnitude of effect, dose-response gradient, and if no effect was observed when all possible confounding would reduce the effect or increase the effect. At the end of this process, systematic reviewers do not grade the overall quality of the evidence across outcomes, but they rate the evidence for each outcome as high, moderate, or low.

Weis et al. (7) used the Cochrane Risk of Bias tool to rate two of three RCTs at low risk of bias (31,32), and one at high risk of bias (33).

Overall survival. The reviewers rated the quality of the evidence for overall survival (OS) as moderate. When pooling the results from all three trials (31-33) using a random effects model, OS was not statistically significantly different between groups: hazard ratio (HR) 0.71, (95% confidence interval [CI] 0.44-1.15). However, when pooling data using a fixed effects model, OS reached statistical significance
in favour of surgical resection: HR 0.76, (95% CI 0.58-1.00). Further, in a subgroup analysis, when only the two low risk of bias trials (31,32) were pooled, surgical resection yielded better results than RFA for OS (HR 0.56; 95% CI 0.40-0.78).

*Event free survival.* The reviewers considered the quality of the evidence for this outcome as moderate. At three years, surgical resection produced better results than RFA: the pooled estimates for three RCTs (31-33) was: HR 0.70 (95% CI 0.54, 0.91), I^2=34%.

*Local progression.* The reviewers considered the quality of the evidence as low because only one trial reported on this outcome. Local progression was better for surgical resection than RFA (one RCT): HR 0.48 (95% CI 0.28-0.82).

*Length of hospital stay.* The reviewers rated the evidence for this outcome as high. RFA produced shorter lengths of stay than surgery: standardized mean difference: 2.18 days, 95% CI 1.97-2.39.

**Radiofrequency ablation versus Percutaneous Ethanol Injection (PEI).**

*Overall survival.* The authors of both reviews (7,8) considered the quality of the evidence, and both evaluated it with the GRADE method (30) for OS as moderate. OS was superior in the RFA group than in the PEI group in both reviews.

Weis et al. pooled seven RCTs; five, (represented by four publications), of which they considered at low risk of bias (34-37) and two at high risk of bias (38,39). For OS, they reported a better results for RFA vs. HR 1.64, (95% CI 1.31-2.07) with I^2 = 0.0% (7).

Belinson et al. identified three RCTs (39), also included in the Weis review: one compared RFA to PEI alone (34,36,39); one compared RFA with high-dose PEI (34); and one compared RFA to PEI and percutaneous acetic acid injection (PAI) (36). Most patients in the included studies had a solitary tumour, and data on lesion size were not reported. The authors conducted a quantitative pooling for OS at three years; the RFA group had a significantly higher OS than the PEI/PAI group (risk difference 0.16 (95% CI, 0.03-0.28, I^2=48%) (8).

*Event-free survival.* Weis et al. (7) rated the quality of the evidence for EFS as moderate, whereas Belinson et al. considered the strength of evidence as low (8). After pooling the previously mentioned seven RCTs (34-39) RFA resulted in a better EFS: HR 1.55, 95% CI 1.31 to 1.85 (7). Belinson et al. (8) reported narratively about cancer-free survival, and stated that the RFA group had significantly higher survival rates in both of the included studies (34,36).

*Local recurrence.* Local recurrence was better with RFA in both reviews: Weis et al. pooled results from six studies, four of which rated at low risk of bias (34-37) and two of which they rated of high risk of bias(38,39): HR 2.44, 95% (CI 1.71-3.49) (7). Belinson et al. (8) reported a narrative summary of the results from two RCTs (34,36) (no numerical data provided) and considered the strength of the evidence low for this outcome.
Length of hospital stay. Belinson et al. reported that patients in the RFA group stayed in hospital longer than patients in the PEI group (no numerical data provided) (8). The reviewers rated the quality of this outcome as low.

Quality of life. Quality of life was not reported by the studies included in either reviews.

Radiofrequency Ablation versus Microwave Ablation.

Weis et al. (7) identified one RCT (40) that presented data by nodules and not by patient which prevented extraction of data on OS, and EFS. The Belinson et al review did not report on this comparison (8).

Local progression. Local progression was not statistically significantly different between the RFA and MA in the study by Shibata et al. (40) as reported by Weis et al. (7) (HR 2.14, 95% CI 0.67-6.80)

Radiofrequency Ablation versus Laser Ablation.

When RFA was compared with laser ablation in one RCT (41) identified by the Weis et al. review (7), no statistically significant difference was detected for OS. This result is consistent with the findings of the conference abstract we identified through our search for RCTs (28). In the latter abstract, no difference was shown for complete tumour ablation or for time to recurrence. Belinson et al did not report on this comparison (8).

Radiofrequency Ablation versus Transarterial Chemoembolization.

Weis et al. (7) did not identify any study for this comparison. Belinson et al. (8) identified one retrospective cohort study (42).

Overall survival. OS was not statistically significantly different between groups in the study by Chok et al. (42) and the reviewers concluded that the evidence was insufficient to draw conclusions.

B. Colorectal Liver Metastases

Four high-quality systematic reviews (21-24) and one RCT (29) were included. All these reviews concluded that the available evidence was insufficient to draw conclusions; Ruers et al. (29) concluded that RFA plus chemotherapy resulted in better progression-free survival (PFS) than chemotherapy alone, but that uncertainty remained for OS. A more detailed description of the finding of these studies follows. Bala et al. (22) evaluated the evidence with the GRADE method (30), Belinson et al. used the Agency for Healthcare Research and Quality (AHRQ) Methods Guides (43); Cirocchi et al. (23) used a component approach (i.e., generation of randomization sequence, adequacy of allocation concealment and of follow-up) to evaluate the quality of included RCTs, and Loveman et al. (21) used the approach recommended by the Centre for Reviews and Dissemination (44).

Bala et al. sought studies comparing MA with surgical resection in patients with liver metastases of any primary tumour (22) and found one RCT (45) which they rated as very low quality.
Belinson et al. sought studies examining ablation strategies in patients with unresectable or recurrent colorectal cancer liver metastases. These authors found only case series that reported no comparisons (24). The reviewers concluded that the evidence was insufficient to draw conclusions.

Cirocchi et al. included studies of RFA in patients with colorectal liver metastases (23). These authors found seven observational and six non-RCTs that compared RFA with surgical resection (46-58); one abstract publication of an RCT (the full publication of which was identified by our search for RCTs (29)) that compared RFA plus chemotherapy with chemotherapy alone, one non-RCT of RFA plus adjuvant hepatic arterial infusion chemotherapy (HAI) versus RFA plus HAI plus surgical resection (59), one observational study RFA alone versus RFA plus surgical resection versus surgical resection alone versus chemotherapy alone (60), one observational study of RFA plus surgical resection versus surgical resection plus cryosurgical ablation (61), and four non-RCTs comparing RFA with RFA plus HR (46,49,50,54). Cirocchi et al. considered all the identified studies at high risk of bias, either because patients in the intervention and control groups had different initial prognosis (i.e., in the non-RCTs) opening the possibility to selection bias, or because of lack of reporting about important data to assess quality (i.e., in the abstract publication of the only RCT included). Therefore the authors concluded that the evidence from the included studies was insufficient to recommend RFA for a radical treatment of colorectal liver metastases.

Loveman et al. (21) included studies of minimally invasive strategies in patients with liver metastases of any primary tumour, and included RCTs, prospective non-RCTs, case series with sample size >100, and economic evaluations. The authors identified 16 unique studies within 19 publications. Among these, one RCT of MA versus surgical resection that the authors considered at low risk of measurement bias (45), found no statistically significant difference in survival and less surgical invasiveness for microwave ablation; one non-RCT of RFA versus surgical resection and of RFA versus surgical resection plus RFA (46) reported few relevant data, and five studies (in seven publications) were case series of RFA (52,62-67) and therefore did not report of any comparisons. The authors concluded that the overall quality of the studies was low. The other studies included by the Loveman et al. review reported on laser ablation, chemoembolization, and radioembolization, and were out of scope for this review.

We identified the Ruers et al. RCT of patients with nonresectable colorectal liver metastases (29) by our systematic review of RCTs. This study was conceived as a phase III trial, but was stopped early because of slow accrual; it did not reach the required sample size, and was downsized to a phase II trial. In total, 59 patients were treated with systemic treatment and 60 with systemic treatment plus RFA. RFA was performed by laparotomy, laparoscopy, or percutaneously. Patients had a median of four lesions in the RFA plus chemotherapy arm, and a median of five lesions in the chemotherapy alone arm.

The quality of this study was evaluated with the Cochrane Risk of Bias tool (see Table 4). Ruers et al. (29) compared RFA and chemotherapy versus chemotherapy alone in patients with nonresectable liver metastases. We present its results in the following paragraphs.

**Overall survival.** At 30 months, OS was not statistically significantly different between groups: 61.7% (95% CI 48.2–73.9) for the RFA and chemotherapy group and 57.6% (95% CI 44.1–70.4) for the
chemotherapy alone group. Median OS was 45.3 months (95% CI 33.1–NA) versus 40.5 months (95% CI 29.5–50.1) and HR = 0.74, (95% CI 0.46–1.19, p = 0.22).

Progression-free survival. Median PFS was 16.8 months (95% CI 11.7–22.1) in the RFA and chemotherapy group versus 9.9 months (95% CI 9.3–13.7) in the chemotherapy alone group (HR = 0.63, 95% CI 0.42–0.95, p = 0.025), corresponding to an absolute 17% increase in the PFS rate at three years from 10.6% (95% CI 4.2–20.5) to 27.6% (95% CI 16.9–39.5).

Health related quality of life (HRQoL). Health related quality of life (HRQoL) scores were similar in both treatment groups, although the limited sample size limits definite conclusions on this outcome.
**Question 2: Subgroups of Patients Most Likely to Benefit from Thermal Ablation**

**A. Hepatocellular Carcinoma**

Two systematic reviews presented results on patients subgroups (11,12). Cucchetti et al. (11) included studies of ablation techniques for patients with HCC. Shen et al. (12) included studies comparing RFA and PEI in patients with HCC. Cucchetti et al. (11) evaluated the quality of the included studies using the Newcastle Ottawa quality scale for observational studies (68), and Shen et al. (12) used the GRADE method (30).

Cucchetti et al. (11) reported on three RCTs (31-33) and on 16 observational, retrospective studies of RFA compared with surgery. The population of the RCTs was heterogeneous and had different proportions of HCC beyond early stages.

Among these three studies, Chen et al. (33) included 71 patients treated with RFA and 90 patients treated with surgery. OS and DFS were the same at three years in both RFA and surgical ablation groups for patients with tumours \(<5\) centimetres. However, surgical resection had more adverse events (33); Huang et al. (31) included 115 patients per group. At five years OS was better with surgical resection versus RFA (RFA OS = 58.4\% vs. surgical resection 75.7\%, \(p=0.001\)). Benefits of resection were maintained when patients were stratified by tumour size and number (31). Finally, Feng et al. (32) included 84 patients per group. OS at three years was not statistically significantly different between groups (RFA 67.2\% and surgery 74.8\%, \(p=0.34\)). This study did not provide stratification by tumour stage.

Shen et al. (12) pooled the results of four RCTs (35,36,38,39) and excluded studies with patients whose lesions were \(>3\) centimetres and/or follow-up was less three years. The reviewers rated all four studies at high risk of bias; their confidence in the evidence provided was moderate for three-year survival for the subgroup of patients with HCCs \(<3\) centimetres; low for four-year survival in patients with HCCs \(<3\) centimetres; low for overall intrahepatic recurrence, and for risk of death when patients with liver function Child-Pugh (CP) class B were compared with patients with CP class A; and very low for three-year survival for patients with HCC \(>2\) centimetres, or HCC \(<2\) centimetres and for overall local recurrence.

*Single Tumours \(<2\) centimetres.*

Cucchetti et al. (11) reported on four retrospective observational studies of patients with single tumours \(<2\) centimetres (69-72). Not all of these studies focused on RFA and MA only, and they had populations with different prognoses in the intervention and control group; therefore, conclusions were hampered by potential for bias.

Shen et al. (12) reported that three-year OS was similar for RFA and PEI for patients with HCC \(<2\) centimetres, (HR 0.79, 95\% CI 0.50-1.25, \(p=0.32\), \(I^2 = 0\%\)).

*Single Tumours \(<3\) centimetres*
Cucchetti et al. (11) reported on seven studies for this subgroup (31,33,73-77). The RCT by Chen et al. (33) reported that OS and DFS were not different between ablative strategies and surgical resection groups (data not provided). The study by Huang et al. (31) reported the three- and five-year survival rates for the hepatic resection group and the RFA group were 77.2%, 61.4% and 95.6%, 82.2%, respectively (p = 0.03). DFS and RFS were not reported. According to Cucchetti et al. (11), this subgroup analysis based on 45 resected and 57 ablated patients, is the most robust evidence for the superiority of surgery over RFA. The other five studies identified were retrospective observational studies and are not discussed further here because of their high potential for bias.

Shen et al. (12) reported that three-year OS was better with RFA than with PEI for patients with HCC <3 centimetres, (HR 0.66, 95% CI 0.48-0.90, p=0.009; I²=14.2%). However, the difference between groups narrowed with longer follow-up times (four-year survival, RFA vs. PEI, HR = 0.71, 95% CI: 0.52–0.97, p = 0.03; I² = 0.0%). For tumours >2 centimetres the authors found also a similar result (HR = 0.56; 95% CI 0.31 to 09.9, p=0.045; I² = 0%).

RFA was better than PEI also for recurrence and metastasis (HR = 0.38, 95% CI: 0.15–0.96, p = 0.040; I² = 65.6%).

In a subgroup analysis, Shen et al. (12) found that patients with liver function CP class B had a higher risk of death than patients with CP class A, irrespective of the treatment modality (HR = 2.23, 95% CI 1.26–3.97, p = 0.006; I² = 56.8%).

No significant difference was found in distant intrahepatic recurrence events (HR = 0.95, 95% CI: 0.75–1.22, p = 0.707; I² = 0.0%) by the three studies that reported on this outcome (35,36,39).

**Single Tumors 3-5 centimetres**

Cucchetti et al. (11) identified four articles that reported on this subgroup of patients: two RCTs (31,33) and two observational studies (74,78). Chen et al. (33) reported no between-arm difference, but survival rates and p values were not reported. Huang et al. (31) reported a five-year OS rate of 72.3% after surgery vs. 51.5% after ablation (p = 0.046), and did not provide results for disease free survival (DFS) or recurrence-free survival (RFS). Cucchetti et al. (11) reported that the results of the observational studies, which were retrospective with very small sample size, did not show any between-group differences for DFS or OS, and the reviewers recommended more studies for this subgroup of patients.

Shen et al. (12) did not report on this subgroup of patients.

**Multiple Tumors**

Cucchetti et al. (11) included two studies that reported analyses for patients with multiple tumours: one RCT (31), and one observational study (74). The RCT by Huang et al. reported a better survival after surgery than after RFA (surgical resection: 69.23%, RFA: 45.16, p=0.04) in a subgroup of 26 resected patients compared with 31 ablated patients with multifocal disease, but did not report on DFS. On the other hand, Ueno et al. (74) reported OS favouring RFA over surgical resection: at five years, survival was not reached in the surgical group (n = 13) and the three-year survival was better for RFA (n = 54; surgical
Focal Tumour Ablation in Ontario: Recommendation Report, 2015

resection: 67%, RFA: 93% p = 0.002), although DFS was similar. The reviewers pointed out that in most of the non-RCT studies, having multifocal disease was a criterion to be allocated to thermal ablation as opposed to surgical resection (11).

**B. Colorectal Cancer Liver Metastases**

The systematic reviews by Loveman et al. (21) and Bala et al. (22) identified a RCT that compared MA with surgical resection (45). Loveman et al. considered this trial of reasonable quality, whereas Bala et al. rated it at high risk of bias. The Shibata et al. RCT (45) included 40 patients with multifocal disease (MA group: mean number of lesions 4.1, largest tumour 27 mm; surgical resection group: mean number of lesions 3.0, largest tumour 34 mm), and did not find any statistically significant between-group differences in OS at one, two, and three years (MA group: 71%, 57%, 14%, respectively; surgical resection group 69%, 56%, 23% respectively p = 0.83). Similar results were found for DFS (MA group: mean DFS: 11.3 months, surgical resection group: mean DFS 13.3 months, p = 0.47).

Cirocchi et al. (23) included the non-RCT by Kim et al. (46) which analyzed subgroups of patients with different tumour size and single versus multiple lesions. Kim et al. (46) reported for patients with a single metastatic lesion (n=226) <3 centimetres in size: the DFS rate was 33.6% in the RFA group and 31.6% in the surgical resection group at five years. In patients with a single lesion ≥3 centimetres, the five-year DFS rates were 23.1% in the RFA and 36.6% in the surgical resection group (p=0.01). As well, RFA resulted in lower DFS rates in patients with multiple liver lesions (6.4% in the RFA group vs. 16.2% in hepatic resection group). All of the studies in the Cirocchi et al. (23) review included patients with a worse prognosis in the RFA group than they did in the surgical resection group.

Belinson et al. (24) performed a multivariate analysis to identify characteristics that could improve overall survival (entered as dependent variable). Characteristics that were associated with improved survival were: Eastern Cooperative Oncology Group (ECOG) status (0 vs. ≥1 and in another study 0 or 1 vs. ≥2), performance status (0 or 1 vs. ≥ 2), number of extrahepatic metastases sites (0 or 1 vs. ≥2), number of lines of previous chemotherapy (0–1 vs. ≥ 2), performance status (0 or 1 vs. ≥ 2), carcino-embryonic antigen response (yes, no), and Response Evaluation Criteria in Solid Tumors (RECIST).

**Question 3: Potential Adverse Events**

Serious adverse events considered included: gastric bleeding, hemoperitoneum, hemothorax, thrombosis, treatment-related death.

**A. Hepatocellular carcinoma**

**Radiofrequency Ablation versus Surgical Resection**

Weis et al. (7) in a meta-analysis of three RCTs reported that the rate of complications was higher in the surgical groups compared with the RFA groups, (OR 8.24, 95% CI 2.12-31.95). The reviewers considered the evidence for rate of complications as high.
Radiofrequency Ablation versus Percutaneous Ethanol Injection.

Weis et al. (7) reported that the proportion of patients with serious adverse events was not significantly different between groups (PEI/PAI vs. RFA; OR 0.70, 95% CI 0.33- 1.48), and they rated the quality of the evidence for this outcome as moderate. Belinson et al. reported that none of the included studies reported on liver failure, hepatic hemorrhage or abscess; two studies reported hemoperitoneum: 1.4% in each group (36,39); hemothorax in the RFA group: 3.2% (36) and 1.4% (39); one death in the PEI group (39); and 1.6% gastric bleeding and perforation (36). The reviewers rated the quality of evidence as insufficient to draw conclusions (8).

The studies included by Shen et al. (12) reported only minor adverse events for both RFA and PEI procedures and no statistically significant difference in major adverse events such as hemothorax.

Radiofrequency Ablation versus Microwave Ablation (MA).

Adverse events were not statistically significantly different between groups in the Shibata study (40) identified by Weis et al. (7).

Radiofrequency Ablation versus Laser Ablation

None of the included systematic reviews reported on complications for this comparison.

Radiofrequency Ablation versus Transarterial Chemoembolization

None of the included systematic reviews reported on complications for this comparison.

B. Colorectal Liver Metastases

Ruers et al. (29) reported of one postoperative death due to sepsis in the RFA and chemotherapy arm. Adverse effects from systemic treatment was comparable in both arms.

MA versus surgical resection

Shibata et al. (45) (in Loveman et al. (21)) reported statistically significantly less intraoperative blood loss in the MA group compared with the surgical resection group (MA: mean 360 mL, standard deviation [SD] 230 mL; surgical resection 910 mL, SD 490 mL, p = 0.03). No difference was detected in adverse events (p=0.87).
DISCUSSION AND CONCLUSIONS

The following points summarize the conclusions of the Working Group:

**Hepatocellular Carcinoma:**

1. There is strong evidence in support of percutaneous RFA or MA in the treatment of nonresectable HCC. Evidence for MA is less extensive. Excellent outcomes can be expected when RFA and MA are used to treat HCC measuring ≤3 centimetres, and moderate outcomes in the treatment of nonresectable HCC measuring 3-5 centimetres.

2. RFA is equivalent in the treatment of small nonresectable HCC compared with MA, and superior compared with PEI. There is insufficient evidence comparing RFA to TACE/TABE in the treatment of nonresectable HCC (although in clinical practice RFA and TACE are generally used with different intent - curative vs. “palliative”, respectively).

3. Percutaneous ablative therapies are associated with lower complication rates, and shorter hospital admission stays compared with surgery.

**Colorectal liver metastases:**

1. There is preliminary evidence in support of percutaneous RFA in the treatment of nonresectable colorectal metastases. Evidence for MA is less extensive. Outcomes are best when used to treat tumours measuring ≤3 centimetres, and moderate when used to treat tumours measuring 3-5 centimetres.

2. Percutaneous ablative therapies are associated with lower complication rate, and shorter hospital admission stays compared with surgery.

   There is preliminary evidence suggesting that combination therapy with one or more percutaneous ablative therapies and/or TACE/TABE may provide additional DFS benefit versus singular intervention. Additional data are necessary to further delineate the effectiveness and indication(s) for combination therapy.

   Additional data are necessary in order to determine specific scenarios of when a given ablative technology would be superior to another.

**CONFLICT OF INTEREST**

RB declared he was the director of the industry sponsored “Master Class in Interventional Oncology” 2013 at Toronto General Hospital, and declared he spoke at an industry sponsored symposium. For these activities, he received an honorarium of less than $5000. MB declared he was a temporary consultant for documents related to intravenous lines for Cook Inc. The other two authors (LAD and FGB) declared no conflict of interest.
All the members of the Advisory Committee completed a conflict of interest statement. Their conflict of interest disclosures are summarized in Appendix 4.

Updating

This document will be reviewed in three years to determine if it is still relevant to current practice and to ensure that the recommendations are based on the best available evidence. The outcome of the review will be posted on the CCO website. If new evidence that will result in changes to these recommendations becomes available before three years have elapsed, an update will be initiated as soon as possible.

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Phone: 905-527-4322, ext. 42842  Fax: 905-526-6775  E-mail: ccopgi@mcmaster.ca
APPENDIX 1: Search strategies for systematic reviews and practice guidelines.

Database: Ovid MEDLINE(R) without Revisions, MEDLINE Daily Update, MEDLINE in-Process and Other non indexed citations <March 6, 2014>
Search Strategy:
--------------------------------------------------------------------------------
1    meta-Analysis as topic/
2    meta analysis.pt.
3    (meta analy$ or metaanaly$).tw.
4    (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthet?s or quantitative overview).tw.
5    (systematic adj (review$ or overview?)').tw.
6    (exp Review Literature as topic/ or review.pt. or exp review/) and systematic.tw.
7    or/1-6
8    (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
9    (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
10   (selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
11   (study adj selection).ab.
12   10 or 11
13   review.pt.
14   12 and 13
15   exp Carcinoma, Hepatocellular/
16   exp Liver Neoplasms/
17   ((Hepat* or liver) and (carcinom* or tumo?r* or neoplasm* or malign* or cancer*)).mp.
18   HCC.mp.
19   15 or 16 or 17 or 18
20   exp Catheter Ablation/
21   ((radiofrequenc* or radio-frequenc* or radio frequenc*) and (ablation* or therap* or treat*)).mp.
22   (RFTA or RFA or RFT of RFCA).mp.
23   thermotherapy.mp. or exp Hyperthermia, Induced/
24   exp microwaves/ or coagulation therapy.mp. or exp Electrocoagulation/
25   7 or 8 or 9 or 14
26   20 or 21 or 22 or 23 or 24
27   19 and 25 and 26
28   limit 27 to english language
29   animal/
30   human/
31   29 not 30
32   28 not 31
Database: EMBASE <1996 to 2014 Week 10>
Search Strategy:
--------------------------------------------------------------------------------
1  exp Meta Analysis/ or exp "Systematic Review"/
2  (meta analy$ or metaanaly$).tw.
3  (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthe$ or quantitative overview).tw.
4  (systematic adj (review$ or overview?)).tw.
5  exp Review/ or review.pt.
6  (systematic or selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
7  (study adj selection).ab.
8  6 or 7
9  5 and 8
10  1 or 2 or 3 or 4 or 9
11  (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab. (55190)
12  (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
13  10 or 11 or 12
14  exp liver cell carcinoma/
15  ((Hepat* or liver) and (carcinom* or tumo?r* or neoplasm* or malign* or cancer*)).mp.
16  HCC.mp.
17  14 or 15 or 16
18  exp radiofrequency ablation/
19  exp Catheter Ablation/
20  ((radiofrequenc* or radio-frequenc* or radio frequenc*) and (ablation* or therap* or treat*)).mp.
21  (RFTA or RFA or RFT of RFCA).mp.
22  Hyperthermic Therapy.mp. or hyperthermic therapy/
23  microwave radiation#.mp. or exp microwave radiation/
24  ((coagulation adj therapy) or ablation).tw.
25  18 or 19 or 20 or 21 or 22 or 23 or 24
26  13 and 17 and 25
27  limit 26 to english language
28  Animal/
29  Human/
30  28 not 29
31  27 not 30
32  (editorial or note or letter erratum or short survey).pt. or abstract report/ or letter/ or case study/
33  31 not 32
Database Cochrane Library:
Search terms: “Ablation” AND “Cancer”

Database: National Guidelines Clearinghouse (http://www.guideline.gov/):
Search terms: “Ablation” AND “Cancer”

National Institute for Health and Care Excellence (http://guidance.nice.org.uk/CG/Published):
Search terms: “Ablation” AND “Cancer”
APPENDIX 2. Search strategies for randomized controlled trials.

Database: Ovid MEDLINE up to April 25, 2014
Search Strategy:
--------------------------------------------------------------------------------
1  exp randomized controlled trials as topic/ or exp clinical trials, phase III as topic/ or exp clinical trials, phase IV as topic/
2  (randomized controlled trial or clinical trial, phase III or clinical trial, phase IV).pt.
3  random allocation/ or double blind method/ or single blind method/
4  (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
5  1 or 2 or 3 or 4
6  (phase II or phase 2).tw. or exp clinical trial/ or exp clinical trial as topic/
7  (clinical trial or clinical trial, phase II or controlled clinical trial).pt.
8  (6 or 7) and random$.tw.
9  (clinic$ adj trial$1).tw.
10  ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
11  placebos/
12  (placebo? or random allocation or randomly allocated or allocated randomly).tw.
13  (allocated adj2 random).tw.
14  9 or 10 or 11 or 12 or 13
15  exp Carcinoma, Hepatocellular/
16  exp Liver Neoplasms/
17  ((Hepat* or liver) and (carcinom* or tumo?r* or neoplasm* or malign* or cancer*)).mp.
18  HCC.mp.
19  15 or 16 or 17 or 18
20  exp Catheter Ablation/
21  (radiofrequenc* or radio-frequenc* or radio frequenc*) and (ablation* or therap* or treat*).mp.
22  (RFTA or RFA or RFT of RFCA).mp.
23  thermotherapy.mp. or exp Hyperthermia, Induced/
24  exp microwaves/ or coagulation therapy.mp. or exp Electrocoagulation/
25  20 or 21 or 22 or 23 or 24
26  animal/
27  human/
28  26 not 27
29  (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
30  19 and 25 and 14
31  30 not 28
32  31 not 29
33  limit 32 to english language
34  limit 33 to yr="2012 -Current"

Database: EMBASE <2012 to 2014 Week 16>
Search Strategy:
--------------------------------------------------------------------------------
1  exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/
2  randomization/ or single blind procedure/ or double blind procedure/
3  (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
Limit 40 to yr=2012 to current

Registries:
Clinicaltrials.gov (http://www.clinicaltrials.gov) :
Search terms: “Radiofrequency” AND “Ablation”;
“Microwave” AND “Ablation”
APPENDIX 3 A). Study flow chart: systematic reviews.

APPENDIX 3 B). Study flow chart: primary randomized controlled trials.
Appendix 4A. Excluded systematic reviews

DUPLICATE PUBLICATION – SYSTEMATIC REVIEWS


ABSTRACT of SYSTEMATIC REVIEW


NOT INTERVENTION OF INTEREST


**NOT IN ENGLISH**


**SEARCH OLDER THAN 2009**


NOT OUTCOME OF INTEREST


NOT SYSTEMATIC REVIEW


Appendix 4B. Excluded RCTs

ABSTRACT OF INTERIM ANALYSIS


ALREADY IN INCLUDED SYSTEMATIC REVIEWS


DUPLICATE PUBLICATIONS


NOT IN ENGLISH

NOT INTERVENTION OF INTEREST


NOT RCT


**Appendix 4: Conflict of Interest Disclosures: Focal Ablation Committee**

<table>
<thead>
<tr>
<th>Members</th>
<th>Role</th>
<th>Conflict of Interest</th>
</tr>
</thead>
</table>
| John Kachura    | Co-Chair  | Past President of CIRA (Canadian Interventional Radiology Association). The following parties contribute financially to CIRA: Abbott Vascular, Angiodynamics, Bard, Boston Scientific, Cook Medical, Cordis Endovascular, Covidien, GE Healthcare, Gore, InterV Medical, Medtronic and Philips  
Co-applicant for patent regarding an invention for thermal therapy  
Investigator in a sponsored research agreement between University Health Network and Bard regarding thermal therapy invention. |
| Sriharsha Athreya | Member    | None declared                                                                                                                                 |
| Mark Baerlocher | Member    | Temporary consultant to Cook Inc to help with documents related to PICC lines                                                                                                                                         |
| Robert Beecroft | Member    | Course director of master class in Interventional Oncology at Toronto General Hospital. Honorarium of $3000 sponsored by Covidien  
Spoke at industry sponsored symposium at CIRA (May 2013) -- Sponsored by Covidien ($400 Honorarium) |
<p>| Elizabeth David | Member    | Principle Investigator on Philips HIFU trial for fibroids                                                                                                                                                           |
| Darren Knibutat | Member    | None declared                                                                                                                                          |
| George Markose  | Member    | None declared                                                                                                                                          |
| Alex Menard     | Member    | Unlikely to experience increase in salary greater than $5000/year if Focal Tumour Ablation program were further developed. Volumes would need to increase 10 fold |
| Mehran Midia    | Member    | None declared                                                                                                                                          |</p>
<table>
<thead>
<tr>
<th>Members</th>
<th>Role</th>
<th>Conflict of Interest</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amol Mujoomdar</strong></td>
<td>Member</td>
<td>Speaker honorarium received from Covidien and Cook Medical</td>
</tr>
<tr>
<td><strong>Wael Shabana</strong></td>
<td>Member</td>
<td>Will be attendee for Ablation Master Class at Toronto General Hospital Advanced Imaging and Education - sponsored by Covidien Company</td>
</tr>
<tr>
<td><strong>Laura Dawson</strong></td>
<td>Member</td>
<td>Bayer Clinical Trials - paid to Institution</td>
</tr>
<tr>
<td></td>
<td></td>
<td>In 2005, published editorial/commentary regarding objects of study</td>
</tr>
<tr>
<td><strong>Richard Malthaner</strong></td>
<td>Member</td>
<td>None declared</td>
</tr>
<tr>
<td><strong>Guillaume Martel</strong></td>
<td>Member</td>
<td>Part of Fellowship conference travel stipend in 2013 was covered by a bursary from Covidien (&lt;$5000)</td>
</tr>
<tr>
<td><strong>Catherine Wang</strong></td>
<td>Member</td>
<td>Managerial responsibility on unrestricted research/education grants from Bard, Medtronic, Covidien, Gore, Boston Scientific, Sorin Medical</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Managerial responsibility on research studies funded by: Cook, Medtronic, Biotronic, Terumo, Gore</td>
</tr>
<tr>
<td><strong>Ania Kielar</strong></td>
<td>Member</td>
<td>GE CHAR grant for MRI post RFA investigation</td>
</tr>
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<td><strong>Calvin Law</strong></td>
<td>Member</td>
<td>None declared</td>
</tr>
<tr>
<td><strong>David Gast</strong></td>
<td>Patient Family Advisor</td>
<td>None declared</td>
</tr>
<tr>
<td><strong>Brigitta Bokkers</strong></td>
<td>Patient Family Advisor</td>
<td>None declared</td>
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REFERENCES


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