Cancer Care Ontario
Action Cancer Ontario

Focal Tumour Ablation in Ontario:
Recommendations Report 2015

Focal Tumour Ablation Advisory Committee

Ontario
Cancer Care Ontario
Action Cancer Ontario

Table of Contents

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:*
  - *For primary liver cancer, "very early stage" or "early stage" disease, according to the Barcelona Clinic Liver Cancer (BCLC) classification, and*
  - *Where the patient is not a surgical candidate, and*
  - *The size of the tumour is up to and including four centimetres, and*
  - *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:*
  - *Unresectable metastases, and*
  - *The size of the tumour is up to an including four centimetres, and*
  - *The maximum number of tumours is three per presentation, and*
  - *No evidence of vascular invasion or unresectable extrahepatic spread.*
  - *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:*
  - *Biopsy proven stage T1a N0 M0 RCC, in whom surgery or active surveillance is not recommended, and*
  - *The size of the tumour is up to and including four centimetres, and*
  - *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:*
  - *Early-stage primary lung cancers, or*
  - *Metastases, where surgery is contraindicated, and*
  - *Unresectable tumour, and*
  - *The size of the tumour is up to and including four centimetres, and*
  - *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:*
  - *Diagnosed "intermediate" stage HCC, using BCLC classification, and*
  - *Unresectable/untransplantable HCC, and*
  - *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
- *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.

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.[a]

> *"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

[a]Naugler WE, Sonnenberg A. *Survival and Cost-Effectiveness Analysis of Competing Strategies in the Management of Small Hepatocellular Carcinoma*. Liver Transplantation 16:1186-1194. 2010.

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

[a] Naugler WE, Sonnenberg A. *Survival and Cost-Effectiveness Analysis of Competing Strategies in the Management of Small Hepatocellular Carcinoma*. Liver Transplantation 16:1186-1194. 2010.

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.

"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.

(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

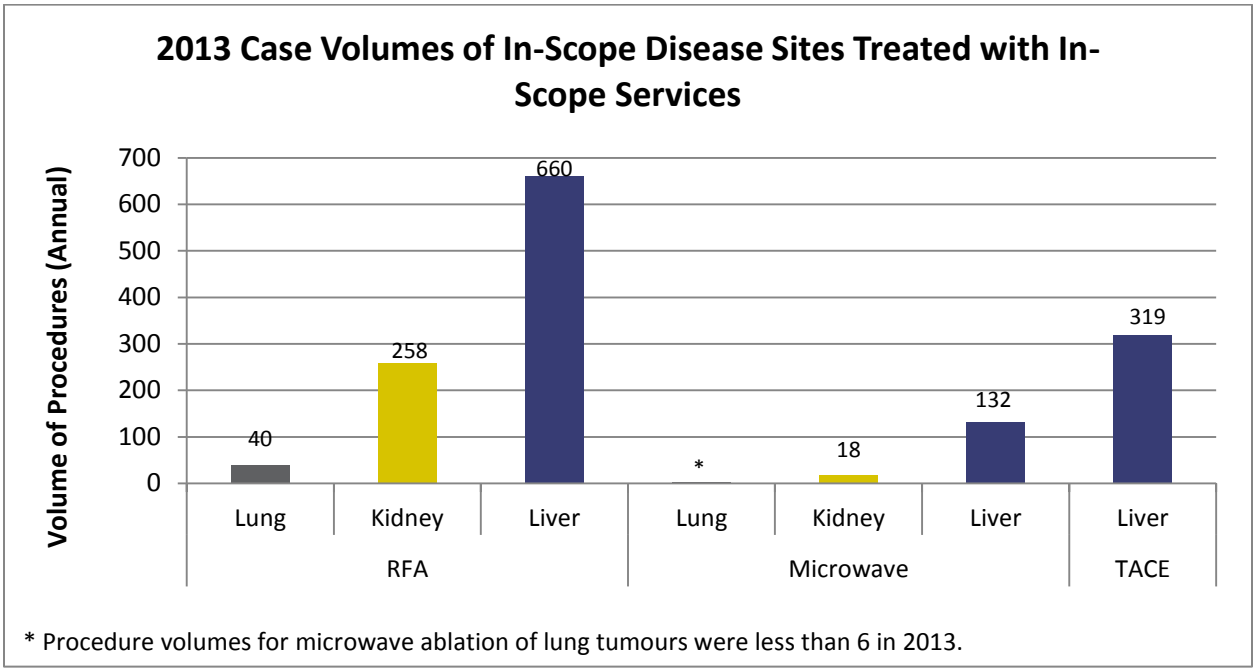
Focal Tumour Ablation Care Path
(Radiofrequency Ablation and Transcatheter Arterial Chemoembolization)

Components of Care Path	Prior to day of Procedure	Pre-Procedure	Procedure	Post-Procedure Monitoring	Post-procedure Follow-Up
	• Consultation(s), blood work and imaging • Decision to Treat made at Multidisciplinary Cancer Conference (MCC) • Scheduling and patient instructions	• Patient arrives at Hospital and registers • Clinical assessment of patient (nursing assessment and consent) • Preparation of patient for procedure (change into gown and IV) **For TACE:** • Chemotherapeutic medication is prescribed and prepared by pharmacy • Patient admission, where clinically appropriate	• Patient safety checklist and safety pause • Conscious/IV sedation administered • Perform focal tumour ablation procedure with intermittent or continuous imaging throughout procedure	• Clinical assessment and observation • Patient discharged **For TACE:** • Patient admission, where clinically appropriate	• Patient follow-up, including appropriate imaging

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)

Figure 2: Clinical case volumes by treatment type for different tumours in 2013



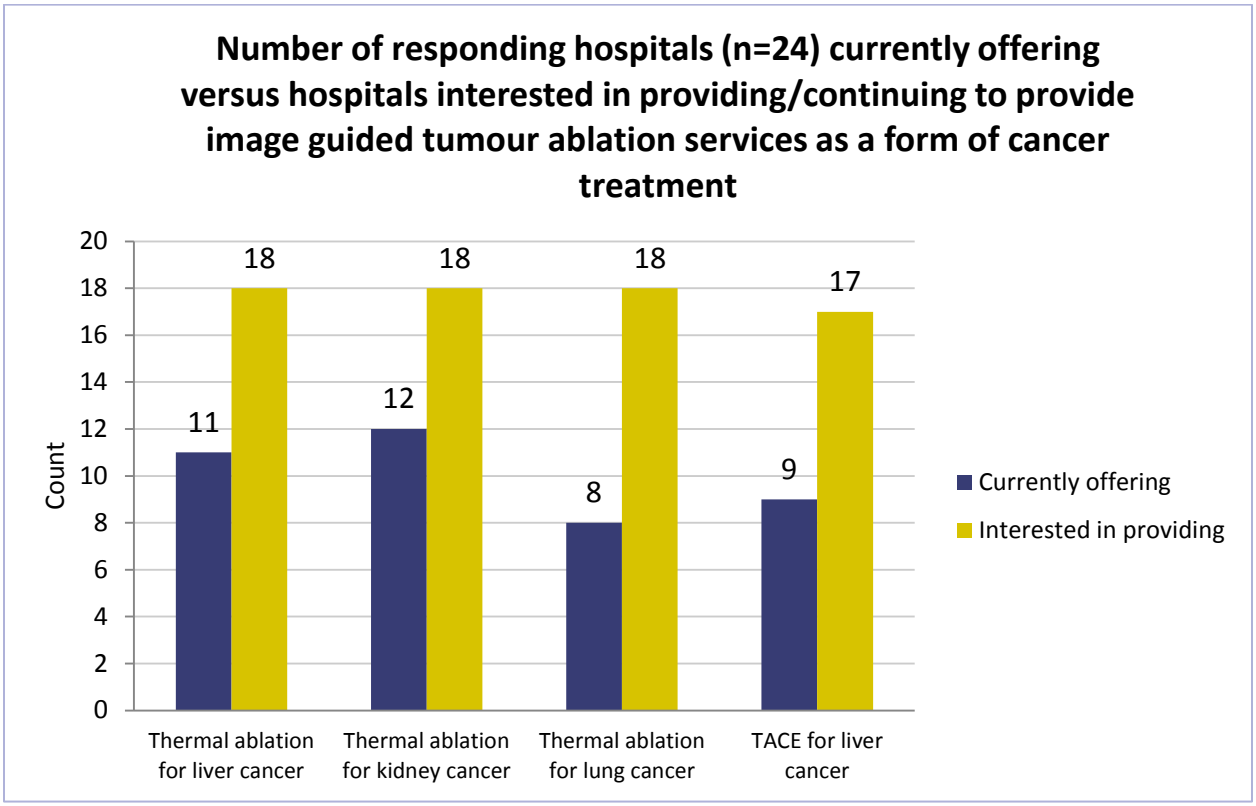
* Procedure volumes for microwave ablation of lung tumours were less than 6 in 2013.

Report Date: January 2014
Data Source: 2014 Current State Survey for RFA/TACE in Ontario
Prepared by: Cancer Care Ontario, Clinical Programs

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.

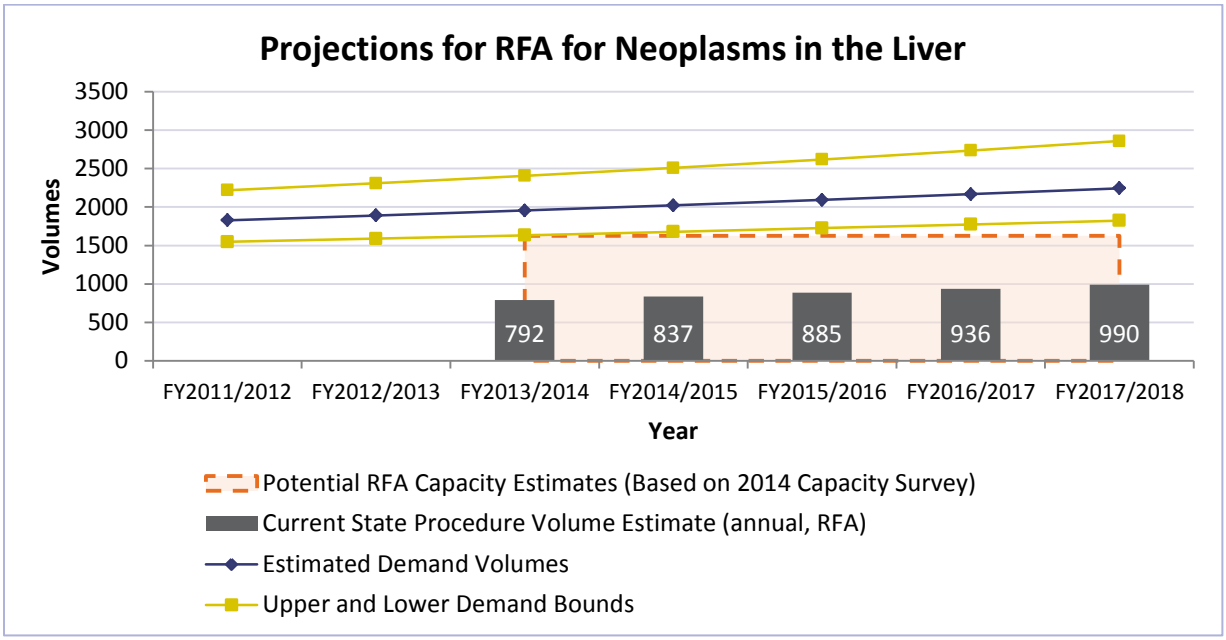
Figure 3: Hospitals providing focal tumour ablation services



Report Date: January 2014
Data Source: 2014 Current State Survey for RFA/TACE in Ontario
Prepared by: Cancer Care Ontario, Clinical Programs

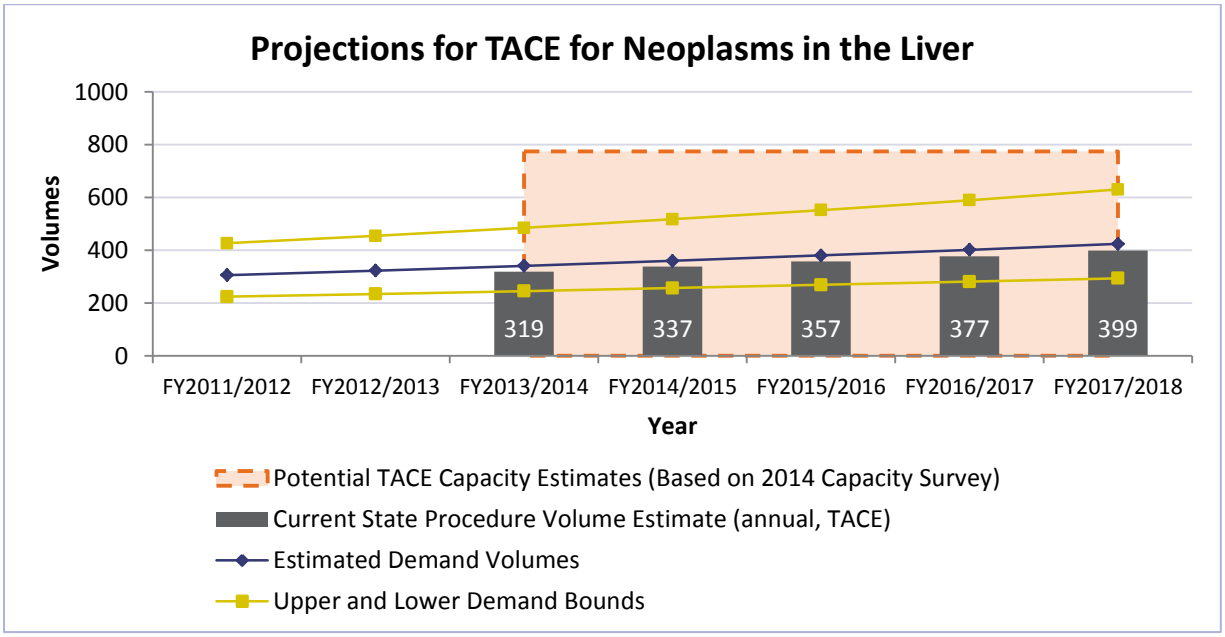
A survey of cancer programs in Ontario revealed that although many physicians are trained and ready to provide this care, they do not have the support within the system to do so. A System Capacity Survey of Ontario hospitals and cancer centres was conducted in April 2014 to examine availability of infrastructure 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



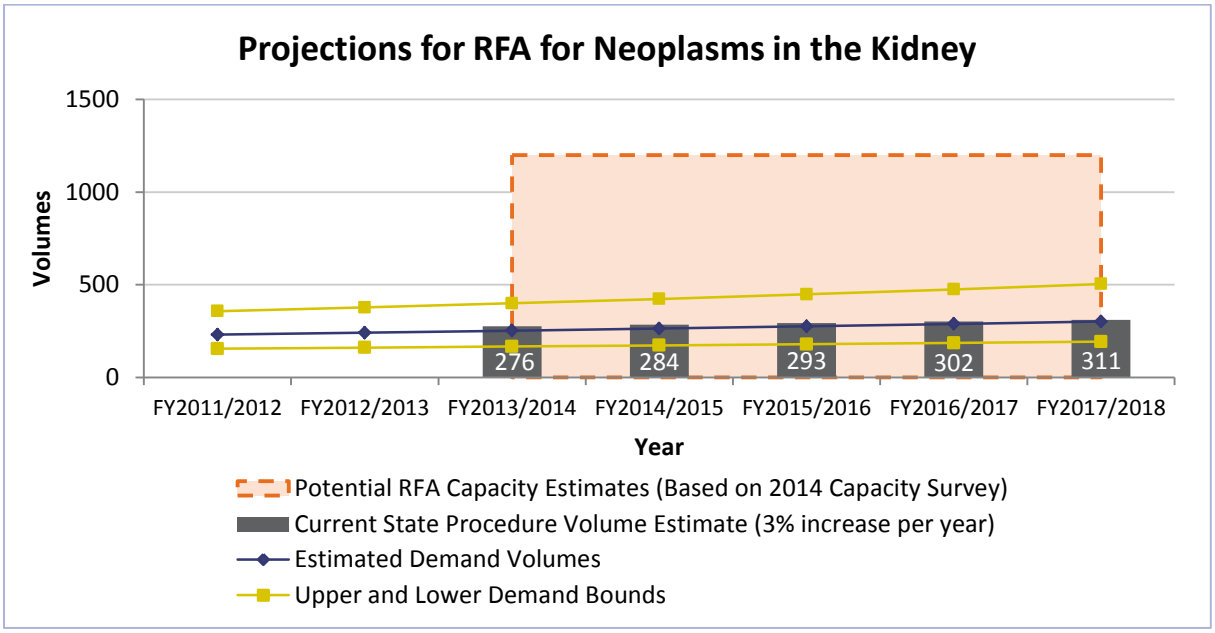
Report Date: February 2014
Data Source: Ontario Cancer Registry and the 2014 Current State Survey for RFA/TACE in Ontario
Prepared by: Cancer Care Ontario, Surveillance Unit and Planning and Regional Program

Figure 5: Projected Demand and Capacity for TACE for Liver



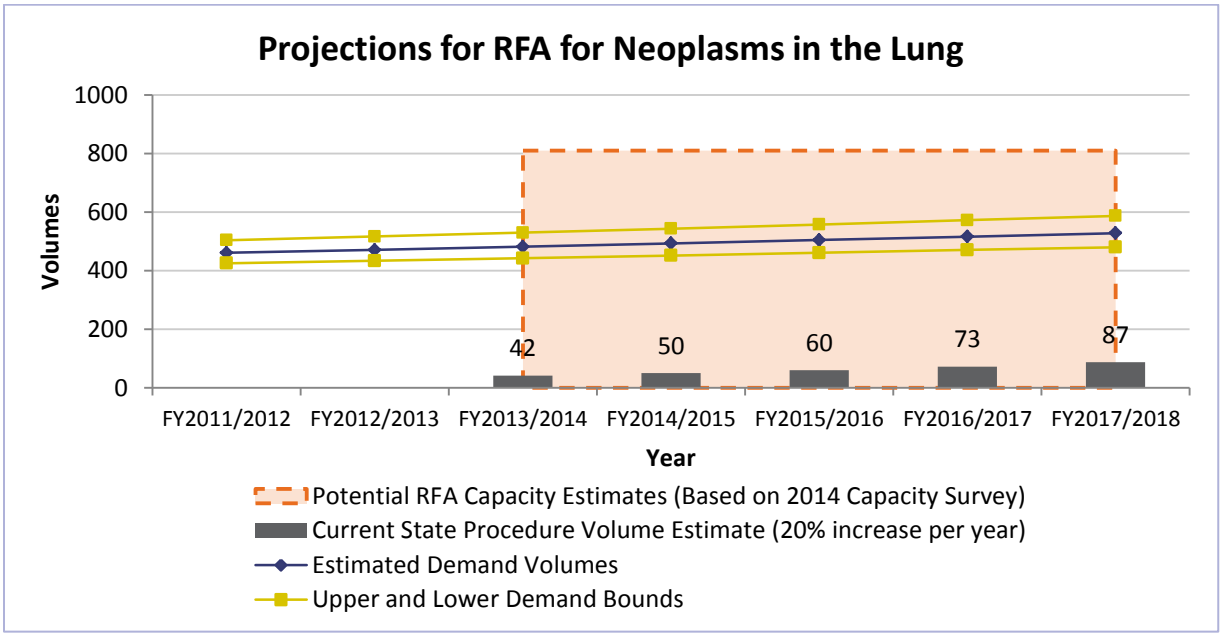
Report Date: February 2014
Data Source: Ontario Cancer Registry and the 2014 Current State Survey for RFA/TACE in Ontario
Prepared by: Cancer Care Ontario, Surveillance Unit and Planning and Regional Programs

Figure 6: Projected Demand and Capacity for RFA for Kidney



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



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:***
  - *For primary liver cancer, "very early stage" or "early stage" disease, according to the Barcelona Clinic Liver Cancer (BCLC) classification, and*
  - *Where the patient is not a surgical candidate, and*
  - *The size of the tumour is up to and including four centimetres, and*
  - *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:***
  - *Unresectable metastases, and*
  - *The size of the tumour is up to and including four centimetres, and*
  - *The maximum number of tumours is three per presentation, and*
  - *No evidence of vascular invasion or unresectable extrahepatic spread.*
  - *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:***
  - *Biopsy proven stage T1a N0 M0 RCC, in whom surgery or active surveillance is not recommended, and*
  - *The size of the tumour is up to and including four centimetres, and*
  - *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:***
  - *Early-stage primary lung cancers, or*
  - *Metastases, where surgery is contraindicated, and*
  - *Unresectable tumour, and*
  - *The size of the tumour is up to and including four centimetres , and*
  - *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:***
  - *Diagnosed "intermediate" stage HCC, using BCLC classification, and*
  - *Unresectable/untransplantable HCC, and*
  - *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.

* 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

Terms	Definition
ablation	The process of removing or destroying part of a biological tissue, while preserving as much of the surrounding tissue as possible.
active surveillance	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.
ambulatory services	Medical care provided on an outpatient basis, including diagnosis, observation, treatment and rehabilitation services.
Barcelona Clinic Liver Cancer (BCLC) Staging System	System used by clinicians and researchers to stage and guide the treatment of hepatocellular carcinoma (HCC).
biopsy	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.
chemoembolization	A procedure to reduce or block the main blood supply to a tumour and deliver chemotherapy drugs directly to the tumour.
chemotherapy	The use of anti-cancer cytotoxic drugs to destroy cancer cells.
co-morbidity	When two or more disorders or illnesses occur in the same person, simultaneously or sequentially.
computed tomography (CT)	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.
contraindicated	The suggestion or indication that a particular drug or other treatment should not be used in the case in question.
contrast-enhanced	Method of enhancing an image to make it easier to see a structure (e.g., tumour, blood vessels).
cryoablation	Procedure that uses extremely cold or freezing temperatures to destroy abnormal cells or tissue.
cytotoxic	Toxic to living cells.
destruction	The act or process of damaging a tissue or tumour so that it no longer exists or cannot be repaired.

drug-eluting beads	Beads that have been impregnated (infused) with a chemotherapy agent. The drug eluting beads are given via catheter directly to the tumour.
eradication	To remove a tumour completely.
extrahepatic spread	Spread of cancer beyond the liver.
hepatic resection	Surgical removal of part of the liver.
hepatic reserve	Portion of functional liver that has not been affected by tumour or disease.
hepatocellular carcinoma (HCC)	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).
Hepato-Pancreatic Biliary (HPB) Centres	Designated centres (hospitals) in Ontario that meet certain safety and quality standards for the delivery of HPB cancer treatment.
intervention	The act or method of interfering with the outcome or course of a condition (as to prevent harm or improve function).
central venous route	Use of a central vein, for example for the administration of medications.
jurisdictional	Proceedings within a defined area.
metastases	Spread of cancer from its primary site to other locations in the body.
microwave ablation	Ablation by use of microwaves to produce heat.
modality	The way in which something is done.
multidisciplinary care team	A group of health care workers who are members of different disciplines, each providing specific services to a patient.
nodule	A small mass of rounded or irregular shape, such as a tumourous growth.
percutaneously	Through the skin and musculature directly in to the targeted tissue (e.g., a liver tumour).
perioperative mortality	Death related to a surgical procedure.
peripheral venous route	Use of a peripheral vein, for example for the administration of medications.
radiofrequency ablation (RFA)	Ablation by use of high frequency alternating electrical current to produce heat.
radiofrequency energy	High-frequency electrical current that creates heat.
renal cell carcinoma (RCC)	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.
surgical resection	Surgical removal of part of an organ or structure.

thermal ablation	Ablation by use of extreme temperatures (either cold or hot).
transcatheter	The delivery of treatment via insertion and navigation of a catheter within blood vessels.
transcatheter arterial chemoembolization (TACE)	Chemoembolization delivered through the insertion of a catheter into a blood vessel.
tumour burden	The total mass of tumour tissue carried by a patient with cancer.
ultrasound	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.
vascular invasion	Growth of a tumour into the veins or arteries.

Appendix B: Advisory Committee Membership List

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

21	**Ms. Fulvia Baldassarre** Health Research Methodologist, Program in Evidence-Based Care, Cancer Care Ontario
22	**Dr. Peter Bevan** Interim Manager, Cancer Imaging Program, Clinical Programs, Cancer Care Ontario
23	**Ms. Irene Blais** Director, Funding Unit, Planning and Regional Programs, Cancer Care Ontario
24	**Ms. Victoria Hagens** Manger, Regional Programs and Performance Management, Planning and Regional Programs, Cancer Care Ontario
25	**Ms. Sherrie Hertz** Program Manager, Specialized Services Oversight, Clinical Programs, Cancer Care Ontario
26	**Mr. Phil Holm** Manager, Contract Management, Planning and Regional Programs, Cancer Care Ontario
27	**Ms. Cassandra Howse** Policy Research Analyst, Specialized Services Oversight, Clinical Programs, Cancer Care Ontario
28	**Ms. Asmaa Maloul** Team Lead, Chief Information Office, Cancer Care Ontario
29	**Dr. Sheila McNair** Assistant Director, Program in Evidence-Based Care, Cancer Care Ontario
30	**Ms. Elaine Meertens** Director, Cancer Planning and Regional Program Development, Planning and Regional Programs, Cancer Care Ontario
31	**Mr. Saul Melamed** Director, Diagnosis and Treatment, Clinical Programs, Cancer Care Ontario
32	**Ms. Huma Tariq** Methodologist, Chief Information Office, Cancer Care Ontario
33	**Mr. Jonathan Wang** Senior Analyst, Capacity Planning, Planning and Regional Programs, Cancer Care Ontario

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.

Service	Availability?	Disease Location	Treatment of this location?	If yes, approximately how many are cases are treated/month? (e.g. 5, 10, 20)
Radiofrequency Ablation (RFA)	○ YES ○ NO	Liver	○ YES ○ NO	
		Kidney	○ YES ○ NO	
		Lung	○ YES ○ NO	
		Breast	○ YES ○ NO	
		Prostate	○ YES ○ NO	
		Other – Specify: _____	○ YES ○ NO	
Microwave Ablation	○ YES ○ NO	Liver	○ YES ○ NO	
		Kidney	○ YES ○ NO	
		Lung	○ YES ○ NO	
		Breast	○ YES ○ NO	
		Prostate	○ YES ○ NO	
		Other – Specify: _____	○ YES ○ NO	

High Intensity Focused Ultrasound	○ YES ○ NO	Uterus	○ YES ○ NO	
		Prostate	○ YES ○ NO	
		Other – Specify: _____	○ YES ○ NO	
Laser Ablation	○ YES ○ NO	Uterus	○ YES ○ NO	
		Prostate	○ YES ○ NO	
		Other – Specify: _____	○ YES ○ NO	
Bland Embolization	○ YES ○ NO	Liver	○ YES ○ NO	
		Other – Specify: _____	○ YES ○ NO	
Radioembolization (Y-90)	○ YES ○ NO	Other – Specify: _____	○ YES ○ NO	
Thermal Balloon Ablation	○ YES ○ NO	Liver	○ YES ○ NO	
		Kidney	○ YES ○ NO	
		Lung	○ YES ○ NO	
		Prostate	○ YES ○ NO	
		Other – Specify: _____	○ YES ○ NO	
Cryoablation	○ YES ○ NO	Liver	○ YES ○ NO	
		Kidney	○ YES ○ NO	
		Lung	○ YES ○ NO	

		Prostate	○ YES ○ NO	
		Other – Specify: _____	○ YES ○ NO	
Chemical Ablation Techniques (including TACE)	○ YES ○ NO	Liver	○ YES ○ NO	
		Other – Specify: _____	○ YES ○ NO	
Irreversible Electroporation (IRE)	○ YES ○ NO	Liver	○ YES ○ NO	
		Kidney	○ YES ○ NO	
		Lung	○ YES ○ NO	
		Breast	○ YES ○ NO	
		Prostate	○ YES ○ NO	
		Other – Specify: _____	○ 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.

Other Focal Ablation Service	Treatment Location	Number of Patients Treated Monthly

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

1	Alberta Health Services. Clinical Practice Guidelines GU-003. Renal Cell Carcinoma; 2012 [cited 2014 Jun 30]. Available from: http://www.albertahealthservices.ca/hp/if-hp-cancer-guide-gu003-renal-cell.pdf
2	American Urological Association. Guideline for Management of the Clinical Stage 1 Renal Mass; 2009 [cited 2014 Jun 30]. Available from: https://www.auanet.org/common/pdf/education/clinical-guidance/Renal-Mass.pdf
3	American Urological Association. Follow-up for clinically localized renal neoplasms: AUA guideline; 2013 [cited 2014 Jun 30]. Available from: https://www.auanet.org/education/guidelines/renal-cancer-follow-up.cfm
4	Australian Safety and Efficacy Register of New Interventional Procedures-Surgical. Microwave ablation for Hepatic tumours; 2013 [cited 2014 Jun 30]. Available from: http://www.health.qld.gov.au/healthpact/docs/updates/WP163_update.pdf
5	Basile A, Carragiello G, Ierardi AM, Tsetis D, Brountzos E. Quality improvement guidelines for hepatic transarterial chemoembolization. *Cardiovascular and Interventional Radiology*. 2012; 35(4):765-774.
6	Brown DB, Cardella JF, Sacks D, Goldberg SN, Gervais DA, Rajan D et al. Quality Improvement guidelines for transhepatic arterial chemoembolization, embolization, and chemotherapeutic infusion for hepatic malignancy. *Journal of Vascular and Interventional Radiology*. 2006; 17(2):225-232.
7	Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. *Journal of Hepatology.* 2011; 53(3):1020-1022.
8	Choi JY. Treatment algorithm for intermediate and advanced stage hepatocellular carcinoma: Korea. *Oncology.* 2011; 81(1):141-147.
9	Crocetti L, de Baere T, Lencioni R. Quality improvement guidelines for radiofrequency ablation of liver tumours. *Cardiovascular and Interventional Radiology*. 2010; 33(1):11-17.
10	European Association for the Study of the Liver. Clinical Practice Guidelines: Management of hepatocellular carcinoma. *Journal of Hepatoloy*. 2012; 56(4):908-943.
11	Gervais DA, Goldberg SN, Brown DB, Soulen MC, Millward SF, Rajan DK. Society of Interventional Radiology position statement on percutaneous radiofrequency ablation for the treatment of liver tumors. *Journal of Vascular and Interventional Radiology*. 2009; 20(7):3-8.
12	Gewanter RM, Rosenzweig KE, Chang JY, Decker R, Dubey S, Kong F et al. ACR Appropriateness Criteria® Nonsurgical Treatment for Non-Small-Cell Lung Cancer: Good Performance Status/Definitive Intent. *Current Problems in Cancer.* 2010; 34(3):228-249.
13	Howington JA, Blum MG, Chang AC, Balekian AA, Murthy CC. Treatment of stage I and II non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence based-clinical practice guidelines. *Chest*. 2013; 143(5):e278S-313S.
14	Jewett MAS, Finelli A, Willacy, J. Management of Kidney Cancer: Canadian Kidney Cancer Forum Consensus Update 2011. *Canadian Urological Association Journal*. 2012; 6(1):16-22.
15	Kouri BE, Funaki BS, Ray CE Jr, Abou-Alfa G, Burke CT, Darcy MD et al. ACR Appropriateness Criteria® radiologic management of hepatic malignancy. *Journal of the American College of Radiology.* 2012; 9(12): 919-925.
16	Ljungberg B, Bensalah K, Bex A, Canfield S, Dabestani S, Hofmann F et al. European Association of Urology. Guidelines on renal cell carcinoma; 2013 [cited 2014 Jun 30]. Available from: http://www.uroweb.org/gls/pdf/10_Renal_Cell_Carcinoma_LR.pdf

17	Ljungberg B, Cowan NC, Hanbury DC, Hora M, Kuczyk MA, Merseburger AS et al. European Association of Urology Guideline Group. EAU Guidelines on Renal Cell Carcinoma: the 2010 update. *European Urology.* 2010; 58(3):398-406.
18	National Institute for Health and Care Excellence. Radiofrequency ablation of hepatocellular carcinoma; 2003 [cited 2014 Jun 30]. Available from: http://www.nice.org.uk/guidance/IPG2
19	National Institute for Health and Care Excellence. Interventional Procedure overview of microwave ablation for primary hepatocellular cancer; 2006 [cited 2014 Jun 30].Available from: http://www.nice.org.uk/guidance/ipg214/resources/microwave-ablation-of-hepatocellular-carcinoma-overview2
20	National Institute for Health and Care Excellence. Microwave ablation of hepatocellular carcinoma; 2007 [cited 2014 Jun 30]. Available from http://www.nice.org.uk/Guidance/IPG214
21	National Institute for Health and Care Excellence. Radiofrequency-assisted liver resection; 2007 [cited 2014 Jun 30]. Available from: http://www.nice.org.uk/guidance/ipg211
22	National Institute for Health and Care Excellence. Radiofrequency ablation for colorectal liver metastases; 2009 [cited 2014 Jun 30]. Available from: http://www.nice.org.uk/guidance/IPG327
23	National Institute for Health and Care Excellence. Percutaneous radiofrequency ablation for primary or secondary lung cancers; 2010 [cited 2014 Jun 30]. Available from: http://www.nice.org.uk/guidance/IPG372
24	National Institute for Health and Care Excellence. Precutaneous radiofrequency ablation for renal cancer; 2010 [cited 2014 Jun 30]. Available from: http://www.nice.org.uk/guidance/IPG353
25	National Institute for Health and Care Excellence. Microwave ablation for the treatment of liver metastases; 2011 [cited 2014 Jun 30]. Available from: http://www.nice.org.uk/guidance/IPG4066
26	National Institute for Health and Care Excellence. Colorectal cancer: the diagnosis and management of colorectal cancer; 2011 [cited 2014 Jun 30]. Available from: http://www.nice.org.uk/guidance/CG131
27	National Institute for Health and Care Excellence. Microwave ablation for treating primary lung cancer and metastases in the lung; 2013 [cited 2014 Jun 30]. Available from: http://www.nice.org.uk/guidance/IPG469
28	Ontario Health Technology Advisory Committee. Advancing Health - Evidence-based advice on health technology; 2009 [cited 2014 Jun 30]. Available from: http://www.health.gov.on.ca/english/providers/program/ohtac/pdf/progress/2009/full_report_2009_en.pdf
29	Pereira PL. Standards of Practice: Guidelines for Thermal Ablation of Primary and Secondary Lung Tumors. *Cardiovascular and Interventional Radiology*, 2012;35:247-254
30	Scottish Intercollegiate Guidelines Network (SIGN). Diagnosis and management of colorectal cancer. Edinburgh: SIGN; 2011. (SIGN publication no. 126). December 2011 [cited 2014 June 30]. Available from URL: http://www.sign.ac.uk

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:

Baldassarre FG, Baerlocher M, Beecroft R, Dawson L. Focal Tumour ablation: thermal ablation of hepatocellular carcinoma and metastases from colorectal carcinoma: evidence summary [Internet]. Cancer Care Ontario; 2014 Jul [cited 2014 Jul 28]. Available from: https://www.cancercare.on.ca/.

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.

- Examined thermal ablation used intraoperatively.
- Examined 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.

	Author, date, funding source	Search cut-off date	# of studies included	Review objectives/Design	Study designs included	Population	Intervention/ comparison(s)	Outcomes	Summary results
1	Wang, 2014 (6) Funding: National Technology Support Program (China)	Nov 2012	28: 3 RCTs and 25 non-RCTs	To evaluate the efficacy and safety of RFA versus hepatic resection for early HCC meeting the Milan criteria Meta-analysis (separately of RCTs and non-RCTs)	RCTs, non-RCTs, retrospective clinical, or cohort studies	N = 11,873 meeting the Milan criteria[a]	RFA vs. SR	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)	**Meta-analysis of RCTs** **OS**: at 1 and 3 y: p = NS; **RFS**: at 1 and 3 y: NS; RFA was lower than SR at 5 y (RR 0.56, 95% CI: 0.40-0.78, NNH= 4.4). **DFS**: 1 RCT: p =NS **Meta-analysis of non-RCTs** **OS**: at 1 and , 2 and 5 y: RFA significantly lower than SR at 1, 3 and 5 y (OR 0.78, 95% CI: 0.63–0.97, OR 0.67, 95% CI: 0.52–0.85, ; and OR 0.58, 95% CI: 0.36–0.94, respectively). **RFS:** at 1, 3 and 5 y RFA lower than SR (OR 0.78, 95% CI: 0.64–0.95, OR 0.67, 95% CI: 0.56–0.79, and OR 0.63 95% CI: 0.40–1.00 respectively). **DFS**: at 1, 3, and 5 y RFA significantly lower than SR (OR 0.46, 95% CI: 0.38–0.55, OR 0.49, 95% CI: 0.34–0.69, and OR 0.52, 95% CI: 0.32–0.84, respectively).
2	Weiss, 2013 (7) Cochrane review	Sept 2012	11 RCTs	To assess the beneficial and harmful effects of RFA versus placebo, no intervention, or any other therapeutic approach in patients with HCC. Meta-analysis (RCTs only)	RCTs	N = 578 pts with HCC without contraindications for RFA (e.g., too many or too large tumours)	RFA vs SR RFA vs PEI RFA vs MA RFA vs LA	OS EFS (recurrence and death) Local recurrence AE (Time intervals NR)	<u>RFA vs SR (3 trials):</u> **OS** NS (random effects model) (HR 0.71; 95% CI 0.44 to 1.15); favoured SR (fixed effect model) (HR 0.76; 95%CI 0.58-1.00). <u>RFA vs PEI (6 trials):</u> **OS** favours RFA (HR 1.64; 95% CI 1.31 to 2.07) **EFS** favours RFA (HR 1.55; 95% CI 1.31-1.85)

	Author, date, funding source	Search cut-off date	# of studies included	Review objectives/Design	Study designs included	Population	Intervention/ comparison(s)	Outcomes	Summary results
									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). <u>RFA vs. MA (1 trial):</u> **AE** for all comparisons: p = NS
3	Belinson, 2013 (8) **Funding:** Agency for Healthcare Research and Quality (USA)	Jul 2012	48: 6 RCTs, 4 non-RCTs, 35 case series, and 3 case reports	To examine the comparative effectiveness of local interventions for HCC Systematic review and meta-analysis (only RCTS)	3 RCTs, 1 non-RCT, 6 case series and 1 case report.	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	RFA vs. PEI/PAI (3 trials) RFA vs. TACE	OS Progression Length of stay AE	<u>RFA vs PEI/PAI</u> **OS** at 3 y: RFA superior to PEI (p=0.031) **TTP** and local recurrence: RFA superior to PEI (high risk of bias) **Length of stay**: shorter with PEI than RFA <u>RFA vs. TACE</u> No RCTs for this comparison available OS at 2 y: RFA: 72% vs. TACE: 58%, p = NS
4	Qi, 2013 (9)	Dec 2012	3 RCTs	To test the efficacy of RFA compared with SR	RCTs	N = 559 with HCC who met the Milan	RFA vs SR	OS RFS	**OS**: SR superior to RFA (p=0.02) **RFS**: SR superior to RFA (p=0.001)

	Author, date, funding source	Search cut-off date	# of studies included	Review objectives/Design	Study designs included	Population	Intervention/ comparison(s)	Outcomes	Summary results
	Funding: ND			Meta-analysis		criteria[a]		Complications Hospital length of stay	**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<0.00001)
5	Duan, 2013 (10) **Funding**: National Science Foundation of China	Jun 2013	12: 2 RCTs and 10 non-RCTs	To compare the effectiveness of RFA with SR Meta-analysis	All	N = 8,612 with early stage HCC	RFA vs SR	OS (at 1, 3, and 5 y) DFS (1, 3 and 5 y) Complications Length of hospital stay	**OS** at 3 and 5 y: RFA shorter than SR
6	Cucchetti, 2013 (11) **Funding:** Siemens, Esaote, Bayer	Dec 2012	19: 3 RCTs and 16 retrospective observational studies	To examine the available literature directly comparing surgical resection with RFA Systematic review	All	N = 12,703 with HCC	RFA vs SR	OS Complications	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)
7	Shen, 2013 (12) **Funding:** National Natural Science Foundation of China and Chongqing Natural Science Foundation of China	Mar 2012	4 RCTs	To perform a systematic review and meta-analysis of RCTs to compare RFA with PEI Meta-analysis	RCTs	N = 766 with HCC <3 centimetres	RFA vs. PEI	OS Complete tumour necrosis Recurrence Metastases Complications Cost Hospital stay	**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
8	Xu, 2012 (13)	Dec 2011	13: 2 RCTs and 11 non-RCTs	To perform a meta-analysis of SR vs RFA	All comparative	N = 2,535 with HCC	RFA vs SR	OS Recurrence	**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,

	Author, date, funding source	Search cut-off date	# of studies included	Review objectives/Design	Study designs included	Population	Intervention/ comparison(s)	Outcomes	Summary results
	Funding: ND			Meta-analysis (together RCTs and non-RCTs)					0.60 95% CI, 0.43 to 0.84.) **Recurrence**: SR better at 1, 3, and 5 y (respectively: OR, 1.48, 95% CI, 1.05 to 2.08; OR, 1.76, 95% CI, 1.49 to 2.08; OR, 1.68, 95% CI, 1.21 to 2.34)
9	Li, 2012 (14) **Funding:** ND	Mar 2011	6: 2 RCTs and 4 non-RCTs	To retrospectively evaluate the long term effects of RFA and SR Meta-analysis (RCTs and non-RCTs together)	All comparative	N = 877 with HCC	RFA vs SR	OS RFS Local recurrence	**OS**: SR better at 1, 3, and 5 y (respectively: OR: 0.50, 95% CI: 0.29–0.86; OR: 0.51, 95% CI: 0.28–0.94; OR: 0.62, 95% CI: 0.45–0.84). For tumours ≥3 centimetres SR better than RFA for the 3-y OS (OR: 0.38, 95% CI: 0.16–0.89) **RFS**: SR better at 1, 3, and 5 y (respectively: OR: 0.65, 95% CI: 0.44–0.97; OR: 0.65, 95% CI: 0.47–0.89; OR: 0.52, 95% CI: 0.35–0.77) **Local recurrence**: RFA had higher rate of local recurrence (OR: 4.08, 95% CI: 2.03–8.20)
10	Tiong, 2011 (15) **Funding:** University of Adelaide, Discipline of Surgery (Australia)	Nov 2010	43: 12 RCTs, and 31 non-RCTs	To test the effect of RFA Meta-analysis (only RCTs)	RCTs, quasi-RCT, and non-RCTs	N = 1,558 with resectable and unresectable HCC	RFA vs. SR, chemotherapy, other ablative treatments (e.g., PEI, microwave coagulation, LITT)	OS (at 1,3 and 5 y) Disease recurrence	RFA vs SR **OS**: inside the Milan criteria: NS; outside the Milan criteria: SR was better (limited to pts with Child-Pugh grade A cirrhosis and a single HCC >3 centimetres) RFA vs PEI: **OS:** RFA better than PEI at 1 y: risk ratio: 0·62 (95% CI 0.41-0.94); and 3 y: risk ratio: 0·79 (95% CI 0.65-0.96)
11	Cho, 2011 (16) **Funding:** ND	Feb 2011	8: 2 RCTs and 6 retrospective analyses	To compare SR with RFA as a primary treatment for HCC. Systematic review	All comparative	N = 1,100 meeting the Milan criteria[a]	RFA vs. SR	OS Safety (perioperative mortality) Local recurrence	Cannot reach a conclusion from available evidence.
12	Salhab, 2011 (17) **Funding**: none	Dec 2010	17 of which 5 of percutaneous treatment and 4 included in meta-analysis	To identify survival benefit for medical modalities in HCC	RCTs	N = 628 with HCC (included in meta-analysis)	RFA vs. PEI	OS (at 1, 2 ,and 3 yrs) Cumulative probability of no recurrence	**OS** at 3 y RFA superior to PEI (p=0.002) **AE** NS

	Author, date, funding source	Search cut-off date	# of studies included	Review objectives/Design	Study designs included	Population	Intervention/ comparison(s)	Outcomes	Summary results
	declared			Meta-analysis (RCTs mixed with Observational)					
13	Xie, 2009, 2010 (18,19) **Funding**: McGill University	Jan 2009	6: 1 RCT and 5 comparative studies	To compare effectiveness and cost of RFA and SR for HCC Meta-analysis (mixed RCTs and observational)	RCTs, non-randomized comparative cohort studies, and cohort studies. (For cohort studies the min sample size was N = 50).	N = 1,014 with either primary HCC or CLM	RFA vs. SR RFA +TACE vs. RFA alone TACE vs. SR	OS DFS Recurrence AE Cost	<u>RFA vs SR:</u> **OS** NS **DFS** SR is superior to RFA **Recurrence**: Either comparable or SR is superior to RFA **AE** RFA has less complications than SR
14	Zhou, (20) **Funding:** ND	Nov 2009	10: 1 RCT and 9 non-RCTs	To test whether RFA is superior to SR Meta-analysis (mixed RCTs and observational)	RCTs and non-RCTs	N = 1411 Pts with a small HCC eligible for SR	RFA vs SR 2 of the studies included laparoscopic RFA and the others included percutaneous RFA	OS Recurrence DFS Safety	**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<0.001 favours SR **Local recurrence** (5 trials): OR: 4.50, 95% CI: 2.45-8.27 p<0.001 favours SR **Distant recurrence**: NS **DFS**: at 1, 2, 3, 5 y: significantly better for HR (p=0.006, p<0.001, p<0.001, p=0.05 respectively) **Morbidity**: OR: 0.29, 95% CI: 0.13-0.65 p= 0.003 favors RFA **Mortality**: p = NS

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.

[a] 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

	Author, date, Funding source,	Search cut-off date	# of studies included	Review objectives/ Design	Study designs included	Population	Intervention/ Comparison(s)	Outcomes	Summary Results
1	Loveman, 2014 (21) **Funding**: Health Technology Assessment Programme, UK	Sep 2011	16: 1 RCT of MA	To evaluate the clinical effectiveness and cost-effectiveness of the different ablative and minimally invasive therapies for treating liver metastases	RCTs, Prospective non-RCTs, Prospective case series (sample >100), Economic evaluations	N = 2,618 with liver metastases	RFA, MA cryoablation, PEI, LA, focused ultrasound, electrolytic ablation, TACE and radioembolization vs. SR, chemotherapy and BSC	Effectiveness and cost	Narrative synthesis: low quality evidence does not permit conclusions or pooling. <u>MA</u> **OS**: from RCT: p = NS **DFS**: p = NS Surgical invasiveness: in favor of MA (p=0.0027) **AE:** p = NS <u>RFA</u> **OS** from 1 non-RCT + 5 case series: contrasting results **Recurrence:** contrasting results **AE:** low
2	Bala, 2013 (22) Cochrane review (sub group of a larger review by Riemsma 2009)	Dec 2012	1	To examine the efficacy and adverse events of MW coagulation. Systematic review	RCTs Quasi-RCTs Other controlled studies	N = 30 with liver metastases regardless of the location of the primary tumour.	MA vs. SR	All-cause mortality Survival at 1, 3-y DFS AE QOL Cancer mortality Failure to clear liver metastases TTP Tumour response	Insufficient evidence to draw conclusions. Body of the evidence of moderate risk of bias **Mortality**: p = NS **DFS**: p = NS **AE:** p = NS

	Author, date, Funding source,	Search cut-off date	# of studies included	Review objectives/ Design	Study designs included	Population	Intervention/ Comparison(s)	Outcomes	Summary Results
3	Cirocchi, 2012 (23) Cochrane review	Jan 2, 2012	18: 1 RCT (abs), 7 CCTs, and 10 observational studies	To systematically review the role of RFA in the treatment of CLMs Systematic review	RCTs; Quasi-RCTs Observational designs	N = 2,709 with CLMs and pts with unresectable extrahepatic disease	RFA alone or in combination compared with any other intervention	OS at 2, 3, and 5 y PFS DFS at 1, 2, and 5 y Recurrence at 1, and 2 y Residual disease AE	Insufficient evidence to draw conclusions. Body of evidence at high risk of bias Data were not summarized. The only RCT showed that PFS was significantly higher for the group that received RFA.
4	Belinson, 2012 (24)	Jun 2012	30: 1 RCT, and 29 case series	To characterize the comparative effectiveness and harms of various local hepatic therapies for metastases to the liver from unresectable colorectal cancer (CRC) Systematic review	Comparative studies	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.	Ablation, embolization, and radiotherapy approaches.	OS QOL AE	Evidence insufficient to draw conclusions. No comparative study met the inclusion criteria.
5	Wu, 2011 (25) **Funding:** ND	2010 (month ND)	7 non-RCTs	To compare the efficacy of RFA with SR Meta-analysis	Comparative studies	N = 847 with solitary colorectal cancer liver metastasis	RFA vs SR	OS (at 5 y) Local intrahepatic recurrence DFS (at 5 y) Safety (morbidity and mortality)	Body of evidence of low quality **OS** at 5 yrs significantly longer for SR (p=0.008) **Local recurrence**: significantly lower for SR (p<0.003) **AE**: p = NS for mortality and morbidity

	Author, date, Funding source,	Search cut-off date	# of studies included	Review objectives/ Design	Study designs included	Population	Intervention/ Comparison(s)	Outcomes	Summary Results
6	Pathak, 2011 (26) **Funding:** No financial support	Jan 2010	75: 13 MA, 36 RFA, and 26 cryo	To systematically review the literature on ablative strategies. Systematic review	RCTs, case series	N = 4,248 with CLM	RFA, Cryoablation, and MA vs. palliative chemotherapy	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)	RFA: No difference in response between pts with extrahepatic disease and those with intrahepatic disease. In the only RCT included: **PFS** at 3 y: 27.6% RFA + chemo vs. 10.7% chemo alone **OS:** p = NS at 30 mo MA: **OS:** p = NS
7	NICE, 2009 (27) **Funding**: National Institute for Health Research, UK	Aug 2009	1 sys rev 2 non-RCTs, 3 case series, and 2 case reports	To produce an evidence base for recommendations Rapid review	1 systematic reviews, 2 non-RCTs, 3 case series,2 case reports	N = 1,570 with CLM	RFA alone or in combination with SR	Efficacy AE	Narrative synthesis Survival rate was higher with SR compared to RFA. No comparative data reported for AE.

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 = 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; yrs = years.

Table 2A. Quality assessment of included systematic reviews with AMSTAR - HCC

Study	An *a priori* design provided	Duplicate study selection and data extraction	Comprehensive literature search performed	Status of publication used as an inclusion criterion	List of studies (included and excluded) provided	Characteristics of included studies provided	Quality of included studies assessed and documented	Quality of included studies used appropriately in formulating conclusions	Methods used to combine the findings of studies appropriate	Likelihood of publication bias assessed	Conflict of interest included
Wang 2014 (6)	**Y**	**Y**	**Y**	N	**Y**[a]	**Y**	**Y**	N	N[b]	**Y**	**Y**
Weiss, 2013 (7)	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**
Belinson, 2013 (8)	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**
Qi, 2013 (9)	Can't determine	**Y**	**Y**	N	**Y**[a]	**Y**	**Y**	N	**Y**	N	N*
Duan, 2013 (10)	Can't determine	Can't determine	N (only MEDLINE)	N	**Y**[a]	**Y**	**Y**	N	N[b]	**Y**	N[c]
Cucchetti, 2013 (11)	Can't determine	N	**Y**	N	**Y**	**Y**	**Y**	N	**Y**	N	N*
Shen, 2013 (12)	Can't determine	N	**Y**	N	**Y**[a]	**Y**	**Y**	N	**Y**	**Y**	N*
Xu, 2012 (13)	Can't determine	N	**Y**	N	**Y**	**Y**	**Y**	**Y**	N[b]	**Y**	N
Li, 2012 (14)	N	N	**Y**	N	**Y**[a]	**Y**	**Y**	N	N[a]	**Y**	N[c]
Tiong, 2011 (15)	N	N	**Y**	N	**Y**	**Y**	**Y**	N	**Y**	N	N[c]
Cho, 2011 (16)	N	N	**Y**	N	**Y**	**Y**	N	N	**Y**	N	N[c]
Salhab, 2011 (17)	Can't tell	N	**Y**	N	**Y**	**Y**	N	N	N[b]	N	N
Xie, 2009, 2010 (18,19)	Can't tell	N	**Y**	N	**Y**	**Y**	N	N	N[b]	N	N
Zhou, (20)	N	N	N	N	**Y**	**Y**	**Y**	**Y**	N[b]	N	N

[a] Only included studies listed

[b] The authors combined observational & RCT studies in meta-analysis.

[c] 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

Study	An *a priori* design provided	Duplicate study selection and data extraction	Comprehen-sive literature search performed	Status of publication used as an inclusion criterion	List of studies (included and excluded) provided	Characteristics of included studies provided	Quality of included studies assessed and documented	Quality of included studies used appropriately in formulating conclusions	Methods used to combine the findings of studies appropriate	Likelihood of publication bias assessed	Conflict of interest included
Loveman, 2014 (21)	Y	Y	Y	Y	Y[a]	Y	Y	Y	Y	Y	Y
Bala, 2013 (22)	Y	Y	Y	Y	Y[a]	Y	Y	Y	Y	Y	Y
Cirocchi, 2012 (23)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Belinson, 2012 (24)	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N*
Wu, 2011 (25)	N	N	Y	N	Y	Y	N	N	N	N	N
Pathak, 2011 (26)	N	Y	Y	Y	Y	Y	Y	N	N	N	N
NICE, 2009 (27)	Y	N	Y	Y	Y	Y	Can't determine	N	Y	N	N[b]

[a] Only included studies listed

[b] 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

Study, year, funding	Objectives	Population	Intervention/comparison	Outcomes	Summary results
Di Costanzo (abs) 2013 (28) **Funding**: ND	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.

Study, year, Funding	Objectives	Population	Intervention/Comparison	Outcomes	Summary results
Ruers, 2012 (29)[a]	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.

[a]*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

Risk of Bias Tool	Di Costanzo, 2013 (28)	Ruers, 2012 (29)
Random sequence generation (selection bias)	Unclear risk	Low risk[a]
Allocation concealment (selection bias)	Unclear risk	Unclear risk
Blinding of participants and personnel (performance bias)	Unclear risk	High risk
Blinding of outcome assessment (detection bias)	Unclear risk	High risk
Incomplete outcome data addressed (attrition bias)	Unclear risk	Low risk[b]
Selective reporting (reporting bias)	Unclear risk	Low risk

[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; I^2=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; I^2 = 0.0%). For tumours >2 centimetres the authors found also a similar result (HR = 0.56; 95% CI 0.31 to 0.99, p=0.045; I^2 = 0%).

RFA was better than PEI also for recurrence and metastasis (HR = 0.38, 95% CI: 0.15–0.96, p = 0.040; I^2 = 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; I^2 = 56.8%).

No significant difference was found in distant intrahepatic recurrence events (HR = 0.95, 95% CI: 0.75–1.22, p = 0.707; I^2 = 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

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 $\geq$ 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.

Funding

The PEBC is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

Copyright

Disclaimer

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

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 synthes?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

33 (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.
34 32 not 33
35 remove duplicates from 34

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 synthes?s 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"

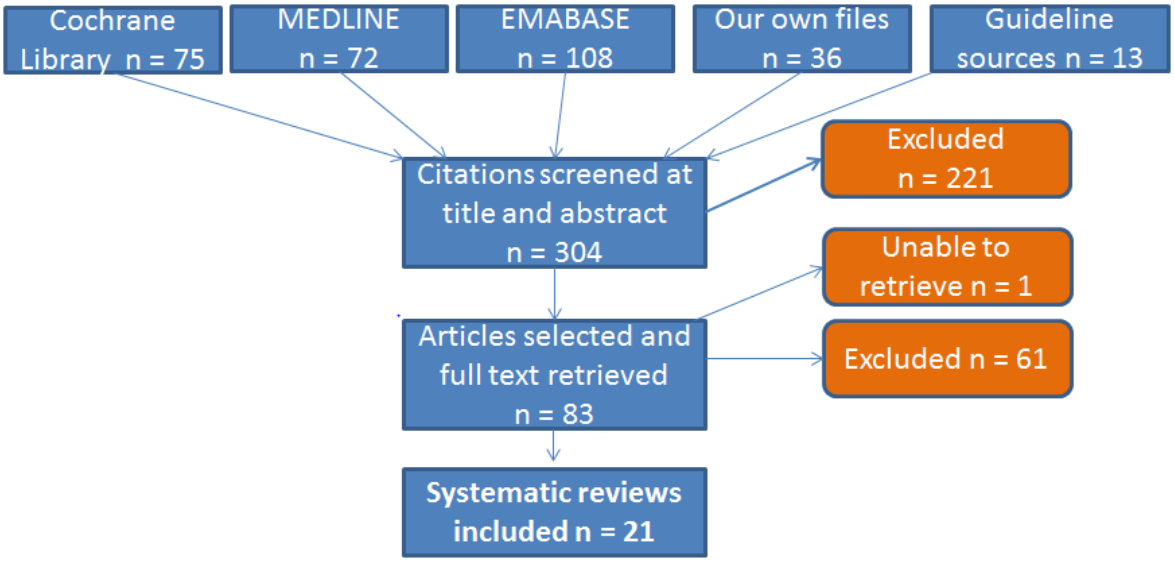
Database: EMBASE <2012 to 2014 Week 16>
Search Strategy:
---

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.

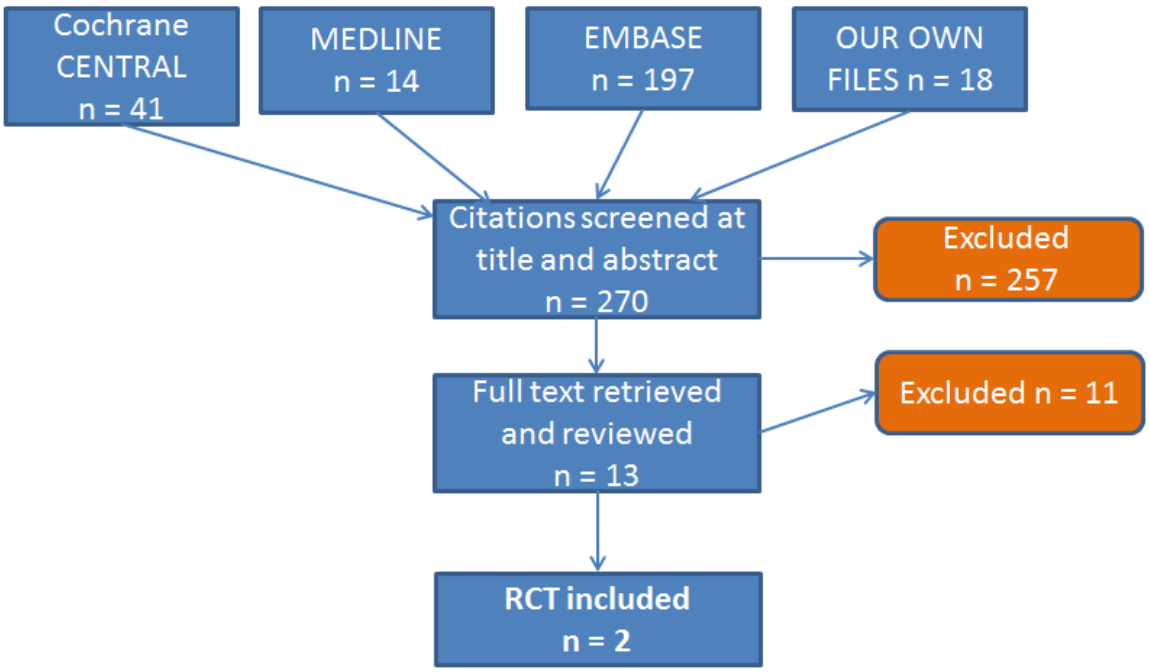
4 1 or 2 or 3
5 (phase II or phase 2).tw. or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/
6 5 and random$.tw.
7 (clinic$ adj trial$1).tw.
8 ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
9 placebo/
10 (placebo? or random allocation or randomly allocated or allocated randomly).tw.
11 (allocated adj2 random).tw.
12 7 or 8 or 9 or 10 or 11
13 4 or 6 or 12
14 (editorial or note or letter erratum or short survey).pt. or abstract report/ or letter/ or case study/
15 13 not 14
16 limit 15 to english
17 animal/
18 human/
19 17 not 18
20 16 not 19
21 exp liver cell carcinoma/
22 ((Hepat* or liver) and (carcinom* or tumo?r* or neoplasm* or malign* or cancer*)).mp.
23 HCC.mp.
24 21 or 22 or 23
25 exp radiofrequency ablation/
26 exp Catheter Ablation/
27 ((radiofrequenc* or radio-frequenc* or radio frequenc*) and (ablation* or therap* or treat*)).mp.
28 (RFTA or RFA or RFT of RFCA).mp.
29 Hyperthermic Therapy.mp. or hyperthermic therapy/
30 microwave radiation#.mp. or exp microwave radiation/
31 ((coagulation adj therapy) or ablation).tw.
32 25 or 26 or 27 or 28 or 29 or 30 or 31
33 20 and 24 and 32
34 (editorial or note or letter erratum or short survey).pt. or abstract report/ or letter/ or case study/
35 33 not 34
36 animal/
37 human/
38 36 not 37
39 35 not 38
40 limit 39 to english
41…..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

1. Salhab M, Canelo R. An overview of evidence-based management of hepatocellular carcinoma- a meta-analysis. Hepatology. 2011;54:1395A.
2. Liao M, Huang J, Zhang T, Wu H. Will we still using chemoembolization separately? A meta-analysis of combined local therapies for hepatocellular carcinoma. Liver Transplantation. 2013;(1):S129.
3. Cucchetti A, Piscaglia F, Cescon M, Colecchia A, Ercolani G, Bolondi L, et al. Radiofrequency ablation versus hepatic resection for early hepatocellular carcinoma: A cost-effectiveness perspective. Digest Liver Dis. 2013;45:S5.

ABSTRACT of SYSTEMATIC REVIEW

1. Pleguezuelo M, Germani G, Gurusamy K, Calvaruso V, Manousou P, Arvaniti V, et al. Percutaneous treatment of hepatocellular carcinoma. Systematic review and metaanalysis [abstract]. J Hepatol. 2009;50:S297.
2. Pathak S, Tang J, Jones R, Malik H, Fenwick S, Postona G. Systematic review: The use of ablative techniques for the treatment of unresectable colorectal liver metastases (CLM) [abstract]. Eur J Surg Oncol. 2010;36 (11):1129.
3. Hu P, Zhang SJ, Sun AX, Qian GJ. Meta-analysis of survival and disease recurrence for small hepatocellular carcinoma after radiofrequency ablation and surgical resection [abstract]. HPB (Oxford). 2013;15 Suppl 2:118.
4. Cai H, Zhou T, Qiu YD. Comparison of radiofrequency ablation and surgical resection in patients with solitary hepatocellular carcinoma within 5 centimetres: a me [abstract]. HPB (Oxfodrd). 2013;15 Suppl 2:221.

NOT INTERVENTION OF INTEREST

1. Cucchetti A, Piscaglia F, Cescon M, Colecchia A, Bolondi L, Pinna AD. Cost-effectiveness of hepatic resection versus percutaneous ablation for hepatocellular carcinoma within the milan criteria. J Hepatol. 2013;58:S112-S3.
2. Bergenfeldt M. Palliative surgery in liver metastases from breast cancer: Is there evidence? An overview. Digest Liver Dis. 2013;45:S242-S3.
3. Huang YZ, Zhou SC, Zhou H, Tong M. Radiofrequency ablation versus cryosurgery ablation for hepatocellular carcinoma: a meta-analysis. Hepato-Gastroenterol. 2013;60(125):1131-5.
4. Carter S, Martin Ii RC. Drug-eluting bead therapy in primary and metastatic disease of the liver. HPB (Oxford). 2009;11(7):541-50.
5. Blake MA, McDermott S, Rosen MP, Baker M, Fidler J, Greene FL, et al. ACR Appropriateness Criteria: suspected liver metastases [Internet]. Reston (VA): American College of Radiology (ACR);

2011 [cited 2014 Mar 11] 9 p.; 2011. Available from http://www.guideline.gov/content.aspx?id=32614.

6. Lalani T, Rosen MP, Blake MA, Cash BD, Fidler JL, Fidler J, et al. ACR Appropriateness Criteria® liver lesion — initial characterization [Internet]. Reston (VA): American College of Radiology (ACR); 2010 [cited 2014 Mar 11]. 8 p. Available from: http://www.guideline.gov/content.aspx?id=32602.
7. Yan S, Xu D, Sun B. Combination of radiofrequency ablation with transarterial chemoembolization for hepatocellular carcinoma: a meta-analysis. Dig Dis Sci. 2012;57(11):3026-31. Epub 2012 May 16.
8. Gurusamy KS, Ramamoorthy R, Imber C, Davidson BR. Surgical resection versus non-surgical treatment for hepatic node positive patients with colorectal liver metastases. 2010 Jan 20 [cited 2014 Mar 11]. In: The Cochrane Database of Systematic Reviews [Internet]. Hoboken (NJ): John Wiley & Sons, Ltd. c1999 - . Record No.: CD006797.
9. Razafindratsira T, Isambert M, Evrard S. Complications of intraoperative radiofrequency ablation of liver metastases. HPB (Oxford). 2011;13(1):15-23.
10. Morihara D, Iwata K, Hanano T, Kunimoto H, Kuno S, Fukunaga A, et al. Late-evening snack with branched-chain amino acids improves liver function after radiofrequency ablation for hepatocellular carcinoma. Hepatology research [Internet]. 2012 [cited 2014 Mar 11];42(7):658-67. Available from:
11. http://onlinelibrary.wiley.com/store/10.1111/j.1872-034X.2012.00969.x/asset/j.1872-034X.2012.00969.x.pdf?v=1&t=humzumdt&s=137f69907cc0e2676762907af0599cdbf56ec569. Subscription required to view full text.
12. Ontario Health Technology Advisory Committee. Advancing health evidence-based advice on health technology. Toronto (ON): Ontario Health Technology Advisory Committee; 2009.
13. Mochizuki H, Kuratomi N, Kuno T, Fukasawa Y, Suzuki Y, Hosoda K, et al. A prospective controlled trial of radiofrequency ablation for hepatocellular carcinoma performed by two hepatogastroenterologists with different training backgrounds. Hepatology International. 2014;(1):S270.
14. Rahbari NN, Mehrabi A, Mollberg NM, Muller SA, Koch M, Buchler MW, et al. Hepatocellular carcinoma: Current management and perspectives for the future. Ann Surg. 2011;253(3):453-69.
15. Rubin J, Ayoub N, Kaldas F, Saab S. Management of recurrent hepatocellular carcinoma in liver transplant recipients: A systematic review. Exp Clin Transplant. 2012;10(6):531-43.
16. Alberts SR. Update on the optimal management of patients with colorectal liver metastases. Crit Rev Oncol/Hematol. 2012;84(1):59-70.
17. Fox M, Fox J, Davies M. Diagnosis and management of chronic liver disease in older people. Rev Clin Gerontol. 2011;21(1):1-15.
18. Scottish Intercollegiate Guidelines Network (SIGN). Diagnosis and management of colorectal cancer: a national clinical guideline. Edinburgh (UK): Healthcare Improvement Scotland; 2011 [cited 2014 Mar 18]. 63 p. Available from: http://www.sign.ac.uk/pdf/sign126.pdf
19. Liao M, Huang J, Zhang T, Wu H. Transarterial chemoembolization in combination with local therapies for hepatocellular carcinoma: a meta-analysis. PloS One. 2013;8(7):e68453. Epub 2013 Jul 12.
20. Gu L, Liu H, Fan L, Lv Y, Cui Z, Luo Y, et al. Treatment outcomes of transcatheter arterial chemoembolization combined with local ablative therapy versus monotherapy in hepatocellular carcinoma: a meta-analysis. J Cancer Res Clin Oncol. 2014;140(2):199-210.

21. Wang W, Shi J, Xie WF. Transarterial chemoembolization in combination with percutaneous ablation therapy in unresectable hepatocellular carcinoma: a meta-analysis. Liver Int. 2010;30(5):741-9. Epub 2010 Mar 25.
22. National Institute for Health and Clinical Excellence. Colorectal cancer: the diagnosis and management of colorectal cancer. Manchester (UK): National Institute for Health and Clinical Excellence; 2011 [cited 2014 Mar 18]. 37 p. Available from: http://www.nice.org.uk/guidance/cg131/resources/guidance-colorectal-cancer-pdf

NOT IN ENGLISH

1. Li Z, Mi D, Yang K, Cao N, Tian J, Ma B. TACE combined with thermotherapy for primary hepatic carcinoma: a meta-analysis. Chinese J Evid-Based Med. 2012;12(6):672-8.
2. Sun B, Zheng CS, Feng GS, Wang Y, Xia XW, Kan XF. Radiofrequency ablation versus surgical resection for small hepatocellular carcinoma: a meta-analysis. World Chinese J Digestol. 2011;19(31):3255-63.
3. Wang YQ, Li XL, Li YP, Deng SL, Luo QQ, Wei SY. Status quo of global interventional therapy for tumors: a systematic review. Chinese J Evid-Based Med. 2013;13(9):1060-72.

SEARCH OLDER THAN 2009

1. Bhardwaj N, Strickland AD, Ahmad F, Dennison AR, Lloyd DM. Liver ablation techniques: a review. Surg Endosc. 2010;24(2):254-65.
2. Germani G, Pleguezuelo M, Gurusamy K, Meyer T, Isgro G, Burroughs AK. Clinical outcomes of radiofrequency ablation, percutaneous alcohol and acetic acid injection for hepatocelullar carcinoma: a meta-analysis. J Hepatol. 2010;52(3):380-8.
3. Poulou LS, Ziakas PD, Xila V, Vakrinos G, Malagari K, Syrigos KN, et al. Percutaneous radiofrequency ablation for unresectable colorectal liver metastases: time for shadows to disperse. Rev Recent Clin Trials. 2009;4(3):140-6.
4. Liu Z, Zhou Y, Zhang P, Qin H. Meta-analysis of the therapeutic effect of hepatectomy versus radiofrequency ablation for the treatment of hepatocellular carcinoma. Surg Laparosc Endosc Percutan Tech. 2010;20(3):130-40.
5. Liu J, Mittendorf T, Von Der Schulenburg JM. A structured review and guide through studies on health-related quality of life in kidney cancer, hepatocellular carcinoma, and leukemia. Cancer Invest. 2010;28(3):312-22.
6. Shukla PJ, Barreto SG. Surgery for malignant liver tumors. J Cancer Res Ther. 2009;5(3):154-60.
7. Wong SL, Mangu PB, Choti MA, Crocenzi TS, Dodd GD, 3rd, Dorfman GS, et al. American Society of Clinical Oncology 2009 clinical evidence review on radiofrequency ablation of hepatic metastases from colorectal cancer. J Clin Oncol. 2010;28(3):493-508.
8. Lau WY, Lai EC. The current role of radiofrequency ablation in the management of hepatocellular carcinoma: a systematic review. Ann Surg. 2009;249(1):20-5.
9. Stang A, Fischbach R, Teichmann W, Bokemeyer C, Braumann D. A systematic review on the clinical

benefit and role of radiofrequency ablation as treatment of colorectal liver metastases. Eur J Cancer. 2009;45(10):1748-56.
10. Liu JG, Wang YJ, Du Z. Radiofrequency ablation in the treatment of small hepatocellular carcinoma: a meta analysis. World J Gastroenterol. 2010;16(27):3450-6.
11. Ong SL, Gravante G, Metcalfe MS, Strickland AD, Dennison AR, Lloyd DM. Efficacy and safety of microwave ablation for primary and secondary liver malignancies: a systematic review. Eur J Gastroenterol Hepatol. 2009;21(6):599-605.
12. Cho YK, Kim JK, Kim MY, Rhim H, Han JK. Systematic review of randomized trials for hepatocellular carcinoma treated with percutaneous ablation therapies. Hepatology. 2009;49(2):453-9.
13. Orlando A, Leandro G, Olivo M, Andriulli A, Cottone M. Radiofrequency thermal ablation vs. percutaneous ethanol injection for small hepatocellular carcinoma in cirrhosis: meta-analysis of randomized controlled trials. Am J Gastroenterol. 2009;104(2):514-24.
14. Bouza C, Lopez-Cuadrado T, Alcazar R, Saz-Parkinson Z, Amate JM. Meta-analysis of percutaneous radiofrequency ablation versus ethanol injection in hepatocellular carcinoma. BMC Gastroenterol. 2009;9:31.

NOT OUTCOME OF INTEREST

1. Cucchetti A, Piscaglia F, Cescon M, Colecchia A, Bolondi L, Pinna AD. Cost-effectiveness of hepatic resection versus percutaneous ablation for hepatocellular carcinoma within the milan criteria. J Hepatol. 2013;58:S112-S3.
2. Bertot LC, Sato M, Tateishi R, Yoshida H, Koike K. Mortality and complication rates of percutaneous ablative techniques for the treatment of liver tumors: a systematic review. Eur Radiol. 2011;21(12):2584-96.
3. Cucchetti A, Piscaglia F, Cescon M, Colecchia A, Ercolani G, Bolondi L, et al. Cost-effectiveness of hepatic resection versus percutaneous radiofrequency ablation for early hepatocellular carcinoma. J Hepatol. 2013;59(2):300-7.
4. Khajanchee YS, Hammill CW, Cassera MA, Wolf RF, Hansen PD. Hepatic resection vs minimally invasive radiofrequency ablation for the treatment of colorectal liver metastases: a Markov analysis. Arch Surg. 2011;146(12):1416-23.

NOT SYSTEMATIC REVIEW

1. Cucchetti A, Piscaglia F, Cescon M, Colecchia A, Bolondi L, Pinna AD. Cost-effectiveness of hepatic resection versus percutaneous ablation for hepatocellular carcinoma within the Milan criteria. J Hepatol. 2013;58:S112-S3.
2. Bruix J. Chemoembolisation and ablation for HCC. Hepatol Int. 2009;3 (1):18-9.
3. Bale R. RF ablation vs. surgery in small HCC. Cardiovasc Intervent Rad. 2010;33:41-2.
4. Burroughs AK. Radiofrequency ablation of hepatocellular carcinoma. J Gastroen Hepatol. 2012;27:35.

5. Burak KW, Kneteman NM. An evidence-based multidisciplinary approach to the management of hepatocellular carcinoma (HCC): the Alberta HCC algorithm. Can J Gastroenterol. 2010;24(11):643-50.
6. National Institute for Health and Clinical Excellence. Microwave ablation for the treatment of liver metastases [Internet]. Location: Publisher; 2011 Aug [cited 2014 Mar 18]. 5 p. Available from: http://www.nice.org.uk/guidance/ipg406/resources/guidance-microwave-ablation-for-the-treatment-of-liver-metastases-pdf
7. Jones C, Badger SA, Ellis G. The role of microwave ablation in the management of hepatic colorectal metastases. Surgeon. 2011;9(1):33-7.
8. Cho YK, Kim JK, Kim WT, Chung JW. Hepatic resection versus radiofrequency ablation for very early stage hepatocellular carcinoma: a Markov model analysis. Hepatology. 2010;51(4):1284-90.
9. Cho YK, Wook Chung J, Kim Y, Je Cho H, Hyun Yang S. Radiofrequency ablation of high-grade dysplastic nodules. Hepatology. 2011;54(6):2005-11.
10. Cucchetti A, Piscaglia F, Cescon M, Colecchia A, Ercolani G, Bolondi L, et al. Cost-effectiveness of hepatic resection versus percutaneous radiofrequency ablation for early hepatocellular carcinoma. J Hepatol. 2013;59(2):300-7.
11. Jiang K, Zhang W, Su M, Liu Y, Zhao X, Wang J, et al. Laparoscopic radiofrequency ablation of solitary small hepatocellular carcinoma in the caudate lobe. Eurn J Surg Oncol. 2013;39(11):1236-42.
12. Khajanchee YS, Hammill CW, Cassera MA, Wolf RF, Hansen PD. Hepatic resection vs minimally invasive radiofrequency ablation for the treatment of colorectal liver metastases: a Markov analysis. Arch Surg. 2011;146(12):1416-23.

Appendix 4B. Excluded RCTs

ABSTRACT OF INTERIM ANALYSIS

1. Ricke J, Bulla K, Walecki J, Schott E, Sangro B, Kolligs F, et al. Safety and toxicity of the combination of Y90-radioembolization and sorafenib in advanced HCC: an interim analysis of the European multicenter trial soramic. J Hepatol. 2013;58:S114.

ALREADY IN INCLUDED SYSTEMATIC REVIEWS

1. Tanis E, Nordlinger B, Mauer M, Sorbye H, Van Coevorden F, Gruenberger T, et al. Local recurrence rates after radiofrequency ablation or resection of colorectal liver metastases. Analysis of the European Organisation for Research and Treatment of Cancer #40004 and #40983. Eur J Cancer. 2014;50(5):912-9.
2. Feng K, Yan J, Li X, Xia F, Ma K, Wang S, et al. A randomized controlled trial of radiofrequency ablation and surgical resection in the treatment of small hepatocellular carcinoma. J Hepatol. 2012;57(4):794-802.

DUPLICATE PUBLICATIONS

1. Mochizuki H, Tsukui Y, Suzuki Y, Hoshino Y, Hosoda K, Kojima Y, et al. A prospective controlled trial of radiofrequency ablation for hepatocellular carcinoma performed by two hepatogastroenterologists with different training backgrounds. Hepatol Int. 2012;6 (1):220-1.
2. Mochizuki H, Ishida Y, Kawakami S, Kuno T, Fukasawa Y, Hirose S, et al. A prospective controlled trial of radiofrequency ablation for hepatocellular carcinoma performed by two hepatogastroenterologists with different training backgrounds (4). Hepatol Int. 2013;7:S602.

NOT IN ENGLISH

1. Zhao XX, You FP, Yuan QZ, Pan GZ, Bu QA, Hao L, et al. Safety and effectiveness of radiofrequency combined with laparoscopic cholecystectomy in management of liver cancer near the gallbladder. World Chinese Journal of Digestology [Internet]. 2013 [cited 2014 Mar 18]; 21(22):2212-6. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/684/CN-00910684/frame.htmlhttp://www.wjgnet.com/1009-3079/21/2212.pdf. Subscription required to view full text.

NOT INTERVENTION OF INTEREST

1. Morihara D, Iwata K, Hanano T, Kunimoto H, Kuno S, Fukunaga A, et al. Late-evening snack with branched-chain amino acids improves liver function after radiofrequency ablation for hepatocellular carcinoma. Hepatology research [Internet]. 2012 [cited 2014 Mar 18]; 42(7): 658-67. Available from: http://onlinelibrary.wiley.com/store/10.1111/j.1872-034X.2012.00969.x/asset/j.1872-034X.2012.00969.x.pdf?v=1&t=humzumdt&s=137f69907cc0e2676762907af0599cdbf56ec569. Subscription required to view full text.
2. Mochizuki H, Kuratomi N, Kuno T, Fukasawa Y, Suzuki Y, Hosoda K, et al. A prospective controlled trial of radiofrequency ablation for hepatocellular carcinoma performed by two hepatogastroenterologists with different training backgrounds (5). Hepatol Int. 2014;(1):S270.

NOT RCT

1. Ayuso C. How to follow up and when to reintervene. Cardiovasc Intervent Rad. 2012;35:S22.
2. Lee J, Lee JM, Yoon JH, Lee JY, Kim SH, Lee JE, et al. Percutaneous radiofrequency ablation with multiple electrodes for medium-sized hepatocellular carcinomas. Korean journal of radiology [Internet]. 2012 [cited 2014 Mar 18]; 13(1):34-43. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3253401/pdf/kjr-13-34.pdf.
3. Duan JC. Percutaneous radiofrequency ablation versus repeat hepatectomy for recurrent hepatocellular carcinoma: a prospective RCT study. HPB (Oxford). 2013;15:109.

Appendix 4: Conflict of Interest Disclosures: Focal Ablation Committee

Members	Role	Conflict of Interest
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)
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

Members	Role	Conflict of Interest
Amol Mujoomdar	Member	Speaker honorarium received from Covidien and Cook Medical
Wael Shabana	Member	Will be attendee for Ablation Master Class at Toronto General Hospital Advanced Imaging and Education - sponsored by Covidien Company
Laura Dawson	Member	Bayer Clinical Trials - paid to Institution
		In 2005, published editorial/commentary regarding objects of study
Richard Malthaner	Member	None declared
Guillaume Martel	Member	Part of Fellowship conference travel stipend in 2013 was covered by a bursary from Covidien (<$5000)
Catherine Wang	Member	Managerial responsibility on unrestricted research/education grants from Bard, Medtronic, Covidien, Gore, Boston Scientific, Sorin Medical
		Managerial responsibility on research studies funded by: Cook, Medtronic, Biotronic, Terumo, Gore
Ania Kielar	Member	GE CHAR grant for MRI post RFA investigation
Calvin Law	Member	None declared
David Gast	Patient Family Advisor	None declared
Brigitta Bokkers	Patient Family Advisor	None declared

REFERENCES

1. McDermott S, Gervais DA. Radiofrequency Ablation of Liver Tumors. Semin Intervent Radiol. 2013;30(1):49-55. Epub 2014/01/18.

2. Goldberg SN, Grassi CJ, Cardella JF, Charboneau JW, Dodd GD, 3rd, Dupuy DE, et al. Image-guided tumor ablation: standardization of terminology and reporting criteria. Radiology. 2005;235(3):728-39. Epub 2005/04/23.

3. Ahmed M, Solbiati L, Brace CL, Breen DJ, Callstrom MR, Charboneau JW, et al. Image-guided Tumor Ablation: Standardization of Terminology and Reporting Criteria-A 10-Year Update. Radiology. 2014:132958.

4. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol. 2007;7:10. Epub 2007/02/17.

5. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.

6. Wang Y, Luo Q, Li Y, Deng S, Wei S, Li X. Radiofrequency ablation versus hepatic resection for small hepatocellular carcinomas: a meta-analysis of randomized and nonrandomized controlled trials. PLoS ONE [Electronic Resource]. 2014;9(1):e84484.

7. Weis S, Franke A, Mössner J, Jakobsen Janus C, Schoppmeyer K. Radiofrequency (thermal) ablation versus no intervention or other interventions for hepatocellular carcinoma. Cochrane Database of Systematic Reviews [Internet]. 2013; (12). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003046.pub3/abstract

8. Belinson S, Yang Y, Chopra R, Shankaran V, Samson D, Aronson N. Local therapies for unresectable primary hepatocellular carcinoma. Health Technology Assessment Database [Internet]. 2013; (1). Available from: http://onlinelibrary.wiley.com/o/cochrane/clhta/articles/HTA-32013000728/frame.html.

9. Qi X, Tang Y, An D, Bai M, Shi X, Wang J, et al. Radiofrequency Ablation Versus Hepatic Resection for Small Hepatocellular Carcinoma: A Meta-analysis of Randomized Controlled Trials. J Clin Gastroenterol. 2013.

10. Duan C, Liu M, Zhang Z, Ma K, Bie P. Radiofrequency ablation versus hepatic resection for the treatment of early-stage hepatocellular carcinoma meeting Milan criteria: a systematic review and meta-analysis. World J Surg Oncol. 2013;11(1):190. Epub 2013/08/15.

11. Cucchetti A, Piscaglia F, Cescon M, Ercolani G, Pinna AD. Systematic review of surgical resection vs radiofrequency ablation for hepatocellular carcinoma. World J Gastroenterol. 2013;19(26):4106-18.

12. Shen A, Zhang H, Tang C, Chen Y, Wang Y, Zhang C, et al. Systematic review of radiofrequency ablation versus percutaneous ethanol injection for small hepatocellular carcinoma up to 3centimetres. J Gastroenterol Hepatol. 2013;28(5):793-800.

13. Xu G, Qi FZ, Zhang JH, Cheng GF, Cai Y, Miao Y. Meta-analysis of surgical resection and radiofrequency ablation for early hepatocellular carcinoma. World J Surg Oncol. 2012;10:163.

14. Li L, Zhang J, Liu X, Li X, Jiao B, Kang T. Clinical outcomes of radiofrequency ablation and surgical resection for small hepatocellular carcinoma: a meta-analysis. J Gastroenterol Hepatol. 2012;27(1):51-8.

15. Tiong L, Maddern GJ. Systematic review and meta-analysis of survival and disease recurrence after radiofrequency ablation for hepatocellular carcinoma. Br J Surg. 2011;98(9):1210-24. Epub 2011/07/19.

16. Cho YK, Rhim H, Noh S. Radiofrequency ablation versus surgical resection as primary treatment of hepatocellular carcinoma meeting the Milan criteria: a systematic review. J Gastroenterol Hepatol. 2011;26(9):1354-60.

17. Salhab M, Canelo R. An overview of evidence-based management of hepatocellular carcinoma: a meta-analysis (Provisional abstract). Database of Abstracts of Reviews of Effects [Internet]. 2011; (1):[463-75 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/cldare/articles/DARE-12012010091/frame.html.

18. Xie X, Dendukuri N, McGregor M. Percutaneous radiofrequency ablation for treatment of hepatocellular carcinoma (Structured abstract). Health Technology Assessment Database [Internet]. 2009; (1). Available from: http://onlinelibrary.wiley.com/o/cochrane/clhta/articles/HTA-32010000172/frame.html.

19. Xie X, Dendukuri N, McGregor M. Percutaneous radiofrequency ablation for the treatment of early stage hepatocellular carcinoma: a health technology assessment. Int J Technol Assess Health Care. 2010;26(4):390-7.

20. Zhou Y, Zhao Y, Li B, Xu D, Yin Z, Xie F, et al. Meta-analysis of radiofrequency ablation versus hepatic resection for small hepatocellular carcinoma. BMC Gastroenterol. 2010;10:78.

21. Loveman E, Jones J, Clegg AJ, Picot J, Colquitt JL, Mendes D, et al. The clinical effectiveness and cost-effectiveness of ablative therapies in the management of liver metastases: systematic review and economic evaluation. Health Technol Assess. 2014;18(7):1-284.

22. Bala Malgorzata M, Riemsma Robert P, Wolff R, Kleijnen J. Microwave coagulation for liver metastases. Cochrane Database of Systematic Reviews [Internet]. 2013; (10). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010163.pub2/abstract.

23. Cirocchi R, Trastulli S, Boselli C, Montedori A, Cavaliere D, Parisi A, et al. Radiofrequency ablation in the treatment of liver metastases from colorectal cancer. Cochrane Database of Systematic Reviews [Internet]. 2012; (6). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006317.pub3/abstract.

24. Belinson S, Chopra R, Yang Y, Shankaran V, Aronson N. Local hepatic therapies for metastases to the liver from unresectable colorectal cancer. Comparative Effectiveness Review No. 93. (Prepared by Blue Cross and Blue Cross Blue Shield Association Technology Evaluation Center under Contract No. 290-2007-10058-I.). Rockville, MD: AHRQ Publication No. 13-EHC014-EF: Agency for Healthcare Research and Quality. December; 2012. Available from: http://onlinelibrary.wiley.com/o/cochrane/clhta/articles/HTA-32013000239/frame.html.

25. Wu YZ, Li B, Wang T, Wang SJ, Zhou YM. Radiofrequency ablation vs hepatic resection for solitary colorectal liver metastasis: a meta-analysis. World J Gastroenterol. 2011;17(36):4143-8.

26. Pathak S, Jones R, Tang JM, Parmar C, Fenwick S, Malik H, et al. Ablative therapies for colorectal liver metastases: a systematic review. Colorectal Dis. 2011;13(9):e252-65.

27. National Institute for Health and Clinical Excellence. Interventional procedure overview of radiofrequency ablation for colorectal liver metastases2009 [cited 2014 Mar 18]. Available from: https://www.nice.org.uk/guidance/IPG327/chapter/1-guidance.

28. Di Costanzo GG, Tortora R, D'Adamo G, Galeota Lanza A, Lampasi F, Addario L, et al. Radiofrequency ablation versus laser ablation for the treatment of small hepatocellular carcinoma: A randomized controlled trial. Dig Liver Dis. 2013;45:S5.

29. Ruers T, Punt C, Van coevorden F, Pierie JPEN, Borel-Rinkes I, Ledermann JA, et al. Radiofrequency ablation combined with systemic treatment versus systemic treatment alone in patients with non-resectable colorectal liver metastases: A randomized eortc intergroup phase ii study (EORTC 40004). Ann Oncol. 2012;23(10):2619-26.

30. Schünemann H, Brożek J, Guyatt G, Oxman A, editors. GRADE handbook for grading quality of evidence and strength of recommendations. Updated October 2013. The GRADE Working Group, 2013. Available from www.guidelinedevelopment.org/handbook.2013.

31. Huang J, Yan L, Cheng Z, Wu H, Du L, Wang J, et al. A randomized trial comparing radiofrequency ablation and surgical resection for HCC conforming to the Milan criteria. Ann Surg. 2010;252(6):903-12.

32. Feng K, Yan J, Li X, Xia F, Ma K, Wang S, et al. A randomized controlled trial of radiofrequency ablation and surgical resection in the treatment of small hepatocellular carcinoma. JHepatol. 2012;57(4):794-802.

33. Chen MS, Li JQ, Zheng Y, Guo RP, Liang HH, Zhang YQ, et al. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. Ann Surg. 2006;243(3):321-8.

34. Lin SM, Lin CJ, Lin CC, Hsu CW, Chen YC. Radiofrequency ablation improves prognosis compared with ethanol injection for hepatocellular carcinoma < or =4 centimetres. Gastroenterology [Internet]. 2004; 127(6):[1714-23 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/857/CN-00492857/frame.html.

35. Shiina S, Teratani T, Obi S, Sato S, Tateishi R, Fujishima T, et al. A randomized controlled trial of radiofrequency ablation with ethanol injection for small hepatocellular carcinoma. Gastroenterology. 2005;129(1):122-30.

36. Lin SM, Lin CJ, Lin CC, Hsu CW, Chen YC. Randomised controlled trial comparing percutaneous radiofrequency thermal ablation, percutaneous ethanol injection, and percutaneous acetic acid injection to treat hepatocellular carcinoma of 3 centimetres or less. Gut. 2005;54(8):1151-6.

37. Lencioni RA, Allgaier HP, Cioni D, Olschewski M, Deibert P, Crocetti L, et al. Small hepatocellular carcinoma in cirrhosis: randomized comparison of radio-frequency thermal ablation versus percutaneous ethanol injection. Radiology. 2003;228(1):235-40.

38. Giorgio A, Di Sarno A, De Stefano G, Scognamiglio U, Farella N, Mariniello A, et al. Percutaneous radiofrequency ablation of hepatocellular carcinoma compared to percutaneous ethanol injection in treatment of cirrhotic patients: an Italian randomized controlled trial.[Erratum appears in Anticancer Res. 2012 Mar;32(3):1117]. Anticancer Res. 2011;31(6):2291-5.

39. Brunello F, Veltri A, Carucci P, Pagano E, Ciccone G, Moretto P, et al. Radiofrequency ablation versus ethanol injection for early hepatocellular carcinoma: A randomized controlled trial. Scand J Gastroenterol. 2008;43(6):727-35.

40. Shibata T, Iimuro Y, Yamamoto Y, Maetani Y, Ametani F, Itoh K, et al. Small hepatocellular carcinoma: comparison of radio-frequency ablation and percutaneous microwave coagulation therapy. Radiology. 2002;223(2):331-7.

41. Ferrari FS, Megliola A, Scorzelli A, Stella A, Vigni F, Drudi FM, et al. Treatment of small HCC through radiofrequency ablation and laser ablation. Comparison of techniques and long-term results. Radiol Med. 2007;112(3):377-93.

42. Chok KS, Ng KK, Poon RT, Lam CM, Yuen J, Tso WK, et al. Comparable survival in patients with unresectable hepatocellular carcinoma treated by radiofrequency ablation or transarterial chemoembolization. Arch Surg. 2006;141(12):1231-6.

43. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(12)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality. April 2012. Chapters available at: www.effectivehealthcare.ahrq.gov.2012.

44. Centre for Reviews and Dissemination. Systematic Reviews: CRD's guidance for undertaking systematic reviews in health care. York, UK: Centre for Reviews and Dissemination; 2008.

45. Shibata T, Niinobu T, Ogata N, Takami M. Microwave coagulation therapy for multiple hepatic metastases from colorectal carcinoma. Cancer. 2000;89(2):276-84.

46. Kim KH, Yoon YS, Yu CS, Kim TW, Kim HJ, Kim PN, et al. Comparative analysis of radiofrequency ablation and surgical resection for colorectal liver metastases. J Korean Surg Soc. 2011;81(1):25-34.

47. Otto G, Duber C, Hoppe-Lotichius M, Konig J, Heise M, Pitton MB. Radiofrequency ablation as first-line treatment in patients with early colorectal liver metastases amenable to surgery. Ann Surg. 2010;251(5):796-803.

48. Schiffman SC, Bower M, Brown RE, Martin RC, McMasters KM, Scoggins CR. Hepatectomy is superior to thermal ablation for patients with a solitary colorectal liver metastasis. J Gastrointest Surg. 2010;14(12):1881-6; discussion 6-7.

49. McKay A, Fradette K, Lipschitz J. Long-term outcomes following hepatic resection and radiofrequency ablation of colorectal liver metastases. HPB Sur. 2009;2009:346863.

50. Vyslouzil K, Klementa I, Stary L, Zboril P, Skalicky P, Dlouhy M, et al. [Radiofrequency ablation of colorectal liver metastases]. Zentralblatt fur Chirurgie. 2009;134(2):145-8. Radiofrequenzablation von kolorektalen Lebermetastasen.

51. Hur H, Ko YT, Min BS, Kim KS, Choi JS, Sohn SK, et al. Comparative study of resection and radiofrequency ablation in the treatment of solitary colorectal liver metastases. Am J Surg. 2009;197(6):728-36.

52. Berber E, Tsinberg M, Tellioglu G, Simpfendorfer CH, Siperstein AE. Resection versus laparoscopic radiofrequency thermal ablation of solitary colorectal liver metastasis. J Gastrointest Surg. 2008;12(11):1967-72.

53. Lee WS, Yun SH, Chun HK, Lee WY, Kim SJ, Choi SH, et al. Clinical outcomes of hepatic resection and radiofrequency ablation in patients with solitary colorectal liver metastasis. J Clin Gastroenterol. 2008;42(8):945-9.

54. Gleisner AL, Choti MA, Assumpcao L, Nathan H, Schulick RD, Pawlik TM. Colorectal liver metastases: recurrence and survival following hepatic resection, radiofrequency ablation, and combined resection-radiofrequency ablation. Arch Surg. 2008;143(12):1204-12.

55. Park IJ, Kim HC, Yu CS, Kim PN, Won HJ, Kim JC. Radiofrequency ablation for metachronous liver metastasis from colorectal cancer after curative surgery. Ann Surg Oncol. 2008;15(1):227-32.

56. White RR, Avital I, Sofocleous CT, Brown KT, Brody LA, Covey A, et al. Rates and patterns of recurrence for percutaneous radiofrequency ablation and open wedge resection for solitary colorectal liver metastasis. J Gastrointest Surg. 2007;11(3):256-63.

57. Aloia TA, Vauthey JN, Loyer EM, Ribero D, Pawlik TM, Wei SH, et al. Solitary colorectal liver metastasis: resection determines outcome. Arch Surg. 2006;141(5):460-6; discussion 6-7.

58. Oshowo A, Gillams A, Harrison E, Lees WR, Taylor I. Comparison of resection and radiofrequency ablation for treatment of solitary colorectal liver metastases. Br J Surg. 2003;90(10):1240-3.

59. Scaife CL, Curley SA, Izzo F, Marra P, Delrio P, Daniele B. Feasibility of adjuvant hepatic arterial infusion of chemotherapy after radiofrequency ablation with or without resection in patients with hepatic metastases from colorectal cancer. Ann Surg Oncol. 2003;10:348-54.

60. Abdalla EK, Vauthey JN, Ellis LM, Ellis V, Pollock R, Broglio KR, et al. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. Ann Surg. 2004;239(6):818-25; discussion 25-7.

61. Kornprat P, Jarnagin WR, DeMatteo RP, Fong Y, Blumgart LH, D'Angelica M. Role of intraoperative thermoablation combined with resection in the treatment of hepatic metastasis from colorectal cancer. Arch Surg. 2007;142(11):1087-92.

62. Berber E, Pelley R, Siperstein AE. Predictors of survival after radiofrequency thermal ablation of colorectal cancer metastases to the liver: a prospective study. J Clin Oncol. 2005;23(7):1358-64.

63. Gillams AR, Lees WR. Five-year survival in 309 patients with colorectal liver metastases treated with radiofrequency ablation. Eur Radiol. 2009;19(5):1206-13.

64. Gillams AR, Lees WR. Radio-frequency ablation of colorectal liver metastases in 167 patients. Eur Radiol. 2004;14(12):2261-7.

65. Sorensen SM, Mortensen FV, Nielsen DT. Radiofrequency ablation of colorectal liver metastases: long-term survival. Acta Radiol. 2007;48(3):253-8.

66. Solbiati L, Livraghi T, Goldberg SN, Ierace T, Meloni F, Dellanoce M, et al. Percutaneous radio-frequency ablation of hepatic metastases from colorectal cancer: long-term results in 117 patients. Radiology. 2001;221(1):159-66.

67. Siperstein AE, Berber E, Ballem N, Parikh RT. Survival after radiofrequency ablation of colorectal liver metastases: 10-year experience. Ann Surg. 2007;246(4):559-65; discussion 65-7.

68. Wells GA, Shea BJ, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses. 2014 [cited 2014 Jul 29]; Available from: http: //www.ohri.ca/programs/clinical_epidemiology/oxford.htm.

69. Peng ZW, Zhang YJ, Liang HH, Lin XJ, Guo RP, Chen MS. Recurrent hepatocellular carcinoma treated with sequential transcatheter arterial chemoembolization and RF ablation versus RF ablation alone: a prospective randomized trial. Radiology. 2012;262(2):689-700.

70. Wang JH, Wang CC, Hung CH, Chen CL, Lu SN. Survival comparison between surgical resection and radiofrequency ablation for patients in BCLC very early/early stage hepatocellular carcinoma. J Hepatol. 2012;56(2):412-8.

71. Hung HH, Chiou YY, Hsia CY, Su CW, Chou YH, Chiang JH, et al. Survival rates are comparable after radiofrequency ablation or surgery in patients with small hepatocellular carcinomas. Clin GastroenterolHepatol. 2011;9(1):79-86.

72. Takayama T, Makuuchi M, Hasegawa K. Single HCC smaller than 2 centimetres: surgery or ablation?: surgeon's perspective. J Hepatobiliary Pancreat Sci. 2010;17(4):422-4.

73. Hiraoka A, Horiike N, Yamashita Y, Koizumi Y, Doi K, Yamamoto Y, et al. Efficacy of radiofrequency ablation therapy compared to surgical resection in 164 patients in Japan with single hepatocellular carcinoma smaller than 3 centimetres, along with report of complications. Hepatogastroenterology. 2008;55(88):2171-4.

74. Ueno S, Sakoda M, Kubo F, Hiwatashi K, Tateno T, Baba Y, et al. Surgical resection versus radiofrequency ablation for small hepatocellular carcinomas within the Milan criteria. J Hepatobiliary Pancreat Surg. 2009;16(3):359-66.

75. Nishikawa H, Inuzuka T, Takeda H, Nakajima J, Matsuda F, Sakamoto A, et al. Comparison of percutaneous radiofrequency thermal ablation and surgical resection for small hepatocellular carcinoma. BMC Gastroenterol. 2011;11:143.

76. Guglielmi A, Ruzzenente A, Valdegamberi A, Pachera S, Campagnaro T, D'Onofrio M, et al. Radiofrequency ablation versus surgical resection for the treatment of hepatocellular carcinoma in cirrhosis. J Gastrointest Surg. 2008;12(1):192-8.

77. Vivarelli M, Guglielmi A, Ruzzenente A, Cucchetti A, Bellusci R, Cordiano C, et al. Surgical resection versus percutaneous radiofrequency ablation in the treatment of hepatocellular carcinoma on cirrhotic liver. Ann Surg. 2004;240(1):102-7.

78. Lupo L, Gallerani A, Panzera P, Tandoi F, Palma G, Memeo V. Randomized clinical trial of radiofrequency-assisted versus clamp-crushing liver resection. Br J Surg [Internet]. 2007; 94(3):[287-91 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/727/CN-00578727/frame.html.