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Interventional Oncology in the Management of Metastatic Colorectal Cancer

Ieva Kurilova

Interventional Oncology in the Management of Metastatic Colorectal Cancer

PROEFSCHRIFT

Ter verkrijging van de graad van doctor aan de Universiteit Maastricht,
Op gezag van de Rector Magnificus, Prof. Dr. Rianne M. Letschert
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Ieva Kurilova

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General introduction and
outline for the thesis

INTRODUCTION

It is estimated that at least 1 in 25 people will be diagnosed with colorectal cancer (CRC) at some point during their lifetime [1]. In the past decades minimally invasive approaches have increasingly been adopted as part of the spectrum of treatment options for metastatic CRC. These therapies aim to achieve complete tumor eradication or local control of the metastatic lesions with limited morbidity.

Interventional oncology (IO) has established itself as a pillar in the armamentarium of minimal invasive therapies alongside with surgery and radiation therapy [2]. As a result, there is an international consensus, that interventional radiologists should be standing members of institutional CRC tumor boards and of dedicated guideline bodies such as the National Comprehensive Cancer Network [3]. There is evidence that the utilization of interventional therapies can increase the overall survival of CRC patients [4, 5].

IO has multiple advantages compared to other local and loco-regional therapies for metastatic CRC. Compared to surgical resection, IO procedures carry lower morbidity and mortality rates, less direct economic costs and shorter hospitalization stay [6-8]. Compared to radiation oncology, IO procedures are generally less expensive; do not require multiple treatment sessions or treatment effective dose modification to spare healthy tissues at risk in case of unfavorable tumor location [9]. While systemic therapies remain the mainstay in treatment of metastatic CRC, they very rarely result in complete tumor eradication or cure. IO techniques have potential to prolong patient's survival by eradicating total tumor load without systemic toxicity. IO treatments can be used as a single treatment or combined with systemic therapies to further improve disease-free and overall survival.

In CRC patients with oligometastatic disease IO treatment is specifically useful in those patients, who not amenable to resection and those at risk for subsequent recurrences and the need for additional local treatments. Oligometastatic disease is defined as small volume disease, localized to a few sites - usually up to 2-3 organs with up to 5 distinct tumors [10]. While small volume oligometastatic CRC is potentially curable and local control can be obtained with potentially curative interventional treatments such as tumor ablation [11], patients with more advanced metastatic disease and substantial liver-confined tumor load may also benefit better from liver directed, IO intra-arterial therapies.

Image-guided percutaneous procedures are available for different stages of metastatic disease (early, intermediate or advanced/chemorefractory) as well as in different

treatment settings (monotherapy, neoadjuvant, adjuvant and salvage setting) [12-20].

Thermal ablation is the most common percutaneous image guided ablative technique for oligometastatic CRC [4,5,21-25]. Thermal ablation utilizes extreme hyperthermia (>60 °C) or hypothermia (< -40°C) delivered via needles which directly target the tumor aiming to achieve complete tumor cell death [26]. There are several techniques available, radiofrequency (RFA) [27-32], microwave (MWA) [33-36], laser ablations [37-39], high intensity focused ultrasound (HIFU) [40] and cryoablation [41], with each technique having its specific indications. RFA and MWA are the most widely adopted techniques in metastatic CRC [42].

Radioembolization is a form of intra-arterial brachytherapy where tiny microspheres (20-60 µm in size) impregnated with radioactive isotope (most commonly yttrium-90, ⁹⁰Y) are permanently injected in the tumor-feeding blood vessels emitting high doses of radiation for the following two weeks. Radioembolization is mostly used in the advanced and chemorefractory stage of CRC metastatic disease. Several studies showed safety and efficiency of this therapy in controlling the liver disease with response rates usually over 40% (ranging from 10 to 55%) [43], that are at the higher end of spectrum of response amongst therapeutic options for the patients with advanced and chemorefractory stage of disease.

Despite multiple advantages in the field of local and locoregional therapies the relatively high local tumor progression rates in general remain a significant problem for interventional therapies too. In routine practice the proper sequence of locoregional therapies pose a daily challenge in terms of maximizing oncologic benefits and minimizing toxicity. In the era of precision medicine and more minimal invasive treatment strategies the use of IO therapies in CRC subtypes require further investigation.

The gap of knowledge

The selection of the appropriate patients that can benefit from minimally invasive therapies is critical in order to maximize the oncologic benefits and minimize risks. Several factors have been identified as predictors of outcome, including tumor size and genetic markers. Although most of these factors are non-modifiable, some can guide technique modification. For example in KRAS-mutant CRC patients with liver metastases the minimal ablation margin needs be larger in order to achieve reasonable local control than what is needed in KRAS wild-type tumors [44-46].

Major complication rates following liver thermal ablation are generally lower than those

encountered after liver resection, with reported ranges of 4-33% for radiofrequency and 0-19% for microwave ablations [37,47]. However there is only limited data available on the risk factors that may predispose to complications. Such data might help to personalize treatment.

Radioembolization in chemorefractory patients, performed in salvage setting, has the goal to prolong patients' life. Historical survival at this stage of disease is 5 months, with systemic treatment offering 6 weeks survival benefit [48,49]. Median survival after ^{90}Y radiomebolization ranges around 9-12 months [50]. Despite the fact, that such overall survival may seem modest, it still far exceeds overall survival following best supportive care or that achieved with FDA-approved systemic treatments (lonsurf and regorafenib) [51-53]. It is unknown whether combining the FDA-approved agents with ^{90}Y radioembolization could further improve survival in this advanced disease stage and this is an area of much needed future investigations.

One of the severe complications of radioembolization is gastrointestinal ulceration. Although this is extremely rare with incidence less than 2% in most series that have applied proper preparatory arteriography and $^{99\text{m}}\text{Tc}$ macroaggregated albumin mapping [54], non-target delivery has been reported in 0-20% of procedures with a median incidence of 8% when using advanced antireflux protective techniques [55]. Clearly, there is room to improve safety and patient selection in order to identify the patients who will truly benefit from this salvage treatment the most avoiding unnecessary morbidity.

In addition, there is limited data available about treatment of the patients with metastatic disease and limited curative treatment options, such as those who are not amenable for resection or thermal ablation. ^{90}Y radiation segmentectomy is an emerging radioembolization approach, intended for selective delivery of an ablative radiation dose to achieve complete tumor eradication. However, to date the data about radiation segmentectomy outcomes in the patients with metastatic disease is very scarce and requires further investigation.

The aim of this thesis is to identify predictive factors in order to improve safety and outcomes of image guided, thermal ablative and radioembolization therapies in patients with liver and lung metastases from CRC.

The two main study aims are:

- a. Define the factors that can predict local tumor control while minimizing the incidence of complications in patients with hepatic and pulmonary CRC metastases managed with thermal ablation;

- b. Create a predictive nomogram to improve selection of the patients with refractory CRC liver metastases for ^{90}Y radioembolization and to assess ^{90}Y radiation segmentectomy outcomes.

OUTLINE OF THIS THESIS

Chapter 2. *Liver-directed and Systemic Therapies for Colorectal Cancer Liver Metastases*

This literature review provided an overview on the role of different local and systemic therapies to treat metastatic CRC in the liver, including IO therapies. It also overviewed new treatment modalities on the pipeline and key driving mutations which are important for better patient selection.

Chapter 3. *Factors Associated with Local Tumor Control and Complications after Thermal Ablation for Colorectal Cancer Liver Metastases: a 15-year Retrospective Cohort Study*

This study was conducted to analyze the incidence of local tumor progression as well as complications following thermal ablation of colorectal liver metastases and to identify potential predictive factors.

Chapter 4. *Factors Affecting Oncologic Outcomes of ^{90}Y Radioembolization of Heavily Pre-Treated Patients with Colon Cancer Liver Metastases*

The aim of this study was to analyze metabolic, anatomic, laboratory, pathologic, primary disease-related and genetic biomarkers, procedure-related factors as well as pre- and post-radioembolization therapies, that can be associated with liver progression-free and overall survivals. In addition, our goal was to create and internally validate a 1-year overall survival prognostic nomogram using pre-treatment patient characteristics.

Chapter 5. *^{90}Y Resin Microspheres Radioembolization for Colon Cancer Liver Metastases Using Full-Strength Contrast Material*

This work was undertaken to specifically address the safety and efficacy of radioembolization with ^{90}Y resin microspheres for CRC liver metastases using undiluted non-ionic contrast material in both "B" and "D" infusion lines for real-time microspheres infusion monitoring.

Since neither the ^{90}Y microspheres, nor the vehicle used during this infusion are radiopaque, the standard sandwich infusion technique does not allow continuous

monitoring of the microsphere flow toward the target tumor. This limits the ability to detect microspheres' stasis or reflux, which can result in non-target delivery with unnecessary toxicity, as well as diminished radioactivity reaching the target tumor. This modified infusion technique can potentially decrease incidence of stasis, reflux and non-target delivery.

Chapter 6. Radiation Segmentectomy of Hepatic Metastases with ^{90}Y Glass-Based Microspheres: Technical Considerations, Correlations to Dosimetry and Preliminary Results

The aim of this study was to evaluate safety and efficacy of ablative-dose radiation segmentectomy with ^{90}Y glass-based microspheres in patients with limited metastatic liver disease not amenable to surgery or percutaneous ablation.

Chapter 7. Image-Guided Thermal Ablation for the Treatment of Pulmonary Malignancies

This literature review focused on reviewing a variety of image-guided thermal ablation techniques for patients with oligometastatic lung disease and non-small cell lung carcinoma.

Chapter 8. Microwave Ablation in the Management of Colorectal Cancer Pulmonary Metastases

Thermal ablation has shown safety and efficacy in the treatment of secondary lung malignancies in non-surgical candidates. However, local progression remains a limitation for these therapies.

This study assessed oncologic outcomes and complications of MW ablation in the management of patients with colorectal pulmonary metastases as well as factors affecting these outcomes.

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PART 1

Management of Colorectal
Liver Metastases
In Interventional
Oncology Setting

Liver-directed and Systemic Therapies for Colorectal Cancer Liver Metastases

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**Joint co-authors due to equal contribution to this work*

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EPIDEMIOLOGY, PREDISPOSING FACTOR AND PATHOLOGY

Colorectal cancer (CRC) is the third most common cancer worldwide, resulting in an estimated 140,250 new cases and 50,630 deaths in 2018 [1,2]. Liver is the most common visceral metastatic site due to the portal venous drainage from the colon. About 15% of patients present with synchronous liver metastases at initial diagnosis, which is an independent poor prognostic factor [3]. Approximately 50% of patients ultimately develop liver metastasis during the course of the disease.

The risk factors for CRC are classified to *non-modifiable* (age, family history, hereditary predisposition, inflammatory bowel disease and adenomatous polyp) and *modifiable* (diets, smoking, obesity and high alcohol consumption) [4].

Left-sided and right-sided CRCs harbor different clinical and biologic characteristics with different exposures to potential carcinogenic toxins and microbiota, which can potentially impact the prognosis. Right-sided primary CRCs are more likely to have genome-wide hypermethylation via the CpG island methylator phenotype (CIMP), hypermutated state via microsatellite instability, *BRAF* mutation [5], greater proportions of the “microsatellite unstable/immune” CMS1 and the “metabolic” CMS3 consensus molecular subtypes. Molecular tumor subtypes (different from primary tumor) have been defined for colorectal liver metastases (CLM) [6] and impact prognosis.

KRAS mutation is detected in 35-45% of CRCs and it is a strong negative *prognostic* biomarker (associated with more infiltrating/migratory characteristics of cancer cells [7]) and a negative *predictive* biomarker in terms of resistance to anti-EGFR treatment [8], higher incidence of positive and narrow margins at surgery [9] and worse oncologic outcomes after ablation of CLM [10,11]. BRAF-mutant cancers, comprising 10% of all CRCs, represent a distinct subset of CRC with its own clinical implications with regard to prognosis, treatments and emerging therapeutic strategies. BRAF-mutant CRCs tend to be microsatellite instable (MSI-high), mucinous histology, poorly differentiated, less likely to have metastatic disease amenable for surgical resection as well as poorer overall survival (OS) [12]. Approximately, 15-20 % of colorectal cancers display MSI with prognostic and therapeutic implications as these tumors are highly immunogenic and can be targeted with immunotherapy [13].

Main limitation of the studies, analyzing outcomes of CLM include heterogeneity in terms of prior therapies (treatment-naïve, patients after first-, second-, or subsequent treatment lines) and tumor subtypes.

Summary of the most important facts about liver-directed and systemic therapies for CLM is presented in **Tables 1A-B**.

Table 1A Liver-directed therapies for colorectal cancer liver metastases

10 most important points of the cancer	
1.	Colorectal cancer (CRC) is the third most common cancer worldwide. Liver is the most common metastatic site, with synchronous metastasis being an independent poor prognostic factor [3]
2.	Genetic molecular profiles not only have impact on prognosis, but also provide therapeutic values. KRAS mutation is detected in 35-45% of CRCs and it is a strong negative <i>prognostic</i> biomarker and <i>predictive</i> biomarker. BRAF-mutant cancers comprise 10% of all CRCs and associated with poorer overall survival
3.	Systemic chemotherapies are proven to have survival benefit in all clinical settings from postliver metastatectomy, converting unresectable liver metastasis to resectable to maintaining quality of life
4.	Cytotoxic chemotherapies remain the mainstream therapy for metastatic CRC, even in patients with resectable or amenable to ablation disease. Chemotherapy combined with resection or ablation of all metastatic sites significantly improve outcomes in this patient population [14]
5.	Treatment options for liver-only or dominant metastasis include surgical resection/ablation, loco-regional debulking interventions, systemic cytotoxic chemotherapy, intra-arterial pump chemotherapy, biological therapy as well as immunotherapy, with immune checkpoint inhibitors benefiting small percentage of patients whose tumor is MMR deficient
6.	When liver metastases are completely resected and/or ablated, long-term survival and potential cure could be achieved. Clinical Risk Score (CRS) and margins impact surgical outcomes and potential for cure [15, 16]
7.	Despite a relevantly high recurrence rate following resection and or ablation of liver metastases, ablation (with or without resection) of CLM in addition to chemotherapy prolongs patient survival [14]. Modified CRS impacts outcomes of ablation similarly to surgery. Ablation with margins over 10 mm offers the best local tumor control [17, 19]
8.	Intra-arterial therapies and in particular Y-90 radioembolization is recommended for CLM treatment in the salvage setting with liver disease progression while on or after second line chemotherapy with encouraging oncologic outcomes [20]
9.	Liver-directed chemotherapy through hepatic arterial pump demonstrated survival benefit in multiple clinical settings including adjuvant, neoadjuvant and metastatic
10.	Loco-regional interventions are also being combined with different systemic therapies to enhance anti-tumor effect and to facilitate drug delivery

Table 1B Liver-directed therapies for colorectal cancer liver metastases

5 most important numbers of the cancer	
1.	There are estimated 140,250 new cases of CRC, and 50,630 patients will die from CRC in 2018 in the USA
2.	15% patients present with synchronous liver metastases, 50% patients with CRC will ultimately develop liver metastasis
3.	Only around 15-20% of the patients with CLM are eligible for liver resection
4.	The recurrence rate following resection of liver metastases from CRC is in the order of 60-70%
5.	Up to 38% patients with initially unresectable liver metastases could have disease converted to surgically resectable after receiving proper therapy
3 major pivotal studies for the last 5 years	
1.	Ruers, T. <i>et al</i> . Local Treatment of Unresectable Colorectal Liver Metastases: Results of a Randomized Phase II Trial. <i>Journal of the National Cancer Institute</i> 109 , doi:10.1093/jnci/djx015 (2017)
2.	Groot Koerkamp B, Sadot E, Kemeny NE, et al. Perioperative hepatic arterial infusion pump chemotherapy is associated with longer survival after resection of colorectal liver metastases: a propensity score analysis of 2,368 consecutive patients. <i>J Clin Oncol</i> . 2017;35:1938–1944

Table 1B continued.

3 major pivotal studies for the last 5 years	
3.	Wasan HS, Gibbs P, Sharma NK, Taieb J, Heinemann V, Ricke J, et al. First-line selective internal radiotherapy plus chemotherapy versus chemotherapy alone in patients with liver metastases from colorectal cancer (FOXFIRE, SIRFLOX, and FOXFIRE-Global): a combined analysis of three multicentre, randomised, phase 3 trials. <i>The Lancet Oncology</i> . 2017;18(9):1159-71
2 messages about the cancer	
1.	All metastatic colorectal cancer with liver metastasis should be managed by multidisciplinary teams including medical oncologist, surgical oncologist, interventional radiologist as well as diagnostic radiologist
2.	All patients should be considered for clinical trials
1 prediction for the 5 future years	
Combination of loco-regional plus systemic therapies might be the leading approach in this patient population in an effort to prolong overall survival	

DIAGNOSIS AND INITIAL WORK-UP

Most primary CRCs are diagnosed through colonoscopy either through regular screening or due to symptoms such as change in bowel habits, GI bleeding (hematochezia, melena, occult blood loss and iron deficiency anemia) or abdominal pain. Some cases are diagnosed due to signs or symptoms caused by metastatic disease.

CRCs can spread by lymphatic and hematogenous dissemination, as well as contiguous and transperitoneal spread. The most common metastatic sites are regional lymph nodes, liver, lung and bones.

This article reviews management of CLM. The only potentially curative treatment option for CLM is surgical resection and/or complete ablation [15]. Recent advances in chemotherapy, surgical and interventional techniques allow a subset of initially unresectable CLMs to be downsized to resection or ablation. Thus precise assessment of the extent of disease is critical to determine the resectability. Several imaging modalities are used to identify CLM. Commonly used imaging modalities are ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), ¹⁸F-FDG PET/CT and more recently fully integrated ¹⁸F-FDG PET/MR. The utility of different imaging modalities is described in **Table 2**.

Our recommendation of working up CLMs is to start with CT chest/abdomen/pelvis with triphasic liver protocol. If the patient is potentially resectable, liver MRI should be the next step to further define the extent of disease to ensure a proper selection for surgery. ¹⁸F-FDG PET/CT is also advisable especially prior to resection or ablation of metastatic disease [26].

Table 2 Imaging modalities used for colorectal liver metastases (CLM) detection and follow-up

Imaging modality	Description
CT of the chest/ abdomen/ pelvis with triphasic liver protocol	It is the most commonly used imaging modality in diagnosis of both intrahepatic and extrahepatic metastases as well as post-treatment follow-up [21-23]; however, CT is not sensitive enough to detect lesions smaller than 1 cm
MRI with liver-specific contrast agents and diffusion-weighted imaging	It is more sensitive than CT for detecting smaller CLM, it is more often chosen by surgeons when planning metastatectomy [21-23]
¹⁸ F-FDG PET/CT imaging	It is not routinely used in CRC work-up, however, if CT or MRI detects suspicious but inconclusive abnormalities, ¹⁸ F-FDG PET/CT may be considered. It is recommended for restaging prior to resection or ablation of metastatic disease
¹⁸ F FDG PET/MRI imaging	It is gaining some popularity for its sensitivity and specificity in diagnosing CLMs [24], however it is not available in many institutions
Traditional ultrasound (US), contrast-enhanced ultrasound (CEUS), and intra-operative US	They all have a role in detecting CLM [25], especially useful for image-guided needle biopsy of CLM

APPROVED/RECOMMENDED TREATMENTS

Liver resection is considered to be a “gold standard” for CLM treatment, with median OS in liver resected patients of 28-46 months [27]. However, only 15%-20% of the patients are considered to be eligible for liver surgery [28, 29]. Patients with oligometastatic disease (OMD), located in anatomically favorable territory and low tumor burden may be considered to have upfront liver metastatectomy, followed by 6-months adjuvant therapy. National Comprehensive Cancer Network (NCCN) guidelines recommend surgery or ablation alone or in combination as long as all visible metastases can be eradicated [26].

When liver metastases are completely resected and/or ablated, long-term survival and potential cure could be achieved. In patients who can undergo liver resection followed by adjuvant systemic therapy plus HAI, 5-year OS as high as 78% can be achieved [30], which is significantly better than 5-year OS of the patients treated with chemotherapy-alone, which is around 10%. Clinical Risk Score (CRS) and margins impact surgical outcomes and potential for cure [15, 16].

Cytotoxic chemotherapies remain the mainstream therapy for metastatic CRC, even in patients with resectable or amenable to ablation disease. Chemotherapy combined with resection or ablation of all metastatic sites significantly improves outcomes in this patient population [14].

Adjuvant therapies after CLM resection

Adjuvant therapy options following liver resection include systemic chemotherapy with FOLFOX or 5-FU/LV [31] and hepatic arterial infusion chemotherapy (HAI) with floxuridine (FUDR) alone or in combination with systemic chemotherapy in certain institutions.

HAI FUDR demonstrated liver progression-free survival (PFS) and OS benefit, based on four randomized trials in the adjuvant setting [32-35] (*please see Supplement 1 for detailed HAI data*). NCCN guidelines conclude that HAI infusion with or without systemic chemotherapy is an option as adjuvant or peri-operative therapy in the setting of liver metastasectomy. In addition to FUDR, several other chemotherapeutic agents can be administered through HAI, including 5-FU, mitomycin, oxaliplatin and irinotecan [36-38]. However, due to the complexity of hepatic pump placement, management of HAI pump and administration of chemotherapy via HAI, this approach has only been utilized in certain institutions with relevant expertise.

Neoadjuvant conversion therapy

Among patients with CLM, up to 30% of initially unresectable patients could have disease converted to surgically resectable after receiving systemic therapy. The options of conversion therapy are as follows:

Systemic conversion therapies include the following:

- *FOLFOX or CAPOX +/- bevacizumab*: for the patients without prior oxaliplatin exposure [39-41]. Bevacizumab has modest benefit when in combination of FOLFOX or XELOX in the peri-operative setting but with potential complications such as arterial thromboembolic events, hemorrhage, delayed wound healing, gastrointestinal perforation, biliary complications, or severe hypertension. Its use in the peri-operative setting requires caution; in general, it is recommended avoiding bevacizumab 4 weeks before and after invasive operations [41].
- *FOLFIRI +/- cetuximab or panitumumab*: for the patients with prior oxaliplatin as adjuvant therapy, left sided primary cancer and wild-type KRAS [42-44];
- *FOLFOXIRI +/- bevacizumab*. This regimen is generally used in younger, healthier patients; thus the patients with high tumor burden, risk of chemotherapy-related toxicity should be under consideration when choosing this regimen. This regimen was associated with conversion rate of up to 40% with significantly prolonged OS [45-48].

Locoregional therapies include the following:

- HAI therapy alone or with systemic chemotherapy. HAI with FUDR plus systemic chemotherapy (FOLFOX, FOLFIRI) as conversion therapy resulted in CLM resectability in nearly 50% of the patients [49, 50].
- Neoadjuvant ⁹⁰Y radiation lobectomy [51] or transarterial chemoembolization with drug-eluting beads (DEBIRI-TACE) [52].

Unresectable CLMs

If complete resection /ablation of CLM is not feasible or patients are not fit surgical candidates, other locoregional therapies, such as HAI, percutaneous ablation, chemoembolization, radioembolization (RE), and radiation therapy (RT), including stereotactic body RT (SBRT) can all be considered for the patients with OMD. Also, in selected patients percutaneous ablation within the “test of time” concept maybe preferable to surgery as the initial local cure while observing the disease biology in potentially resectable patients. In the event of local failure in the ablation site, in patients without multifocal progression during the follow - up period surgery remains a subsequent option. “Test of time” allows expression of disease biology and can spare patients with aggressive tumor biology the morbidity of a non-beneficial surgery [53]. Percutaneous ablation can also be useful for disease control without systemic chemotherapy administration in selected patients, allowing for “chemotherapy holiday”.

Systemic palliative therapies

For this category, goals of therapy focus on palliative and non-curative measures with expectation of maintaining quality of life and potentially prolonging OS. Many combinations are available, consisting of cytotoxic chemotherapeutic agents including irinotecan, oxaliplatin, capecitabine; monoclonal antibodies targeting VEGF and EGFR pathways such as bevacizumab, ramucirumab, cetuximab, panitumumab; tyrosine kinase inhibitor regorafenib, recombinant fusion protein aflibercept, and trifluridine-tipiracil, as well as immunotherapy. Overall principle is to expose patients to all active agents sequentially if they can tolerate. Enrollment in a clinical trial is always recommended in this setting.

First-line and beyond first line palliative locoregional and systemic treatment options for the patients with CLM are described in **Table 3**.

Table 3 Palliative treatment options for the patients with colorectal liver metastases, adopted from several current guidelines. TACE- transarterial chemoembolization, TARE- transarterial radioembolization

Treatment regimen	Description
First line systemic palliative chemotherapy options	
FOLFOX and FOLFIRI +/- bevacizumab or cetuximab [54, 55]	Left-sided wild-type KRAS colorectal cancer (CRC) patients have significant survival benefit from cetuximab, while right-sided CRC patients have survival benefit from bevacizumab [56] Combining both anti-VEGF and anti-EGFR agents is not recommended due to poorer outcome [57,58].
FOLFOX or FOLFIRI + panitumumab	For the patients with RAS wild-type tumor [59, 60]
S-1 plus oxaliplatin or irinotecan	S-1 is only used in selected countries, such as Japan and Korea [61, 62]
FOLFIRINOX or FOLFOXIRI	This regimen is used only in selected younger patients with high tumor burden and RAS or BRAF mutation
HAI with FUdR or in combination with FU/LV, FOLFOX or FOLFIRI	For patients with unresectable liver metastasis [49, 50]
Beyond first line systemic chemotherapy options	
Irinotecan-based chemotherapy	For patients received oxaliplatin based initial therapy, irinotecan-based chemotherapy is considered to be the next treatment choice. The following regimens are recommended: FOLFIRI FOLFIRI + bevacizumab (for patients with tumor bearing RAS mutation) FOLFIRI + cetuximab/ panitumumab (for patients with RAS wild-type tumor) FOLFIRI with intravenous aflibercept [63, 64] FOLFIRI with ramucirumab [65]
Oxaliplatin-based chemotherapy	For patients received irinotecan-based initial therapy, changing to oxaliplatin-based chemotherapy with or without biological agents depending on RAS mutational status would be reasonable For RAS wild-type, anti-EGFR therapy would be appropriate, anti-VEGF agent can be also be considered, although only anti-VEGF agent would be indicated if RAS mutations present
Regorafenib or trifluridine-tipiracil	For the patients who have received and failed both oxaliplatin- and irinotecan-based be offered for additional therapy based on performance status and organ functions, we suggest single agent regorafenib or trifluridine-tipiracil [66, 67]
HAI therapy	HAI therapy remains effective treatment for patients who had prior systemic chemotherapy exposure [49, 50, 68]
Immunotherapy (in selective patients)	Mismatch repair protein (MMR) deficient or MSI-high tumors may benefit from check point inhibitors Patients with MMR-deficient metastatic CRC had a 50% objective response rate (ORR) and a 89% disease control rate (DCR) when treated with pembrolizumab, while in contrast, the ORR and DCR were 0 and 16% respectively in MMR-proficient mCRC [69, 70] Similar results were also seen in CheckMate-142, in which patients received nivolumab with or without ipilimumab. Significantly higher ORR and PFS were demonstrated in MMR-deficient mCRC [71]
Reutilizing the regimen initially used in the treatment sequence	During the often lengthy phase of sequential therapy, tumors may regain sensitivity to the previously used agents.
Locoregional treatment options	
HAI therapy	For liver-dominant metastatic CRC (early stage multifocal liver-only disease)
TACE, TARE	For liver-dominant metastatic CRC (late stages multifocal liver-only disease)

ROLE OF INTERVENTIONAL ONCOLOGY /RADIOLOGY (IO/IR)

The main focus of IO/IR in metastatic CRC (mCRC) is OMD. It is characterized by disease localization to a few sites and tumors allowing the option to use local and ablative treatments (LAT) aiming to improve disease control and therefore clinical outcome in these patients [72]. Although the mortality of CRC patients has dramatically decreased in the last 20 years following the introduction of new systemic treatments, the management of mCRC remains a major challenge with surgical resection and ablation being the only potentially curative options.

IO/IR plays an important role in the management of mCRC from disease diagnosis through tissue sampling, treatment of unresectable OMD, bridging potentially resectable patients or treating chemorefractory metastatic disease in the salvage setting [73] to palliation. Therefore, there is a strong international consensus that the interventional oncologist/radiologist should be a standing member of the institutional tumor board [74].

Most frequent clinical scenarios for LAT include the following:

Neoadjuvant setting. In this setting LAT can be used as:

- Potentially curative treatment for unresectable patients with limited metastatic tumor burden;
- Induction therapy in order to downsize tumor in potentially resectable patients [52];
- Percutaneous ablation can be applied within the “test of time” concept, when it is used instead of surgery in order to observe the disease biology in potentially resectable patients [53].

Adjuvant setting. In this setting LAT can be used for:

- Combination with first-line chemotherapy in carefully selected patients [52, 75];
- Treatment of CLM by means of combined percutaneous and endovascular therapies [76-80];
- Induction of distant tumor response by combining LAT with immunotherapy;
- Disease control without systemic chemotherapy administration in selected patients, allowing for “chemotherapy holiday”.

Salvage setting: for chemorefractory patients with a goal to improve disease control and OS with minimal impact on the quality of life [81].

Percutaneous ablative techniques

Percutaneous ablative techniques include a wide range of modalities, which are divided into two groups:

- Thermal modalities (heat- and cold-based). They include radiofrequency (RFA) [82-87], microwave (MWA) [17, 88-90], cryoablation [91], laser ablation [92-94] and high intensity focused ultrasound [95];
- Non-thermal modality, which include irreversible electroporation [96-98].

RFA is the most extensively studied ablation modality with multiple larger retrospective case matched comparisons as well as meta-analyses available, comparing RFA to surgical resection or using RFA in addition to systemic chemotherapy [14, 99-104].

For treatment of CLM, hepatocellular carcinoma algorithm of the West and Japan is often applied, which recommends RFA for < 3 cm liver metastases in unresectable patients with ≤ 3 tumors [105-107]. However, for CLM the lesion number is not an absolute limiting factor for RFA, if successful treatment of all metastases can be accomplished, with most centers preferentially treating patients with ≤ 5 lesions. Several studies demonstrated highest rates of complete tumor destruction with RFA for lesions of ≤ 3 cm [108-110], with oncological outcomes similar to surgical resection [18, 108, 111-114].

Recent thermal ablation literature focuses on improving the relatively high local tumor recurrence rates (2%-60%) [17, 86, 115-117]. This can be achieved by creating sufficient (ideally >10 mm) minimal ablation margins ("Ao ablation" concept) [17, 118], incorporating metabolic image-guidance for tumor ablation by means of ^{18}F FDG-PET [119] as well as stratifying the patients based on modified clinical risk scores and genetic mutation profile, such as KRAS mutation [11, 18, 19, 86, 118, 120]. Essentially ablation with margins of >10 mm are associated with few if any local failures [17, 18]. Similarly ablation margins of > 5 mm with immediate post-ablation zone center and margin biopsy confirming complete tumor necrosis offered over 97% local progression-free survival 30 months post-RFA [19].

The CLOCC trial is extremely important as it the only randomized-controlled trial (RCT), providing the evidence of OS advantage when using LAT (by means of RFA) in combination with systemic chemotherapy vs. systemic chemotherapy alone, with OS at 8 years of 36% and 8%, respectively [14, 102]. However, due to trial's limitations, new multicenter prospective COLLISION trial has been initiated, comparing thermal ablation (TA) and liver resection outcomes for CLM [121]. The main hypothesis is that TA might enable to achieve similar local tumor control and OS rates to surgical resection while reducing

morbidity, mortality, direct economic costs, hospitalization days and improving quality of life [121]. Achieving similar local tumor control and OS with TA compared to surgery, will further establish the terms "resectable" and "ablatable" as synonyms.

The outcomes following RFA and MWA in term of safety and toxicity are comparable. Although there is data on MWA superiority than RFA for CLM [122], when stratified by margin size there was no difference in local tumor progression-free survival [17] with no local tumor progression for tumors ablated with margins > 10 mm. The latest generation MWA systems offer technical advantages such as greater intra-tumoral temperature, deeper penetration of energy, propagation across the poorly conductive tissues, less sensitivity to the heat-sink effect, and larger ablation volume, enabling to treat larger tumors with adequate safety margin when compared to RFA [123-125].

Endovascular approaches

While ablation and resection are the only potentially curative options for mCRC, only around 20% of CLM patients are eligible for these treatments. Endovascular approaches, such as transarterial chemoembolization (TACE) [126-132] and ^{90}Y radioembolization (RE) [26, 75, 133-141] demonstrated improvement in OS and quality of life in chemorefractory CLM.

RE

^{90}Y RE is an FDA approved liver brachytherapy, recommended through the NCCN and the ESMO guidelines for the treatment of CLM in the salvage setting with liver disease progression while on or after second line chemotherapy with encouraging oncologic outcomes [26, 72, 75, 133, 136, 137, 142-153]. It is also used to treat unresectable non-colorectal liver metastases [154-156]. However, when the patients present to the RE in salvage setting with advanced tumor load, unfavorable biological tumor characteristics and comorbidities, the range of outcomes post-RE is highly variable, with objective response rates varying between 10%-48% when RE is applied in the third and subsequent chemotherapy regiment setting [146, 152, 157, 158].

The main effect of RE is attributed to radiation as it has a minimal embolic effect. Three types of particles are currently being used for RE: ^{90}Y microspheres (resin or glass-based) and ^{166}Ho microspheres.

^{90}Y microspheres are the most commonly used microspheres for RE. ^{90}Y is β -emitter, with 96% of radiation delivered within 12 days in the tumor, with up to 1-cm penetration depth

around each microsphere, enabling to achieve treatment margins around the tumor, similarly to surgical resection or thermal ablation [159].

Physical properties of glass-based and resin microspheres are different due to the size and number of the particles required to deliver the same radiation dose. RE with resin microspheres enables to deliver higher number of microspheres with potentially more homogeneous tumor coverage with a risk of embolic effect and stasis prior to total dose delivery [133, 160, 161]. ⁹⁰Y microspheres are not radiopaque, making real-time infusion monitoring challenging. Modified infusion methods using diluted or undiluted contrast medium have been explored with resin microspheres and resulted in decrease incidence of stasis as well as fluoroscopy time [153, 162]. No substantial difference between the oncological outcomes when using resin or glass microspheres for CLM have been shown [20].

¹⁶⁶Ho microspheres emit γ-radiation and are paramagnetic, thus they are getting increased attention due to facilitated imaging with MRI, enabling real-time infusion and tumor coverage monitoring [163]. In addition, ¹⁶⁶Ho microspheres scout dose is used for treatment planning, enabling more accurate prediction of intra- and extrahepatic distribution of radiation activity. The differences between the RE particles are summarized in the **Table 4**.

Although recent RCT failed to demonstrate the OS benefit of combination of RE with systemic chemotherapy compared with systemic chemotherapy alone in the first-line CLM treatment setting [164], subset of the patients with right-sided CRC showed OS advantage from this combinational treatment [165]. This is very important as the patients with right-sided CRC have less treatment options available than the left-sided CRC. Further investigation is of course needed to further assess this preliminary finding prior to its acceptance as a standard of care recommended in guidelines.

TACE

The objective of TACE is to generate a hypoxic/ischemic environment as well as to synergistically induce chemotherapeutic tumor destruction. TACE showed promising results for patients progressing on irinotecan-based systemic chemotherapy. TACE is usually applied to treat unresectable CLM in chemorefractory setting [72]. The data on 2nd and 3rd line TACE is collected from RCT [130] as well as from observational studies demonstrating wide variation of response (35-85%) and median OS of 13.3-37 months [166], which compares favorably to other standard of care therapies for CLM.

Table 4 Comparison of ⁹⁰Y (resin and glass-based) and ¹⁶⁶Ho microspheres for radioembolization

	SIR-Spheres™	Therasphere™	QuiremSpheres™
Matrix	Resin	Glass	PLLA
Diameter	20-60µm (mean 32 µm)	25 µm	30 µm
Isotope		Yttrium-90	Holmium-166
T 1/2		64.5 hours	26.8 hours
Density	1.6 g/cm ³	3.4 g/cm ³	1.4 g/cm ³
Number of spheres	33-50 mln	4 mln	33 mln
Amount per dose	900-1370 mg	110 mg	600 mg
Activity per sphere	50 Bq	1250-2500 Bq	200-400 Bq
Activity per dose	2-3 GBq	5-15 GBq	6-12 GBq
Imaging	Y-90 PET or Bremsstrahlung SPECT/CT		SPECT/MRI/CT
Test dose	99m Tc-MAA		Ho-spheres/Tc-MAA
Company	Sirtex Medical Limited, NSW, Australia	BTG, London, UK	Terumo, Nijmegen, NL
Year of creation	1974	1989	1994
CE trade mark	2002	1999	2014
FDA indications	Unresectable colorectal liver metastases in combination with intrahepatic floxuridine	Humanitarian device exemption for unresectable HCC	Unresectable colorectal liver metastases
Activity calculation	BSA, partition model	MIRD-based approach	Two-compartment-based dosimetry

DEBIRI-TACE [52] have been imposed as a novel drug-delivery vehicle allowing for higher concentrations of drugs (irinotecan) within the target tumor and lower systemic concentrations compared with conventional TACE (cTACE) [167]. cTACE is usually administered selectively/sub-selectively, whereas DEBIRI-TACE is commonly administered in the lobar fashion due to the fact, that irinotecan is a prodrug, activated by normal liver parenchyma, enabling to treat potentially occult liver lesions.

DEBIRI-TACE has been also explored for endovascular induction (neoadjuvant therapy) to target resectable CLM in PARAGON II study, with demonstrated low morbidity and 77% major response rate on pathology [168]. Radiopaque DC Bead LUMI™ beads (BTG plc, United States), loaded with irinotecan, are the first radiopaque beads, which have been recently approved for CLM treatment, enabling to achieve much more precision for targeting, visualization of tumor coverage and defining the endpoints [169, 170]. To date, there is very limited evidence for bland embolization in CLM.

NEW IR TREATMENTS ON THE PIPELINE AND POSSIBLE MOLECULAR DRIVERS

New IR treatments on the pipeline, including treatment of earlier stage metastatic disease, combinational LAT therapies, ablative dose RE as well as combination of immunotherapy and LAT are described in detail in **Supplement 2**.

Shift of the research scope in mCRC

At the time of OMD term introduction (2016), the main focus of IO/IR has been integration of new LATs, such as RFA, MWA, irreversible electroporation, RE and (chemo-) embolization, into mCRC treatment guidelines, improvement of techniques efficacy, identification of prognostic factors and multidisciplinary [72]. LAT were administered for OMD patients with curative or palliative intents [72].

However, since the year 2018, main research focus has been shifted to mCRC molecular determination, identification of the patients with curable OMD based on RNA analysis, exploration of tumor-stromal interaction as well as systemic effects following LAT and immunomodulation to induce abscopal effect (non-targeted tumor response) [171]. Also, mCRC OMD treatment concept has been modified, with recommendation to administer LAT with cytoreduction and curative intent to allow for “chance for cure” [171].

Identification of curable mCRC for better patient selection

It is crucial to be able to distinguish patients with potentially curable OMD from patients whose OMD is a part of a large cascade of widespread disease. This is very important as patients with new lesions following LAT of mCRC have been shown to have a poor prognosis. Prognostication strategies of CLM patients, based on RNA analysis, have been developed, indentifying three distinct CLM similarity network fusion subtypes (SNFs) with unique patterns of mRNA and miRNA expression as well as with distinct histological and genetic features and prognosis, which could help to identify OMD patients with potentially curable disease [6]. Further investigation is needed to define to what extent these concepts apply to patients undergoing LAT and, more generally, to patients with more widespread disease.

Key mutations in LAT for mCRC

Most explored prognostic genetic signatures include in LAT for mCRC include KRAS and PI3K mutations. KRAS mutation was found to be an independent prognostic factor of poor outcomes following ⁹⁰Y RE [172, 173] and thermal ablation of CLM [10, 11, 174]. Concordant data indicate that a minimum ablation margin of > 10 mm is recommended

when ablating KRAS mutant CLM [174]. A minimal margin under 5 mm in KRAS mutant CLM carries 16.8 times the risk of local failure when compared to wild-type CLM ablated with MM over 10 mm. PI3K mutation was found to be associated with longer liver progression-free survival following ⁹⁰Y RE of CLM [138].

Artificial intelligence (AI) in IR

AI has the potential to improve mCRC patient outcomes following LAT by improving patient selection and response assessment via the identification of imaging features associated with oncological outcomes. Texture analysis has demonstrated its utility in the assessment of response to RE for CLM, allowing for the detection of disease progression, on average, 3.5 months before it was visible on RECIST 1.1 [175].

Also, AI has a potential to improve catheter navigation, ablation probe placement, imaging registration and estimation of ablation margins [176].

Conclusion

In conclusion, there is expanding evidence regarding the value of LAT to improve liver and overall progression-free survival in mCRC. Evidence regarding the effect of LAT on patient OS is lacking [14, 75]. At this time, prospective studies comparing different locoregional modalities or ablative modalities to surgery are limited and decision-making relies on limited data and a multidisciplinary decision making process. As IO techniques strive to take additional roles in the management of CLM, progress will ultimately be dependent on the ability to produce substantial prospective trial-based evidence.

SUGGESTED READINGS

Cancer Societies:

- Society of Interventional Oncology (SIO): <http://www.sio-central.org/>
- Society of Interventional Radiology (SIR): <https://www.sirweb.org/>
- Society of Cardiovascular and Interventional Radiology of Europe (CIRSE): <https://www.cirse.org/>
- European Society of Oncologic Imaging (ESOI): <http://www.esoi-society.org/>
- European Organization for Research and Treatment of Cancer (EORTC): <http://www.eortc.org/>
- European Society for Medical Oncology (ESMO): <https://www.esmo.org/>

Guidelines:

- European Society for Medical Oncology (ESMO) consensus guidelines for the management of patients with metastatic colorectal cancer [72];
- NCCN Clinical Practice Guidelines in Oncology for Colon Cancer [26];
- Image-guided tumor ablation: standardization of terminology and reporting criteria—a 10-year update [177];
- Quality Improvement Guidelines for Transarterial Chemoembolization and Embolization of Hepatic Malignancy [178];
- Radioembolization of Hepatic Malignancies: Background, Quality Improvement Guidelines, and Future Directions [179];
- Transcatheter Therapy for Hepatic Malignancy: Standardization of Terminology and Reporting Criteria Reporting Standards [180].

Publications:

Ruers, T. *et al.* Local Treatment of Unresectable Colorectal Liver Metastases: Results of a Randomized Phase II Trial. *Journal of the National Cancer Institute* **109**, doi:10.1093/jnci/djx015 (2017).

Wasan, H. S. *et al.* First-line selective internal radiotherapy plus chemotherapy versus chemotherapy alone in patients with liver metastases from colorectal cancer (FOXFIRE, SIRFLOX, and FOXFIRE-Global): a combined analysis of three multicentre, randomised, phase 3 trials. *The Lancet. Oncology* **18**, 1159-1171, doi:10.1016/s1470-2045(17)30457-6 (2017).

Pitroda, S. P. *et al.* Integrated molecular subtyping defines a curable oligometastatic state in colorectal liver metastasis. *Nature communications* **9**, 1793, doi:10.1038/s41467-018-04278-6 (2018).

Shady, W., *et al.*, Percutaneous Microwave versus Radiofrequency Ablation of Colorectal Liver Metastases: Ablation with Clear Margins (Ao) Provides the Best Local Tumor Control. *J Vasc Interv Radiol*, 2018. 29(2): p. 268-275.e1.

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SUPPLEMENTARY MATERIAL

Supplement 1 HAI therapy in the adjuvant, neoadjuvant and metastatic settings.

HAI therapy as adjuvant after liver metastatectomy

The MSKCC trial enrolled 156 patients after liver metastatectomy to receive six cycles (months) of HAI FUDR in combination with systemic chemotherapy of 5-FU/LV or systemic FU/LV alone. 2-year OS rate was significantly higher in HAI therapy, 86 vs. 72% ($p = 0.03$), so was liver-free recurrence rate (60 vs. 90% ($p < 0.001$), this was confirmed in later report after a 10-year follow up [32, 181].

Another ECOG and SWOG study also demonstrated adjuvant HAI of FUDR plus systemic infusional FU was associated with a better 4-year hepatic recurrence-free survival (67 vs. 43%, $p=0.03$) and 4-year overall recurrence-free survival (46 vs. 25%, $p=0.04$) compared with surgery alone [33].

This clinical benefit was also seen in Lygidakis' study and a German study [34, 35].

HAI therapy alone or in combination with systemic chemotherapy as conversion therapy

Conversion therapy options are as follows:

- HAI therapy alone [182];
- HAI with FUDR in combination with systemic oxaliplatin and irinotecan [183, 184];
- HAI with FUDR/dexamethasone in combination with systemic irinotecan [185];
- HAI with oxaliplatin in combination systemic 5-FU/LV [186];
- HAI with FUDR/dexamethasone in combination with systemic FOLFOX, FOLFIRI [49, 50];
- HAI with 5-FU/oxaliplatin/irinotecan in combination with cetuximab [187].

HAI therapy in metastatic setting

HAI with FUDR/dexamethasone can be used in combination with systemic FOLFOX, FOLFIRI [49, 50, 188].

Supplement 2 New Interventional Oncology/Radiology treatments on the pipeline

Treatment of earlier stage mCRC by LAT

Treatment of earlier stage mCRC by LAT within neoadjuvant, first or second line setting are being actively explored in order to achieve better tumor response rates and delay introduction of systemic chemotherapy to preclude systemic toxicity at early stages of mCRC [51, 52, 75].

Combinational LAT therapies

New combinational LAT treatments are being actively explored in terms of ablative and endovascular therapies combination in order to achieve synergistic effect to treat CLMs [76-80, 189, 190].

Ablative dose radioembolization

^{90}Y radiation segmentectomy [191] and ^{90}Y radiation lobectomy [51] concepts are being actively explored in order to treat CLM patients with limited treatment options, such as those ineligible for liver resection or thermal ablation due to tumor size, insufficient ablation margins or unfavorable tumor location.

Radiation segmentectomy enables selective delivery of very high radiation doses (>190 Gy) [192] to eradicate the tumor-containing liver segments while sparing uninvolved liver parenchyma [193, 194]. ^{90}Y radiation lobectomy additionally induces contralateral liver lobe hypertrophy, enabling portal vein embolization (PVE) - refractory patients treatment or providing a viable alternative to PVE, at the same time enabling to observe disease biology within the "test of time" concept while sufficient hypertrophy is achieved [51, 191].

LAT in combination with immunotherapy: role in tumor priming and selective immunotherapy delivery

LAT has an important role in tumor priming, inducing a systemic effect by local/locoregional tumor targeting by means of heat-, cold-based and mechanical ablation techniques as well as endovascular therapies. Thus, besides having *enestic effect* (response of targeted lesion), it is possible to achieve an *anenestic effect* (response in non-targeted lesion) [195]. This is achieved due to the fact, that LAT create an "internal wound", which initiates a stereotypical wound healing immune response and cytokine release [196-199]. However, LAT can both enhance and inhibit the immune response, with subsequent inhibition or promotion of the tumor growth. Modulation of the immune response to LAT is highly challenging and is an active field of research.

LAT monotherapy is insufficient to induce a clinically significant anenestic effect. The combination of LAT with systemic immunotherapy however has the potential to improve response rates of both immunogenic and non-immunogenic tumors by enhancing tumor immune infiltration and converting “cold” tumors into “hot” tumors [200-212]. Immunomodulatory effects of various LAT therapies are currently being explored, however, it is still to be defined which LAT is the most effective in enhancing immune response [200-203, 206-208, 211].

Another point of potential synergy between immunotherapy and IR would be selective immunotherapy delivery to the target lesion in terms of HIT-IT (human intra-tumoral immunotherapy, e.g. cutaneous or visceral intra-tumoral T-VEC administration) and LOC-IT (locoregional immunotherapy, intra-arterial). The concepts of HIT-IT and LOC-IT are currently being actively explored in advanced metastatic disease. Recent research demonstrated that T-VEC can be delivered safely into the human bloodstream to produce selective infection of CLM and replicate in cancer cells with no signs of viral reactivation elsewhere [205]. Intra-hepatic delivery of anti-CEA CAR-T cells through percutaneous hepatic artery infusions has also been explored [204]. While the application of targeted immunotherapy delivery in neoadjuvant setting is much less explored, it remains very promising in terms of achieving high local tumor control rates with a with the aims of having tumors that do not progress/recur following surgical resection or LAT.

Furthermore, ablation can also induce high systemic levels of IL-6, directly supporting cancer cell survival [213]. This can lead to persistence of viable tumor cells in the ablation zone margin and promote disease progression in distant tumor sites. Thus, IL-6 might also be targeted to enhance the treatment efficacy of thermal ablation [214].

Factors Associated with
Local Tumor Control and
Complications after Thermal
Ablation for Colorectal
Cancer Liver Metastases:
a 15-year Retrospective
Cohort Study

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ABSTRACT

Purpose

To identify risk factors associated with local tumor progression-free survival (LTPFS) and complications after colorectal liver metastases (CLM) thermal ablation (TA).

Methods

This retrospective analysis included 286 patients with 415 CLMs undergoing TA (RFA, MWA) in 378 procedures from 1/2003 to 7/2017. Prior hepatic artery infusion (HAI), bevacizumab, pre-existing biliary dilatation, ablation modality, minimal ablation margin (MM), prior hepatectomy, CLM number and size were analyzed as factors impacting complications and LTPFS. Statistical analysis included Kaplan-Meier method, Cox proportional hazards model, competing risk analysis, univariate/multivariate logistic/exact logistic regressions and Fisher's exact test. Complications were reported according to modified SIR guidelines.

Results

Median follow-up was 31 months. There was no LTP for MM >10mm. Smaller tumor size, increased MM and prior hepatectomy correlated with longer LTPFS. Major complication rate was 28/378 (7%). There were no biliary complications in HAI-naïve patients, vs 11% in HAI patients (p<0.001), of which 7% were major. Biliary complications predictors in HAI patients included: biliary dilatation, bevacizumab and MM >10mm. In HAI patients ablation with 6-10mm and >10mm MM resulted in major biliary complication rates of 4% and 21% (p=0.0011), with corresponding LTP rates of 24% and 0%, (p=0.0033). In HAI-naïve patients LTP rates for 6-10mm and >10mm MM were 27% and 0%, respectively.

Conclusions

No LTP was seen for MM >10mm. Biliary complications occurred only in HAI patients, especially in those with biliary dilatation, bevacizumab and MM >10mm. In HAI patients MM of 6-10mm resulted in 76% local tumor control and 4% major biliary complications incidence.

INTRODUCTION

Thermal ablation (TA) is a minimally invasive treatment for selected patients with relatively small colorectal cancer liver metastases (CLM) [1-4]. When combined with standard of care chemotherapy TA (with or without liver resection) resulted in significant patient survival benefit when compared to the group treated only with chemotherapy in a randomized controlled trial [5].

The most common TA modalities - radiofrequency (RFA) and microwave ablation (MWA) - are safe and effective with similar safety profiles [6,7]. Despite overall survival results, similar to those for surgical resection [8-10], relatively high local tumor progression (LTP) rates remain an obstacle for the widespread use of thermal ablation [2,11,12].

Major complication rates of 4-33% for RFA and 0-19% for MWA have been reported, with pooled mortality rates of 0.15% and 0.23%, respectively [13,14]. A wide range of biliary, vascular and other complications have been reported as a result of the thermal injury to the liver and adjacent organs, infections or deterioration of pre-existing comorbidities [3,15,22]. The trade-off between risks and optimal local tumor control, as well as awareness of certain steps or techniques to avoid complications while maintaining the best possible oncologic outcomes are extremely important.

CLM patients often present for thermal ablation with disease progression after systemic chemotherapy, targeted therapy, hepatic resection and in some institutions after prior hepatic artery infusion therapy (HAI)[23-28]. HAI can prolong liver progression-free and overall survival [29-32], but it has also been associated with hepatocellular injury (chemical hepatitis) and cholestatic hepatic injury (biliary strictures, chemotherapy-induced biliary sclerosis, CIBS)[33-37]. HAI-related symptomatic biliary strictures, with an incidence of 5-25%, potentially result from direct toxicity, fibrotic encasement of the portal triad and hepatic arteritis involving the small vessels, supplying the bile ducts. Subsequent ischemia can result in ischemic biliary strictures that may be detected radiographically.

Bevacizumab exposure predisposes to hemorrhagic complications, wound healing problems, fistula formation as well as arterial and venous thromboembolism after surgery or other interventions [26,38,39]. Bevacizumab increased biliary complications when administered with HAI [30]. Additional possible risk factors associated with complications after TA include the type of approach (e.g. open, laparoscopic, percutaneous), number, size and location of target tumors, underlying hepatic disease

and physicians experience [40-44].

This study was conducted to identify incidence and risk factors associated with local tumor control and complications post-TA of colorectal liver metastases (CLM). Tumor-, procedure-, imaging-related clinical parameters as well as prior treatments were analyzed as risk factors of complications and LTP. Association of complications with overall survival was also analyzed.

Our hypothesis was that prior HAI, pre-existing biliary dilatation, bevacizumab administration within 1-month of TA, prior hepatectomy, increased minimal ablation margin (MM) size [4,45,46], ablation modality, number and size of ablated tumors could impact complication rates and LTPFS following TA of CLM.

MATERIALS AND METHODS

This is an IRB-approved retrospective review of a pre-existing Health Insurance Portability and Accountability Act (HIPAA) compliant, clinical image-guided percutaneous ablation prospectively created and maintained database of CLM patients. All CLM patients treated with thermal ablation (RFA and MWA) from 1/2003 to 7/2017 were included in the study. The database was closed for data collection in 7/2018. The main change in ablation procedures during the study period was introduction of immediate post-ablation contrast-enhanced CT (since November 2009). It enabled evaluation of ablation zones and minimal ablation margins, which resulted in significant reduction of local tumor progression rate [45].

Patient selection

Majority of the patients were considered eligible for ablation following multidisciplinary discussion. However, due to the high workload it was impossible to present all patients in the dedicated multidisciplinary meetings. In these cases the treatment plan was discussed with at least the patient's medical oncologist and most often with surgical oncologist as well.

Inclusion criteria for liver thermal ablation were as follows:

- Age > 18 years;
- Pathology proven colorectal cancer;
- Oligometastatic disease, confined to the liver with up to 3 liver lesions;
- Absent or controllable extrahepatic metastases (up to 5 lesions in 2-3 organ sites);

- Liver recurrence after hepatectomy (majority of the patients were referred for ablation for this reason); OR tumor is unresectable (including cases when patient refused hepatectomy/ resection was challenging due to patient's comorbidities) OR presence of small solitary deep tumor requiring major resection; OR patient was offered local curative therapy by means of ablation instead of surgery within "test of time" concept;
- It is possible to achieve sufficient minimal ablation margins (≥ 5 mm);
- No abutment of major vascular and biliary structures: tumor is > 1 cm distance from the major bile ducts (in hilum as well as away from the main right and left biliary ducts);
- Eastern Cooperative Oncology Group performance status of 0-2.
- Relative contraindication: no risk of diaphragmatic injury (in subcapsular dome lesions) or surrounding organ damage that could not be protected by hydrodissection.

Patient exclusion criteria are depicted in Figure 1.

Figure 1 Exclusion criteria.

Ablation procedure and imaging follow-up

All ablations were performed under general anesthesia, using premedication with cefazolin 1g intravenously in a dedicated interventional radiology (IR) CT suite. As of 2009 the dedicated IR suite included CT fluoroscopy and ^{18}F -FDG PET/CT capabilities. CT guidance was used for all the procedures. CT fluoroscopy and/or ultrasonography were utilized as needed for real-time needle positioning or ablation zone monitoring. In some of the recent sessions, additional ^{18}F -FDG PET/CT or split-dose technique for ^{18}F -FDG PET/CT [47] guidance was utilized. Ablation zone monitoring was performed as previously described [45,48]. Since November 2009 all ablations were performed according to manufacturer's protocol with the aim of creating a MM of at least 5 mm and ideally 10 mm all around the target tumor.

RF ablations were performed using the following ablation systems: Cool-tip RF electrode (Medtronic, Minneapolis, MN) in 110/213 (51%) of procedures; RITA Medical Systems (Angiodynamics, Latham, NY) in 52/213 (24%) and LeVeen Needle electrode (Boston Scientific, Natick, MA) in 39/213 (18%); for 12/213 (6%) of procedures data was not available.

MW ablations were performed using the following antennae: Neuwave (Ethicon, Johnson & Johnson) in 98/165 (61%); Emprint (Medtronic, Minneapolis, MN) in 39/165 (24%); Microsulis (Angiodynamics, Latham, NY) in 10/165 (6%); Amica (Endocare, Health Tronics) in 9/165 (6%); Medwaves (Medwaves, San Diego, CA) in 1/165 (0.6%); Perseon (Perseon Corp, Salt Lake City, UT) in 1/165 (0.6%) and Sota Medical (Cedar Grove, NJ) in 1/165 (0.6%); for 6/165 (1.8%) of procedures data was not available.

Contrast-enhanced CT scan was performed at 4-8 weeks post-ablation and served as the new baseline for future comparisons [49]. Subsequent imaging follow-up was performed every 2-4 months with contrast-enhanced CT, whole body ^{18}F -FDG PET/CT and/or liver MRI. MWA was introduced into clinical practice in July 2012.

Measurement of MM

We utilized a manual minimal ablation margin assessment method using anatomical landmarks on pre- and post-ablation CT. This method was chosen as it is more reproducible and found to be associated with local tumor progression in prior studies [46]. Minimal margin assessment was performed by two radiology readers: A. Bendet (faculty body imaging, 7 years of experience) and W. Shady (research fellow, supervised in margin assessment by C.T. Sofocleous IR faculty with 20 years of experience in thermal ablation).

For margin assessment based on anatomical landmarks, pre- and post-ablation portal

venous phase CT images were reviewed side by side to compare the index tumor and the ablation zone/defect [46].

Study objectives

Study objectives were as follows:

1. To analyze local tumor progression-free survival (LTPFS);
2. To measure the rates of side effects, minor and major complications [50,51];
3. To analyze the factors associated with shorter LTPFS and complications. These included HAI, pre-existing biliary dilatation (within 6 weeks of TA), bevacizumab administration within 1 month of TA, prior hepatectomy, MM size (stratified into the following categories: 0 mm, 1-5 mm, 6-10 mm and > 10 mm), ablation modality (RFA vs. MWA) as well as number and size of ablated tumors.
4. To analyze overall survival and 30-day mortality post-ablation.

Definitions

Complications were reported procedure-based according to the modified SIR guidelines [50] with side effects reported separately as per TA terminology standardization guidelines [51]. Complications were additionally classified by the time post-procedure and by organ/system. Definitions of side effects, minor and major complications as well as additional classification of complications are described in **Supplement 1**.

Definitions of residual tumor, LTP as well as analyzed risk factors, such as MM, pre-existing biliary dilatation and HAI are also stated in **Supplement 1**. LTP was reported when there was at least one post-ablation negative imaging study; otherwise it was considered a residual tumor.

Statistical analysis

Median study follow-up was estimated for survivors. Median overall survival (from the first ablation date) and local tumor progression-free survival were estimated using Kaplan Meier method. Univariate and multivariate logistic regression analyses, adjusted for patient clustering were used to analyze association of risk factors with development of complications. Univariate exact logistic regression analysis was used to analyze predictors with 100% sensitivity for development of complications. Fisher exact test was used to analyze difference in categorical variables between the two groups. Mann-Whitney test was used to analyze difference between medians of two groups of non-normally distributed variables (FUDR infusion number). Cox proportional hazards model was used to assess difference in overall survival between the patients with major complications and those without complications. Univariate and multivariate competing

risk analyses adjusted for clustering were used for analysis of factors associated with decreased LTPFS risk to account for the patients who underwent ablation for more than one tumor (death was considered a competing event in this analysis). Statistical analysis was performed using STATA 11 software. $P < 0.05$ was considered significant. Statistical analysis was reviewed by experienced statistician M. Gonen.

RESULTS

Study population

Two hundred eighty six patients treated from 1/2003 to 7/2017 were included in the study. 169/286 (59%) of patients were men (mean age 59.4 ± 12.7 years) and 117/286 (41%) - women (mean age 59.8 ± 12 years) with a mean age for the entire cohort of 59.5 ± 12.5 years. Median study follow-up period for survivors was 31 months.

Four hundred fifteen tumors were treated in 378 procedures. 213/378 (56%) of procedures were performed using RFA and 165/378 (44%) - MWA. 30/378 (8%) of procedures were performed in patients with history of prior HAI, 100/378 (26%) of procedures were performed to treat recurrence after hepatectomy, 175/378 (46%) - for recurrence after hepatectomy and HAI. The remaining 73/378 (19%) of patients had no HAI and no prior liver resection history. KRAS mutation status was positive for 117/288 (41%) of procedures where genetic information was available.

LTPFS and factors associated with it

Median LTPFS was 30.1 months (IQR, 8.1-NR). One-, two- and three-year LTPFS were 67% (95% CI, 62%-71%), 55% (95% CI, 49%-60%) and 47% (95% CI, 41%-53%).

Increased MM size was statistically significantly associated with LTPFS ($p < 0.001$, $SHR = 0.38$), **Figure 2**. For the entire study population and during the median duration of the 31 months follow-up, a MM over 10 mm offered optimal tumor control with no LTP, compared to LTP rates of 26% for MM of 6-10 mm ($p = 0.0001$), 60% for MM 1-5 mm ($p = 0.0001$) and 79% for no MM or 0 mm ($p = 0.0001$) (**Table 4**). LTPFS, stratified by MM size for the HAI and HAI-naïve groups is depicted in **Supplement 4**.

On univariate analysis, additional factors associated with increased local tumor control were: smaller tumor size ($p < 0.001$, sub-hazard ratio, $SHR = 1.39$), history of liver resection for CLM ($p = 0.017$, $SHR = 0.67$) and prior HAI therapy ($p = 0.032$, $SHR = 0.7$) (**Table 3**).

On multivariate analysis, only three factors remained statistically significant: tumor

size ($p = 0.001$, $SHR = 1.3$), MM ($p < 0.001$, $SHR = 0.37$) and history of liver resection ($p = 0.039$, $SHR = 0.64$).

Figure 2 Minimal ablation margin association with local tumor progression-free survival (LTPFS). There were statistically significant differences between LTPFS of patients ablated with 0 mm minimal margin, compared to 1-5 mm margin ($p = 0.013$), 6-10 mm margin ($p < 0.01$) and >10 mm minimal margin ($p < 0.01$).

Side effects and complications

Complications were encountered after 70/378 procedures (19%, 95% CI 15-23%). After 49/378 (13%) of procedures the patients developed minor complications and after 28/378 (7%) - major complications (7 patients developed both minor and major complications) (**Tables 1-2**).

Incidence of side effects was 66/378 (10%) (**Supplement 2**). Majority of complications (40/70, 57%) occurred within 24-hours from ablation, 5/40 (13%) of these were major immediate complications. The incidence of complications in terms of time after TA is depicted in **Supplement 3**.

Overall complication rates for RFA and MWA were 33/213 (15%) and 37/165 (19%), respectively. Major complications occurred after 11/213 (5%) of RFA and 17/165 (10%) of MWA procedures ($p = 0.07$). Among those treated with MWA all major liver complications occurred in patients with prior HAI history ($p = 0.004$, $OR = 12.01$).

Table 1 Post-ablation minor complications

Minor complications post-liver thermal ablation	
Complication type/description (n=378 procedures)	Incidence
<i>Biliary</i>	8 (2.1%)
Biloma, no drainage required	7
Grade 2-4 hyperbilirubinemia/transaminase toxicity, requiring chemotherapy modification or stop of HAI therapy	1
<i>Vascular/hemorrhagic complications</i>	10 (2.6%)
Grade 1-2 intrahepatic hematoma, no intervention required	6
Portal vein injury/thrombosis ± infarction of corresponding liver, asymptomatic	2
AV fistula, no intervention required	1
Perihepatic bleeding during ablation, required < 48h observation	1
<i>Pulmonary complications</i>	22 (5.8%)
Grade 2-3 pneumothorax, requiring thoracostomy	17
Pleural effusion, requiring thoracentesis	4
Asthma exacerbation + dyspnea/ desaturation, required hospitalization for 48h	1
<i>Other</i>	12 (3.2%)
Abdominal/non-cardiac chest pain/shoulder pain, required <48h hospitalization	5
Post-ablation syndrome	3
Nausea/vomiting ± sedation, requiring <48h observation	1
Syncope, vomiting, sinus bradycardia, bifascicular blockade next day post-TA, hospitalization for 48 hours	1
Grade 3 hypertension + hyperglycemia in patient with risk factors, 48h admission	1
Grade 2 fever, negative microbiology cultures	1
Total number of minor complications	52
Total number of procedures with minor complication(s)*	49 (13%)

*After 3 procedures patient developed two different minor complications per procedure, this is why the total incidence of procedures with minor complication(s) is 49 instead of 52; HAI-hepatic artery infusion

Among the patients who developed major complication following ablation of a single liver metastasis (n=22) median extrahepatic progression-free survival was 40.8 months (IQR, 15.7-143).

Biliary complications

Major complications are detailed in **Table 2**. Of those, biliary complications were the most commonly encountered (15/378, 4%). The most common major biliary complication was intrahepatic biloma requiring drainage (6/378, 2%), with additional subsequent sequelae in 5 out of these 6 cases, including abscess, biliary stricture, bile leak, bacteremia and biliary fistulas to abdominal wall or m. ileopsoas. One of these bilomas developed within an ablation zone previously complicated by hematoma and pseudoaneurysm requiring embolization.

Two more patients developed biliogastric and bilioenteric fistula, requiring intervention, which were not associated with biloma. Total of 3/4 of the patients with biliary fistulas and 1/2 of the patients with arteriportal fistulas requiring intervention received

bevacizumab less than a month before (and/or) after the ablation.

Table 2 Post-ablation major complications

Major complications post-liver thermal ablation	
Complication type/description (n=378 procedures)	Incidence
<i>Biliary</i>	15 (4%)
Intrahepatic biloma, requiring drainage with additional sequelae: abscess (1) / abscess+ secondary biliary stricture + biliary leak (1)/ bacteremia (1)/ biliary fistula to abdominal wall (1) or biliary fistula to m. ileopsoas (1)	6
Secondary biliary stenosis, requiring intervention	3
Hyperbilirubinemia, requiring stenting (1)/ requiring intervention and prolonged hospitalization (1)/ resulting in bacteremia, requiring drainage (1)	3
Bilioenteric/biliogastric fistula with recurrent bacteremia or requiring intervention	2
Extrahepatic biloma + infection + bile leak, requiring intervention	1
<i>Liver vascular complications</i>	7 (1.9%)
Arteriportal fistula, requiring embolization	2
Hepatic pseudoaneurysm ± hematoma, requiring embolization	3
Retroperitoneal hematoma, requiring drainage	1
Bleeding into biliary tree	1
<i>Pulmonary complications</i>	9 (2.4%)
Pulmonary embolism ± pneumonia/bronchiolitis	2
Pneumothorax ± pleural effusion, requiring prolonged admission	2
SVC thrombosis/syndrome + pulmonary vein thrombosis + pulmonary embolism	1
Hemothorax, requiring thoracostomy and prolonged hospitalization	1
Pleural effusion + desaturation, requiring thoracentesis + prolonged hospitalization	1
Diaphragm injury + abscess + hydropneumothorax, requiring >48 h hospitalization	1
Pneumothorax + pneumomediastinum + pneumoperitoneum + subcutaneous emphysema due artificial hydropneumoperitoneum, requiring >48h hospitalization	1
<i>Other</i>	2 (0.5%)
In alcohol abuse patient SIADH+ Alcohol withdrawal syndrome + epistaxis, requiring intervention and prolonged hospitalization	1
Grade 3 abdominal pain + opioid-induced agitation/delirium with prolonged hospitalization	1
Total number of major complications	33
Total number of procedures with major complication(s)*	28 (7.4%)

*After five procedures patients developed two different major complications per procedure, this is why the total incidence of procedures with major complication(s) is 28 instead of 33. SIADH- syndrome of inappropriate anti-diuretic hormone secretion.

Factors associated with biliary complications

Major hepatic complications rates (both biliary and vascular) in HAI patients (208/378) and HAI-naïve patients (170/378) were 18/208 (9%) vs. 1/170 (0.6%), respectively (p=0.0002). All biliary complications (both minor and major) occurred only in HAI patients (p<0.001, OR=28.4), thus prior HAI history could predict biliary complications with 100% sensitivity. 22/208 (11%) of HAI patients developed some type of biliary complication following TA. Major biliary complications rate in the HAI group was 12/208 (6%), compared to 0/170

(0%) for HAI-naïve patients (p=0.0001). HAI and HAI-naïve patients' characteristics are depicted in **Supplement 5**.

Additional predictors of biliary complications in HAI patients on univariate analysis included pre-existing biliary dilatation (p=0.002, OR=7.2), bevacizumab exposure < 1 month before TA (p=0.001, OR=9.5) and larger MM size (assessed as ordinal variable, p=0.007, OR=2.1), all of which retained significance on multivariate analysis (**Table 3**). In the HAI group, incidence of biliary complications in patients with pre-existing biliary dilatation was 19/89 (21%, with major biliary complications rate of 17%), in patients with recent bevacizumab exposure - 6/13 (46%, all were major complications) and in the patients ablated with MM >10 mm - 9/29 (31%, with major biliary complications rate of 21%) (**Table 3**).

Table 3 Factors associated with biliary and hepatic vascular complications

Complication risk factors	Biliary complications				Vascular complications				Local tumor progression			
	UVA		MVA		UVA		UVA		MVA		MVA	
	p	OR	p	OR	p	OR	p	SHR	p	SHR	p	SHR
Prior HAI therapy	0.003	20.0**	-	-	0.2	2.0	0.032	0.7	0.86	0.96		
Pre-existing biliary dilatation*	0.002	7.2	0.005	5.8	-	-	-	-	-	-		
Bevacizumab within 1 month*	0.001	9.5	0.017	14	0.07	4.6	-	-	-	-		
Minimal ablation margins*	0.007	2.1	0.015	2.1	0.24	1.5	<0.001	0.38	<0.001	0.37		
Ablation modality*	0.18	1.89	-	-	0.77	1.16	0.18	0.79	-	-		
Tumor size (cm)*	0.33	1.25	-	-	0.57	0.82	<0.001	1.39	0.001	1.3		
Tumor number *	0.63	1.19	-	-	0.24	1.62	-	-	-	-		
History of liver resection*	0.14	0.40	-	-	0.86	0.90	0.017	0.67	0.039	0.64		
Number of FUDR infusions* (range, 1-40)	0.37	1.03	-	-	-	-	-	-	-	-		
KRAS mutation status	-	-	-	-	-	-	0.49	1.15	-	-		

*These factors association with biliary complications analysis was made only for the HAI patients' subgroup, since biliary complications occurred only in HAI patient population. **Result is based on exact logistic regression analysis. In bold-statistically significant values. UVA-univariate analysis, MVA-multivariate analysis, HAI-hepatic artery infusion pump therapy; FUDR – fluoxuridine, OR-odds ratio; SHR-sub-hazard ratio.

The median number of FUDR infusions, ablation modality, tumor number, size and prior liver resection did not reach statistical significance regarding rates of biliary complications (**Table 3**).

Optimal MM size in terms of local tumor control and safety according to the HAI history

Since all biliary complications were recorded only in the HAI patients, additional subgroup analyses of HAI and HAI-naïve patients were performed. In the HAI population biliary complications were more prevalent for patients who had ablations with larger MM (p=0.007, OR=2.1). Specifically, when ablating with MM of 6-10 mm vs. > 10 mm the incidence of minor biliary complications increased from 0% to 10% (p=0.04), incidence of major complications increased from 4% to 21% (p=0.02) whereas the corresponding LTP rates decreased from 24% to 0% (p=0.0033) (**Table 4**).

There were no biliary complications in HAI-naïve patients, regardless of MM size or any other factor. MM larger than 10 mm provided optimal local tumor control without additional morbidity in this population: LTP rate was 0% for MM > 10 mm compared to 27% for MM of 6-10 mm (p=0.1) (**Table 4**).

Table 4 Biliary complications and local tumor progression rate, stratified based on minimal ablation margin size and HAI history

Minimal ablation margin	0 mm	1-5 mm	6-10 mm	>10 mm
Whole patients cohort*				
Minor biliary complications	0/50 (0%)	4/128 (3%)	0/96 (0%)	3/40 (8%)
Major biliary complications	0/50 (0%)	6/128 (5%)	2/96 (2%)	6/40 (15%)
Total biliary complications incidence	0/50 (0%)	8/128 (6%)**	2/96 (2%)	9/40 (23%)
Local tumor progression rate	41/52 (79%)	79/132 (60%)	25/98 (26%)	0/39 (0%)
Prior-HAI patients subgroup analysis				
Minor biliary complications	0/22 (0%)	4/71 (6%)	0/53 (0%)	3/29 (10%)
Major biliary complications	0/22 (0%)	6/71 (8%)	2/53 (4%)	6/29 (21%)
Total biliary complications incidence	0/22 (0%)	8/71 (11%)**	2/53 (4%)	9/29 (31%)
Local tumor progression rate	18/22 (82%)	38/72 (53%)	13/54 (24%)	0/28 (0%)
HAI-naïve patients subgroup analysis				
Total biliary complication incidence	0/28 (0%)	0/57 (0%)	0/43 (0%)	0/11 (0%)
Local tumor progression rate	23/30 (77%)	41/60 (68%)	12/44 (27%)	0/11 (0%)

* Total of 64 procedures were excluded from analysis: 33 due absence of imaging for minimal ablation margin assessment (contrast-enhanced CT within 6 weeks before treatment and/or at 4-8 weeks after treatment), 22 - due to multiple differing minimal ablation margins present following ablation of multiple tumors per procedure, 5 – due to coalescent ablation zones, 4 - due no follow-up). ** patient(s) had both minor and major complications per procedure. HAI-hepatic artery infusion

Factors associated with vascular complications

Vascular complications developed after 17/378 (4%) of ablations and 7/378 (2%) were major. Vascular complications incidence in the HAI group was 12/208 (6%) vs. 5/170 (3%) in HAI-naïve patients (p=0.22). Vascular complications incidence between patients with recent bevacizumab compared to those with no bevacizumab exposure was 3/19 (16%) vs. 14/359 (4%), respectively (p=0.07).

None of the other analyzed factors in this study were prognostic of vascular complications (Table 3).

Overall survival

There was no 30-day post-procedural death. Median OS for entire cohort was 41.5 months since ablation (IQR, 22.6-71.5,). One-, two-, three- and five-year OS rates calculated from the date of ablation were 91%, 72%, 53% and 37%, respectively. Median OS of the patients with no complications (or only side effects) and major complications were 43.2 months (IQR, 22-75.6) and 29.3 months (IQR, 10.2-NR), respectively (p=0.09), with OS of 41.6 months (IQR, 26.8-53.3) for patients with minor complications (Figure 3).

Figure 3 Overall survival association with complications following thermal ablation (TA). The overall survival difference between the patients without complication or with side-effects-only and the patients with major complications did not reach statistical significance (p=0.09).

DISCUSSION

To our knowledge, this is the first study to note a strong association between post-ablation biliary complications with prior HAI as well as with additional risk factors, such as pre-existing biliary dilatation, bevacizumab and MM. Also, this is one of the few studies documenting the importance of MM on long-term tumor control by thermal ablation [4,45,46,52-56] establishing that a MM>10 mm was associated with no LTP within

a median follow-up of 31 months. On multivariate analysis independent predictors of shorter LTPFS included decreased MM, increased tumor size and no prior history of hepatectomy for CLM similar to prior results [45], accounting for multiple lesions and multiple procedures per patient.

Biliary complications were the most common major complications, encountered after 3% of all ablations. Prior HAI carried 100% sensitivity in predicting biliary complications in this study: all patients with biliary complications (both minor and major) had prior HAI exposure.

For HAI-naïve patients optimal oncologic outcomes were safely achieved with MM over 10 mm (no LTP without biliary complications and minimal morbidity). In the HAI population a MM of >10 mm offered optimal local tumor control without any LTP, but it was associated with significantly higher incidence of overall and major biliary complications. Additional predictors for biliary complications in HAI patients included pre-existing biliary dilatation (increased biliary complications risk 7-fold) and recent bevacizumab administration (increased risk 9-fold), all of which retained statistical significance on multivariate analysis.

In the HAI patient population a MM of 6-10 mm offered local tumor control of 76% with a 4% major biliary complication risk. Since re-ablation to treat LTP is usually feasible and adjuvant systemic and/or HAI chemotherapy are also available in this group, we consider ablation with MM of 6-10 mm to be a reasonable option for HAI patients, especially when there is a history of prior bevacizumab exposure, pre-existing biliary dilatation or biloma on CT imaging. Further improvement of local tumor control, particularly when the MM is within the 6-10 mm category, can be achieved with tissue confirmation of complete tumor necrosis through core biopsy of the center and MM of the ablation zone [52]. A MM > 5 mm with ablation zone biopsy negative for residual tumor after RF ablation of CLM resulted in a 30-month LTPFS of 97%[52]. Thus, biopsy-proven complete ablation with MM of 6-10 mm can potentially decrease both the LTP and complications rates especially in the HAI patients with pre-existing biliary dilatation and prior bevacizumab exposure where a MM of > 10 mm may carry increased risk.

Intrahepatic biliary dilatation is a known relative contraindication for ablation [13]. Pre-existing intra- or extrahepatic biliary dilatation regardless of location (adjacent or not to the ablation zone) was considered a biliary complication risk factor. However, pre-existing biliary dilatation did not result in biliary complications in the HAI-naïve patient group. HAI was associated with biliary dilatation that is likely the result of

multiple (occult) biliary strictures secondary to HAI-related biliary duct ischemia, as previously described [35-37]. Thus, dilatation of even one bile duct most likely reflects a more diffuse liver cholestatic injury in the HAI population. This explains why even minor biliary dilatation was associated with increased incidence of biliary complications in the HAI population in this study and can also explain the difference from HCC patients without exposure to HAI, where mild pre-existing biliary dilatation did not increase the risk of post RFA biliary complications [57].

The addition of bevacizumab to HAI resulted in increased biliary toxicity in three separate prospective studies without any evidence of improved progression-free or overall survival [58]. It is also recommended to withhold bevacizumab for at least 28 days prior to and post-elective surgery [59] to prevent complications or delay healing. Although generally such strict restrictions are not recommended prior to TA, for the patients at risk such as the HAI group a similar precaution should be considered. Administration of bevacizumab within 1 month from TA was borderline significant for liver vascular complications in this study ($p=0.07$). This is probably due to the small overall number of vascular complications. None of the other analyzed factors were prognostic of vascular complications. Analysis of different potential predictors, such as distance of the target tumor to a major vessel, anticoagulation therapy, number of electrodes used and number of performed overlapping ablations could also be analyzed as potential vascular complications risk factors in future larger studies with more events of vascular complications.

Major complication rates (5% for RFA and 10% for MWA) in this cohort fall within previously reported range for RFA (4-33%) and for MWA (0-19%) [13]. The patients who developed major complications following ablation of a single liver metastasis demonstrated good extrahepatic disease control. This shows that locoregional therapies play an important role in overall disease control in this patient population.

Biloma, requiring intervention was the most common major complication, noted in 2% of procedures. This rate was higher, than the previously reported 0.9% rate after RFA for HCC [60] and is attributed to the HAI effects as described in detail [33-37].

There was no 30-day post-ablation death in this study. Overall survival of patients with major complications was lower when compared to the patients without any complications. This difference, although not significant, likely reflects the known trend of worse oncologic outcomes in CRC patients undergoing resection for CLM when compared to those without complications [61].

KRAS mutation was not associated with local tumor control in our study. The lack of statistical significance may also be attributed to minor discrepancy in KRAS status between the primary tumor and metastatic sites (concordance rate is 93.7%) [62]. Also it can be attributed and to the fact, that KRAS mutation is not a binary variable in tumors, and that there is a diversity in mutant alleles and variability in gene copy number, which may also contribute to the heterogeneity of clinical outcomes in cancer patients [63].

Study limitations included its single-center retrospective nature with its inherent limitations. Abutment of major vascular and biliary structures was already an exclusion criterion for ablation in our center; this is why it was not included as a potential risk factor in our study. Ablation technical factors, tumor histopathological characteristics [55,56,64], clinical risk score and chemotherapeutic agents post-ablation were not assessed as potential risk factors of poorer oncological outcomes. These factors could be addressed in the future by larger prospective studies with more events to allow for meaningful conclusions.

CONCLUSION

Thermal ablation of colorectal liver metastases has a favorable safety profile and provides good local tumor control, especially when a MM larger than 5 mm is achieved. Optimal and sustained local control was documented for MM > 10 mm that was associated with no local tumor progression. A larger MM may increase the risk of biliary complications in specific populations at risk such as the patients with prior HAI and particularly those who also have pre-existing biliary dilatation or recent exposure to bevacizumab. For these patients at risk we recommend to hold bevacizumab for 4 weeks before and after ablation and maintaining ablation margins between 6-10 mm.

CLINICAL PRACTICE POINTS

- Thermal ablation (TA) is a minimally invasive treatment for selected patients with relatively small colorectal cancer liver metastases.
- The most common TA modalities - radiofrequency and microwave ablation - are safe and effective with similar safety profiles, with major complication rates of 0-33% and pooled mortality rate up to 0.23% when used to treat CLMs.
- Thermal ablation with minimum ablation margins (MM) > 10 mm offers the best local tumor control and no LTP.

- In the patients at risk such as those with hepatic artery infusion therapy (HAI) and in particular those with additional bevacizumab exposure and pre-existing biliary dilatation, a MM > 10 may further increase the risk of biliary complications.
- MM of 6-10 mm offered 76% local tumor control with a 4% incidence of biliary complications in the HAI patient population.
- In HAI-naïve patients, optimal sustained local tumor control is achieved with MM >10 mm without complications.

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SUPPLEMENTARY MATERIAL

Supplement 1 Definitions of parameters of local tumor control and adverse events

Parameter	Description
Local tumor control	
Residual tumor	Residual tumor and ablation failure was considered to be the imaging evidence of tumor (FDG-avid or nodular enhancement) on the first imaging at 4-8 weeks post-ablation
Local tumor progression (LTP)	Defined as any new FDG-uptake ($SUV_{max} > 2.5$ above background liver uptake) or peripheral/nodular enhancement within 1-cm of the ablation zone or enlargement of the baseline ablation defect, depicted during imaging follow-up on any subsequent CT and/or ^{18}F -FDG PET/CT imaging after ablation. LTP was reported when there was at least one post-ablation negative imaging study; otherwise it was considered a residual tumor
Adverse events	
Side effects	Side effects included expected, undesired consequences of the procedure that occur commonly, but do not lead to an unexpected increased level of care. These included pain, post-ablation syndrome and asymptomatic imaging evidence of pleural effusion/perihepatic fluid or blood as well as imaging findings of thermal damage to adjacent structures without sequelae, nor requiring hospitalization and absent on first post-TA imaging
Minor complications	Minor complications included exacerbation of comorbidities requiring <48 hours hospitalization, imaging evidence of biloma, hematoma or arteriovenous fistula on imaging follow-up, not requiring intervention or hospitalization and not resulting in significant morbidity. They also included laboratory toxicity, requiring modification of systemic chemotherapy or HAI therapy administration
Major complications	Major complications included events that led to substantial morbidity and disability, resulting in > 48 hours hospital admission, substantially lengthening the hospital stay, requiring blood transfusion, intervention or interruption of systemic chemotherapy administration
Complications timing post-procedure	Complications were classified as follows: Immediate complications (6-24h post-ablation) Early complications (24h - 30 days post-ablation) Delayed complications (> 30 days – 6 months post-ablation)
Complications by organ	Complications were classified as follows: hepatic (biliary and vascular); pulmonary and other complications
Classification of pneumothorax and pleural effusion	Pneumothorax and pleural effusion were classified according to the level of severity. They were considered: Side effects if they did not require thoracostomy/thoracentesis Minor complication if they required thoracostomy/thoracentesis Major complication if they required thoracostomy/thoracentesis with > 48 hours of hospitalization and/or had further sequelae
Risk factors	
Minimum ablation margin (MM)	The MM was measured on the first contrast-enhanced triphasic CT scan at 4-8 weeks post-ablation and compared to the pre-ablation contrast-enhanced triphasic CT scan obtained prior to TA as previously described [4, 45, 46]. MM was stratified into the following categories: 0 mm, 1-5 mm, 6-10 mm and >10 mm. The margins were measured at 4-8 weeks post-TA instead of immediate post-treatment CT in order to keep evaluations uniform due to immediate post-procedure contrast-enhanced CT introduction in our institution only in November 2009. The MM was assessed by two radiology readers: A. Bendet (faculty body imaging, 7 years of experience) and W. Shady (research fellow, supervised in margin assessment by C.T. Sofocleous-IR faculty with 20 years of experience in thermal ablation)
Pre-existing biliary dilatation	Pre-existing biliary dilatation was defined as dilatation of at least one intra- or extra-hepatic biliary duct, depicted on contrast-enhanced CT or MRI within 6 weeks before the ablation. It was assessed by faculty radiologist with at least 7-years of experience in diagnostic radiology
Hepatic artery infusion (HAI)	HAI therapy with flouxuridine (FUDR) was analyzed in this study, with dexamethasone being administered at the same setting with FUDR to reduce liver toxicity

Supplement 2 Post-ablation side effects

Side effects (n=378)	Incidence
Grade 1-2 abdominal/chest/shoulder pain, no observation required	32 (8%)
Pneumothorax, required <48h observation (iatrogenic = 2)	16 (4%)
Trace subcapsular/perihepatic fluid/blood collection, no observation/intervention required and not present on follow-up	7 (2%)
Trace pleural effusion with mild chest pain/dyspnea, not affecting daily function/no observation/treatment required and not present on follow-up	6 (2%)
Grade 1-2 nausea/vomiting	5 (1%)
Grade 2 constipation	4 (1%)
Hematoma/skin swelling/induration in ablation zone	4 (1%)
Mild fever	3 (1%)
Hypoxia, requiring overnight observation	2 (0.5%)
Throat soreness/irritation	2 (0.5%)
Minimal bleeding in ablation zone, asymptomatic, not present on follow-up	2 (0.5%)
Subcutaneous emphysema, required <48h observation	2 (0.5%)
Portal hypertension	1 (0.3%)
Hiccups (RFA in proximity to mediastinum)	1 (0.3%)
Dyspepsia	1 (0.3%)
Grade 2 hyperbilirubinemia	1 (0.3%)
Eyelids edema/ abrasion/swelling	1 (0.3%)
Total number of side effects encountered	90
Total number of procedures with side effects reported*	66 (17%)

* Multiple side effects were possible per procedure, this is why the number of the procedures with side effects reported is lower than the number of side effects encountered per se

Supplement 3 Post-thermal ablation complications distribution by time post-procedure

Complications (n=378, according to SIR guidelines, 2003)	Incidence
Immediate complications (6-24h post-ablation) of which pneumothorax s/p thoracostomy in 13 procedures	40 (11%)
Early complications (within 30 days post-ablation)	19 (5%)
Delayed complications (>30 days – 6 months post-ablation)	15 (4%)
Complications >6 months post-ablation	2 (0.5%)
Patient death within 30 days post-ablation	0
Total number of procedures	70 (19%)*

*Multiple complications were possible per procedure

Supplement 4 Local tumor progression-free survival (LTPFS) association with minimal ablation margin (MM) and history of hepatic artery chemotherapy (HAI). CI-confidence interval.

Minimal margin category	Entire cohort, 95%CI	HAI-naïve, 95%CI	HAI patients, 95%CI
MM = 0mm			
1-year LTPFS	38% (25%-51%)	32% (16%-49%)	45% (24%-64%)
2-year LTPFS	23% (12%-35%)	25% (11%-42%)	18% (5%-37%)
3-year LTPFS	10% (3%-21%)	8% (2%-23%)	12% (2%-31%)
MM = 1-5mm			
1-year LTPFS	53% (45%-61%)	53% (40%-64%)	53% (42%-64%)
2-year LTPFS	40% (31%-48%)	31% (19%-44%)	47% (35%-58%)
3-year LTPFS	35% (27%-44%)	28% (16%-41%)	42% (29%-53%)
MM = 6-10mm			
1-year LTPFS	88% (80%-93%)	85% (71%-93%)	91% (80%-96%)
2-year LTPFS	76% (65%-84%)	78% (61%-88%)	75% (59%-85%)
3-year LTPFS	69% (56%-79%)	73% (54%-85%)	65% (45%-79%)
MM >10 mm			
1-year LTPFS	100% (-)	100% (-)	100% (-)
2-year LTPFS	100% (-)	100% (-)	100% (-)
3-year LTPFS	100% (-)	100% (-)	100% (-)

Supplement 5 Comparison on the patients with prior hepatic artery infusion therapy (HAI) and HAI-naïve patients

Parameter	HAI patients	HAI-naïve patients	P-value
Number of patients	140	146	-
Number of procedures	208	170	-
Age	57.1 ± 11 years	62.9 ± 13.4	-
Gender	88/140 (63%) male	82/147 (56%) male	-
Number of FUDR infusions, median	8 (range, 1-40)	-	-
Pre-existing biliary dilatation	89/196 (45%)	26/156 (17%)	0.0001
Incidence of biliary complications			
Minor	8/208 (4%)	0/170 (0%)	0.0094
Major	15/208 (7%)	0/170 (0%)	0.0002
Total	22/208* (11%)	0/170 (0%)	0.0001
Incidence of vascular complications:			
Minor	6/208 (3%)	4/170 (2%)	1
Major	6/208 (3%)	1/170 (0.6%)	0.63
Total	12/208 (6%)	5/170 (3%)	0.59
Number of patients who received bevacizumab within 1-months of TA			
Total bevacizumab administrations within 1-month of TA	11/140 (8%)	6/147 (4%)	0.21
Bevacizumab administered simultaneously with HAI	4/140 (3%)	-	-
Bevacizumab administered not simultaneously with HAI	5/140 (4%)	-	-
Data is on bevacizumab and HAI timing not available	2/140 (1%)	0/147 (0%)	-
Minimum ablation margin sizes			
0 mm	22/208 (11%)	28/170 (16%)	0.096
1-5 mm	71/208 (34%)	57/170 (34%)	0.91
6-10 mm	53/208 (25%)	43/170 (25%)	1
>10 mm	29/208 (14%)	11/170 (6%)	0.02
Not applicable**	33/208 (16%)	31/170 (18%)	-
Local tumor progression-free survival (LTPFS)			
Median (in months, from TA date)	Not reached	21 months	0.026
1-year LTPFS	71% (95%CI,64;77%)	62% (95%CI,54;69%)	-
2-year LTPFS	60% (95%CI,52;66%)	49% (95%CI,40;57%)	-
3-year LTPFS	53% (95%CI,44;60%)	41% (95%CI,32;50%)	-

*One patient had both minor and major complications.**It was not feasible to define minimal ablation margins in presence of confluent tumors or in presence of multiple tumors ablated with different minimal ablation margins per procedure. In bold- statistically significant values. FUDR - floxuridine, TA - thermal ablation; LTPFS – local tumor progression-free survival

Factors Affecting Oncologic Outcomes of ^{90}Y Radioembolization of Heavily Pre-Treated Patients with Colon Cancer Liver Metastases

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ABSTRACT

Objectives

To identify predictors of overall (OS) and liver progression-free survival (LPFS) following ⁹⁰Y radioembolization (RE) of heavily pretreated patients with colorectal cancer liver metastases (CLM). Create and validate a predictive nomogram for OS.

Materials and Methods

Metabolic, anatomic, laboratory, pathologic, genetic, primary-disease and procedure-related factors, as well as pre- and post-RE therapies in 103 CLM patients treated with RE from 9/15/2009 to 3/21/2017 were analyzed. LPFS was defined by RECIST1.1 and EORTC criteria. Prognosticators of OS and LPFS were selected using univariate Cox regression, adjusted for clustering and competing risk analysis (for LPFS) and subsequently tested in multivariate analysis (MVA). The nomogram was built using R statistical software and internally validated using bootstrap resampling.

Results

Patients received RE at a median of 30.9 months (range: 3.4-161.7 months) after detection of CLM. Median OS and LPFS were 11.3 (95%CI, 7.9-15.1) and 4 months (95%CI, 3.3-4.8), respectively. Of the 40 parameters tested, six were independently associated with OS in MVA. These baseline parameters included: number of extrahepatic disease sites ($p<0.001$), carcinoembryonic antigen (CEA) ($p<0.001$), albumin ($p=0.005$), alanine aminotransferase (ALT) level ($p<0.001$), tumor differentiation level ($p<0.001$) and sum of the two largest tumor diameters ($p<0.001$). One-year OS of patients with total points of <25 vs. >80 were 90% and 10%, respectively. Bootstrap resampling showed good discrimination (optimism corrected c-index=0.745) and calibration (mean absolute prediction error = 0.299) of the nomogram. Only baseline standard uptake value (SUV_{max}) was significant in MVA for LPFS prediction ($p<0.001$, SHR=1.06).

Conclusion

The developed nomogram included six pre-RE parameters and provided good prediction of survival post-RE in heavily pretreated patients. Baseline SUV_{max} was the single significant predictor of LPFS.

INTRODUCTION

⁹⁰Y radioembolization (RAE) is an FDA approved liver brachytherapy, recommended through the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO) guidelines for the treatment of colorectal cancer liver metastases (CLM) in the salvage setting with liver disease progression while on or after second line chemotherapy with encouraging oncologic outcomes [1-18].

RAE performed at this advanced stage of a terminal disease has the goal of prolonging patient survival with limited if any impact on quality of life. Currently a decision for RAE is recommended through a multidisciplinary discussion [7]. In clinical practice, recommendations for refractory patients are challenging, because this population often presents with advanced tumor load, unfavorable biologic tumor characteristics, comorbidities or poor performance status. It is thus not surprising, that the range of reported outcomes post-RAE is highly variable. Objective response rates varied between 10%-48% when RAE was applied in the third and subsequent chemotherapy regiment setting [10, 17, 19, 20]. Thus, careful patient selection is extremely important to minimize the risk of treatment-related complications and unnecessary hospitalization. Current exclusion criteria do not always provide adequate risk stratification or an optimal estimation of patient survival. Poor outcome may be a consequence of more extensive disease, but may also be associated with RAE-induced adverse events. A predictive scoring system can aid a rational decision with estimation of each patient's risk/benefit ratio prior to undergoing RAE.

The aim of this study was to analyze metabolic, anatomic, laboratory, pathologic, primary disease-related and genetic biomarkers, procedure-related factors as wells as pre- and post-RAE therapies that can be associated with liver progression-free and overall survival. In addition, our goal was to create and internally validate a predictive survival nomogram using pre-RAE patient characteristics.

MATERIALS AND METHODS

Ethical considerations and patient selection

IRB waiver of approval was obtained for this retrospective review of our prospectively created and maintained HIPAA registered and compliant colorectal cancer liver metastases (CLM) RAE database. All patients with CLM treated with ⁹⁰Y RAE from 9/15/2009 to 3/21/2017 were included.

Inclusion and exclusion criteria

All patients treated with RAE were eligible for inclusion in the study.

Eligibility criteria for RAE in our practice included: age ≥ 18 years; Eastern Cooperative Oncology Group (ECOG) performance status 0-2; histologically confirmed primary adenocarcinoma of the colon or rectum; CLM considered unresectable or not amenable to percutaneous ablation; adequate blood cell counts (WBC $> 1.5 \times 10^9/L$, platelet count $> 50 \times 10^9/L$); adequate renal function (creatinine < 1.5 mg/dL) and total bilirubin level ≤ 1.5 mg/dL.

Exclusion criteria were: prior hepatic radiotherapy; severe cirrhosis; severe portal hypertension; uncorrectable flow to the gastrointestinal tract and/or $>20\%$ shunting to the lungs, as determined by technetium-99m labeled macroaggregated albumin (^{99m}Tc-MAA) hepatic arterial perfusion scintigram (mapping). All patients at the time of RAE had liver-dominant disease and were considered candidates for RAE even in the face of oligometastatic (up to 5 sites) extrahepatic disease that was stable or controlled by chemotherapy.

Pre-procedural work – up and angiographic mapping

All patients were evaluated at a clinic visit within 30 days before RAE. Past medical history was reviewed, physical examination was performed and relevant baseline laboratory values were evaluated. Pre-procedural baseline imaging with liver dynamic (ideally triphasic) CT and ¹⁸F-FDG PET/CT was available within 30 days from RAE for accurate re-staging of disease and for calculation of liver and CLM volumes for ⁹⁰Y dosimetry.

All patients underwent angiographic evaluation and ^{99m}Tc-MAA mapping prior to RAE. During arteriography, hepatic arterial anatomy and tumor vascular supply were assessed. Extrahepatic vessels with hepatofugal flow within 3 cm from the desired point of ⁹⁰Y administration were prophylactically coil-embolized to prevent inadvertent delivery of ⁹⁰Y in extrahepatic sites. Once the desired location(s) of RAE administration(s) was determined, a total of 4-5 mCi of ^{99m}Tc-MAA were injected at desired sites of ⁹⁰Y arterial infusion and subsequent planar scintigraphy and SPECT/CT imaging were performed to calculate the lung shunt fraction and to detect extrahepatic activity [17].

Radioembolization procedure

Approximately two weeks after mapping angiography, patients underwent RAE with SIR-Spheres (Sirtex Medical, Sydney, Australia) or glass microspheres (Therasphere; MDS Nordion, Ottawa, Ontario, Canada). Glass-based microspheres were introduced in March

2015 and were specifically used instead of SIR-spheres in patients with higher risk of developing stasis: in the presence of constricted or small caliber arteries as well as in patients with history of prior non-anatomic liver resections or intra-arterial hepatic infusion pump chemotherapy, who presented with tortuous or constricted vessels at mapping.

As of April 2013 ⁹⁰Y resin microspheres were administered using undiluted contrast medium, which allowed real-time infusion monitoring and resulted in shorter infusion time and reduced fluoroscopy radiation dose as previously described [18].

The total activity of ⁹⁰Y resin microsphere (in GBq) for each patient was calculated using body surface area (BSA) method with the following formula [21]:

$$\text{SIR-spheres Activity} = (\text{treatment liver volume} / \text{total liver volume}) * [(BSA - 0.2) + (\text{fraction of liver with tumor})]$$

For ⁹⁰Y glass microspheres, total activity of ⁹⁰Y was calculated using the following formula [7,22]:

$$\text{Therasphere activity (GBq)} = \text{Desired dose (Gy)} \times \text{Mass of selected live target lobe/50}$$

In cases where lung shunting was between 10-15%, patients received a 20% reduction of the calculated radiation dose. Adjustments were not made based on prior treatment history.

CLMs confined to one lobe were treated in one session whereas bilobar disease was treated in two sessions separated by 4-8 weeks. If the limited extent of disease permitted sublobar microspheres infusions, the patients with bilobar disease were also treated within one session (as long as not more than 50% of liver parenchyma was exposed to the radiation at each session). Patients with a single hepatic lobe post-resection were treated in lobar or sublobar fashion depending on the extent and location of disease. In general, we aimed to treat as selectively as possible to treat all tumors while sparing uninvolved liver parenchyma.

Study objectives

Primary objectives included:

- 1) Analysis of liver progression-free survival (LPFS) and factors associated with LPFS. LPFS was defined as the time between the treatment date until disease progression

or death/last follow-up. It was calculated using competing risk analysis. If there was no liver disease progression and no imaging available within 6 months before death, then the date of last imaging was included in competing risk analysis. If there was no liver disease progression and there was imaging within 6-months before death available, death date was included in the competing risk analysis. LPFS was evaluated using EORTC and RECIST 1.1 criteria, depending on imaging availability. In cases of differing responses between the criteria, the concordance between both modalities imaging findings was used to determine LPFS;

- 2) Overall survival (OS) and factors associated with it. OS was defined as the time from initial RAE to patient death or last follow-up.

Secondary objectives included:

- 1) Evaluation of local tumor response and objective response rate (ORR);
- 2) Assessment of radiologic response within the treated hepatic territory. It was performed using contrast-enhanced CT and ¹⁸F-FDG PET/CT at 4-8 and 12-16 weeks post-RAE and compared to the pre-RAE scans. Scans at 4-8 weeks were used as the new baseline for subsequent imaging obtained every 2-4 months thereafter. Radiologic response in the liver was assessed by changes in size and metabolic activity using RECIST 1.1 and European Organization for Research and Treatment of Cancer criteria (EORTC). Using EORTC criteria, 25% threshold was chosen to define response or disease progression, using the sum of up to 5 liver lesions maximum standard uptake values (SUV_{max}). In patients with two RAE sessions, response was evaluated for each treated region. ORR was defined as the percentage of patients with partial or complete response within 12-16 weeks post-RAE, based on RECIST 1.1 and EORTC criteria.

Prognosticators of LPFS and OS

Total of 24 factors were analyzed as potential prognosticators of LPFS. They included primary disease-related variables, liver tumor burden, CEA level, genetic mutations (KRAS, BRAF, PI3KCA), prior and post-RAE systemic regimens for metastatic CRC, procedure-related parameters (sphere type, delivered radiation dose and occurrence of stasis), pre-RAE laboratory parameters {(neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR))} and metabolic tumor uptake parameters {(SUV_{max}, SUV_{peak}, SUV_{mean}, metabolic tumor volume (MTV) and total lesion glycolysis (TLG))} of the most metabolically active tumor.

Forty factors were analyzed as potential prognosticators of OS. In addition to the factors described above, we included the following factors to overall survival analysis: patients'

age, pre-RAE liver function laboratory parameters, primary disease-related variables, CEA level, pre-and post-RAE therapies, post-RAE NLR and PLR, disease-free survival, time from liver metastases diagnosis to RAE, LPFS and number of extrahepatic disease sites.

Statistical analysis

The median follow-up period was calculated for the patients who were alive on last follow-up. Prognosticators of OS and LPFS were selected using univariate Cox regression, adjusted for clustering and competing risk analysis (for LPFS) and subsequently tested in multivariate analysis (MVA). Only pre-treatment easy-to-obtain and well-established parameters were included into MVA as potential predictors of overall survival. All the nomogram factors were included as continuous variables (except for tumor differentiation level) for more accurate estimation of each factor's predictive value. Liver PFS association with OS was assessed using Cox regression analysis, including only the patients, who had liver disease progression.

The nomogram was built using R statistical software and internally validated using bootstrap resampling. Statistical analysis was performed using STATA 12.1 software. A p-value <0.05 was considered significant.

RESULTS

Study population

One hundred and three patients treated with 136 RAE sessions were included in the study. Median follow-up time was 9.02 months (range, 0.7-42.7 months). Sixty-three/103 (61%) patients were men, 40 (39%) – women, with a median age of 60 years (range, 24-87 years). Seventy-six/103 (74%) patients had synchronous liver metastases. The median time from diagnosis of CLM to RAE was 30.9 months (range: 3.4-161.7 months).

Eighty-one/103 (79%) of patients were treated with resin microspheres, 21/103 (20%) - with glass microspheres, 1/103 (1%) with both (initially with resin and LTP retreatment with glass microspheres almost 3-years later). Seventy-three/103 (71%) of patients were treated in one RAE session, 26/103 (25%) – in two sessions. Seven/103 (7%) of patients underwent repeat RAE for: (1) LTP in previously treated region (in 3 patients); (2) progression of disease in untreated liver lobe (in 3 patients); (3) additional RAE in the same region due to poor tumor coverage during initial RAE (in 1 patient; partial recanalization of embolized vessel precluded flow redirection to a tumor region during initial RAE). Patient characteristics are described in **Table 1**.

Table 1 Patient demographics and disease characteristics.

Patient demographics and disease characteristics	Number of patients
Age (median, range)	60 (range, 24-87 years)
Gender, M: F	63:40
Synchronous liver disease	81: 22
Pathologic evidence of vascular invasion from primary tumor (yes/no/unknown)	44: 33: 26
KRAS mutation (yes/no/unknown)	29: 33: 16
PIK3CA mutation (yes/no/unknown)	10: 41: 52
Surgical resection of primary disease (yes/no/unknown)	82: 20: 1
CEA level before RAE (median, range ng/ml)	55.3 (1.1-23937.6)
Time from diagnosis of CRC to diagnosis of CLM (mean, median, range, in months)	6.3; 0 (range 0-64.2)
Time from diagnosis of CLM to RAE (median, range)	30.9 (range, 3.4-161.7)
Type of microspheres (resin/glass/both)	81: 21: 1
Prior liver surgery (yes/no)	49: 54
Prior HAIP chemotherapy (yes/no)	53: 50
Prior systematic chemotherapy (≥3 lines vs. <3 lines)	30: 73
Prior bevacizumab (yes/no)	63: 40
Extent of hepatic replacement by tumor at time of RAE (<25%; ≥25%)	89: 14
Presence of extrahepatic disease at time of RAE (yes/no)	74: 29
Number of confirmed metastatic extrahepatic organ systems at time of RAE (0: 1: 2: 3: 4)	29: 38: 24: 9: 3
ECOG status at time of RE (Grade 0/1/2/unknown)	33: 26: 2: 42
Distribution of hepatic disease at time of RAE (unilobar/unilobar with one hepatic lobe left/bilobar)	17: 11: 75
Incidence of stasis in resin microspheres infusions	39/146 (27%)
% of prescribed radiation dose delivered to tumor per procedure	96% (range, 19-106%)
Number of RAE sessions per patients (one/two)	73: 30
Post-RAE HAIP* therapy (yes/no)	18: 85
Number of post-RAE systemic chemotherapy lines (0: 1: 2: 3: 4: unknown)	25: 39: 22: 15: 1
Post-RAE ablation (yes/no)	5: 98

*HAIP-hepatic arterial infusion pump therapy; CEA-carcinoembryonic antigen level; CRC-colorectal cancer; CLM-colorectal liver metastases; RAE-radioembolization.

Local tumor response, objective response rate and liver progression-free survival

On the first imaging post-RAE at 4-8 weeks, 39% of patients had partial response according to EORTC criteria, whereas 59% had stable disease according to RECIST 1.1. Objective response rate (complete or partial response) at 12-16 weeks post-RAE was 44/84 (52%) by EORTC and 6/94 (6%) by RECIST 1.1 criteria. Local tumor response at initial 4-8 weeks post-RAE imaging is described in **Table 2**.

Despite the lack of statistical significance, the patients who developed early/late stasis in at least one infusion during ⁹⁰Y RAE, had roughly double the risk for local tumor progression on initial scan, defined by RECIST 1.1 (p= 0.19, OR=1.81) or EORTC criteria (p=0.14, OR=2.2).

Table 2 Local tumor response on first imaging after radioembolization (at 4-8 weeks) and at second follow-up (at 12-16 weeks)

Response	At 4-8 weeks		At 12-16 weeks	
	EORTC	RECIST 1.1	EORTC	RECIST 1.1
Complete response (CR)	5/84 (6%)	1/94 (1%)	3/55 (5%)	0
Partial response (PR)	33/84 (39%)	0	9/55 (16%)	3/76 (4%)
Stable disease (SD)	17/84 (20%)	55/94 (59%)	7/55 (13%)	39/76 (51%)
Progression of disease (POD)	20/84 (24%)	25/94 (27%)	35/55 (64%)	31/76 (41%)
Different response in treatment regions:				
SD+PR	4/84 (5%)	3/94 (3%)	-	-
SD+POD	2/84 (2%)	9/94 (9%)	-	3/76 (4%)
PR+POD	2/84 (2%)	1/94 (1%)	-	-
SD+CR	1/84 (1%)	0	-	-
CR+POD	-	-	1/55 (2%)	-
Not applicable*	19/103 (18%)	9/103 (9%)	48/103 (47%)	27/103 (26%)

LTP-local tumor progression, CR-complete response, PR-partial response, SD-stable disease, POD-progression of disease.* Due to absent follow-up or baseline imaging, measurements could not be obtained due technical problems

Despite the lack of statistical significance, the patients who had ≥ 96% of prescribed radiation dose delivered, had 44% lower risk of local tumor progression at first imaging, compared to patients who received <96% of the dose, when LTP was defined by EORTC criteria (p=0.32, OR=0.56).

Sphere type was neither associated with local tumor progression on first follow-up, evaluated by RECIST1.1 or EORTC criteria (p=0.99 for both), nor with liver progression-free survival (p=0.77, SHR=1.08).

Liver progression-free survival (LPFS) and its prognosticators

Median LPFS was 4 months (95%CI, 3.4-4.9 months). Six-months and 1- year LPFS were 27% (95%CI,18-36%) and 9% (95%CI, 3-16%).

Only increased metabolic tumor parameters (SUVmax, SUVpeak, MTV and TLG) and decreased time from CLM diagnosis to RAE were significantly associated with decreased liver progression-free survival on univariate analysis (**Table 3**). Due to correlation between metabolic parameters, only two variables (SUVmax and time from CLM diagnosis to RAE) were included in the multivariate analysis (MV). Only SUVmax was significant predictor of LPFS on MV analysis (p= 0.003, HR=1.06, 95%CI, 1.02-1.1).

Table 3 Univariate analysis for prognosticators of overall survival (OS) and liver progression-free survival (LPFS) post-radiomebolization (RAE)

Variable group	Variable	OS, p-value	HR	LPFS, p-value	SHR
Patient variable	Age	0.23	0.76	-	-
Time variable	Time from diagnosis of CLM to RAE	0.06	0.99	0.034*	0.99
	Disease-free interval (from primary Rx to CLM)	0.07	0.99	-	-
Primary disease-related variables	Primary tumor resection (no/yes)	0.52	0.82	-	-
	Nodal status of the primary (positive/negative)	0.77	0.33	-	-
	Lymphovascular invasion of primary (yes/no)	0.03*	1.74	0.35	0.79
	Tumor differentiation (good/moderate vs. poor)	0.009*	2.05	0.55	0.81
	Synchronous vs. metachronous liver metastases	0.24	1.31	0.31	1.27
	Side of primary (left vs. right; transverse excluded)	0.33	0.77	0.45	1.25
Disease-related variables at time of RAE	Liver tumor burden (≥25% vs. <25%)	0.056	1.77	0.74	1.12
	Number of EHD sites (range, 0-4)	0.03*	1.26	-	-
	Sum of largest diameters of two liver lesions (cm)*	0.001*	1.08	0.95	1
	CEA level at time of RAE (ng/ml)	<0.001*	1.0001	0.07	1.0005
Genetic mutations	KRAS (positive/negative)	0.16	1.45	0.15	1.48
	PI3KCA (positive/negative)	0.78	1.13	0.69	0.79
	BRAF (positive/negative)	0.88	0.89	0.2	1.38
Prior to RAE variables	Prior HAIP (no/yes)	0.76	0.88	0.71	0.92
	Prior systemic therapy (≥3 lines vs. <3 lines)	0.84	1.05	0.55	0.87
	Prior liver surgery	0.36	0.82	0.75	0.93
RAE-related variables	% of prescribed radiation dose delivered	0.43	1.004	0.6	1.003
	Sphere type (resin vs. glass microspheres)	0.77	0.92	0.87	0.95
	Occurrence of stasis (yes/no)	-	-	0.73	0.93
Metabolic tumor uptake parameters (of 1-5 most FDG-avid lesions)	SUV max (continuous)	0.028*	1.05	<0.001*	1.06
	SUV peak (continuous)	0.025*	1.06	0.001*	1.08
	SUV mean (continuous)	0.004*	1.13	0.41	1.03
	MTV (continuous)	<0.001*	1.001	<0.001*	1.0007
	TLG (continuous)	<0.001*	1.0002	0.046*	1.0001
Pre-RAE laboratory parameters	Pre-RAE NLR	0.02*	1.05	0.4	1.02
	Pre-RAE PLR	0.001*	1.002	0.12	1.001
	Albumin	<0.001*	0.36	-	-
	Total bilirubin	0.4	1.26	-	-
	AST (aspartate aminotransferase)	<0.001*	1.02	-	-
	ALT (alanine aminotransferase)	0.003*	1.01	-	-
	ALP (alkaline phosphatase)	0.001*	1.002	-	-
Post-RAE laboratory parameters/therapies	Post-RAE NLR (neutrophil/lymphocyte ratio)	0.077	1.04	-	-
	Post-RAE PLR (platelet/lymphocyte ratio)	0.6	1.0003	-	-
	Post-RAE HAIP (hepatic artery infusion pump)	0.001*	0.42	-	-
	Post-RAE ablation	0.029*	0.35	-	-
	Post-RAE chemotherapy lines (≤1 vs 2-4)	<0.001*	0.48	-	-
	Post-RAE bevacizumab	0.001*	0.48	-	-
	Liver progression-free survival (in months)	0.002*	0.9	-	-

*Statistically significant factors. Analyzed using Cox regression adjusted for clustering: 3 patients had 2 initial radioembolization treatments, thus were clustered. CLM-colorectal liver metastases, RAE-radioembolization, Rx-resection, EHD-extrahepatic disease, CEA-carcinoembryonic antigen level; SUV-standard uptake value, MTV-metabolic tumor volume, TLG-total lesion glycolysis; SHR- sub-hazard ratio

Overall survival

Median OS was 11.3 months (95% CI 7.9 - 15.1 months). Six months, 1-, 2- and 3 - year OS was 75% (95%CI, 64-81%), 46% (95%CI, 35-55%), 18% (95%CI, 11-27%) and 15% (95%CI, 8-24%), respectively. There were no deaths within 30 days post-RAE.

Total of 11/103 (11%) patients died within 3 months post- RAE. None of these deaths were considered directly or solely related to the RAE: 7/11 (64%) of the patients had evidence of liver disease progression; 8/11 (73%) patients also developed conditions, that resulted in significant morbidity and were at least partially related to RAE, but did not lead to subsequent death. Analysis of deaths within 3-months post-RAE is presented in **Table 4**.

Factors associated with overall survival: creation of predictive nomogram

Twenty-one/40 factors were associated with overall survival post-RAE in univariate analysis (**Table 3**). Considering the number of deaths during the study period {87/103 (84%)}, only 8 factors with low correlation between each other could be included in MV analysis.

Six/8 pre-RAE parameters included into MV analysis were significantly associated with OS and were subsequently used to build an overall survival prediction nomogram (**Table 5**). These factors included: (1) baseline CEA level (2) baseline ALT level (3) albumin level (4) sum of sizes of two largest CLM diameters in the treatment region (5) number of extrahepatic disease sites and (6) tumor differentiation level (**Figure 1**).

One patient had CEA level >20000 ng/ml and was considered as an outlier in our study, that contributed to very high CEA values in the nomogram. It was excluded from internal validation as it was adversely affecting model fit and evaluation.

Each MV analysis factor was assigned points relative to each hazard ratio. The nomogram assigned the probability of 1-year survival by summing the point-scale scores for each variable. The total score projected on the bottom scale indicated the probability of 1-year survival. One-year OS of patients with total points <25 indicated 90% chance of 1-year survival, whereas total sum of points of >80 estimated 10% chance of 1-year survival. Bootstrap resampling showed good discrimination (optimism corrected c- index=0.745) and calibration (mean absolute prediction error=0.299) of the nomogram.

Complications

The incidence of Grade 1-2 toxicities was 44/102 (43%) (**Table 6**). The incidence of Grade 3-4 toxicities was 14/102 (14%) (**Table 6**). Two patients in our study developed hepatic

venous occlusion post-RAE: Budd-Chiari syndrome in one patient and right hepatic vein, inferior vena cava thrombus and bilateral pulmonary embolism in second patient with lung disease progression.

Table 4 Overview of post-procedure course of patients who expired within 3 months post-radioembolization

Baseline patient characteristics	Post-RAE course/potential reason of death	Death time
Hx of HAIP; >25%TB, bilobar liver disease; CEA=766 ng/ml; EHD sites=2	RAE-related major toxicity (grade 3-4 chest pain, SOB, pleural effusion in face of stable lung metastases one-month post-RAE); managed conservatively. Death cancer-related, likely due liver failure with evidence of liver POD (one-month post-RAE) and EHD POD (lungs, lymph nodes)	1.93 months
Hx of HAIP; bilobar liver disease, CEA=1357 ng/ml EHD sites=4	RAE-related major toxicity: grade 4 SOB (acute hypersensitivity to steroids post-procedure), resolved. Cancer-related death in face of EHD POD one-month post-RAE and liver POD on first follow-up; Hx of hemochromatosis	1.53 months
Hx of liver Rx and HAIP; >25% TB, bilobar liver disease, CEA=228 ng/ml EHD sites=2	Cancer-related death, likely due liver failure (ascites/grade 3 hyperbilirubinemia/anasarca) in face of liver POD (which precluded 2 nd RAE session), lung POD and bilateral pulmonary embolism/pleural effusion/IVC and RHV thrombi 1-month post-RAE (treated with anticoagulation)	2.93 months
Hx of HAIP; bilobar liver disease, CEA=218 ng/ml	Unknown death reason; likely liver failure in face of RFA 1-month post-RAE with grade 4 hyperbilirubinemia/fever)	2.27 months
Hx of liver Rx and HAIP; EHD sites=1; ECOG=1	RAE contributed to fatal outcome (dramatic increased of LFTs right post-RAE); also, liver POD, secondary biliary obstruction, coagulopathy, colitis, duodenal stenosis, required stenting, HBV	1.27 months
Hx of HAIP, mitomycin, ≥3 chemotherapy lines, bilobar disease, CEA=4713 ng/ml	Death reason unknown, likely liver failure in patient with history of hemochromatosis (2-months post-RAE admitted for abdominal pain in outside hospital with biliary stricture, cirrhosis, ascites)	2.9 months
Hx of liver Rx, HAIP, ≥3 chemotherapy lines, bilobar disease, EHD sites=2	Post-RAE: ECOG decline (from 0 to 3, 5-days post-RAE). Could not proceed with planned 2 nd RAE session due grade 3 hyperbilirubinemia in face of liver POD on first follow-up	2.47 months
Hx of HAIP, ≥3 chemotherapy lines, bilobar disease, EHD sites=2	Post-RAE: severe abdominal, back pain/anorexia/ SOB/chest pain/ phlegm 1-week post-RAE; 11 days post-RAE admitted for pneumonia, recovered. Death cancer-related (although no records within 3 weeks before death)	1.83 months
Bilobar disease, CEA=130 ng/ml, EHD sites=2, ECOG=1	Death cancer-related in face of untreated liver POD, peritoneal carcinomatosis and not-RAE related adverse event (6 weeks post-RAE obstruction due stomach bleed (patient was on Xarelto) requiring transfusion; significant ECOG decline	1.77 months
Bilobar disease, EHD sites=2 ECOG=1	Grade 3-4 toxicity: Post-embolization syndrome. Six weeks post-RAE urosepsis, 2 months post-RAE: brain radiotherapy for brain metastases, then altered mental status/ hypoxia due fluid overload, leptomeningeal metastases	2.13 months
Hx of HAIP; bilobar disease, CEA=404 ng/ml; EHD sites=1	No report of RAE-related toxicity and other adverse events after RAE	2.3 months

Hx-history, Rx-resection, RAE-radioembolization, TB-tumor burden, CEA-carcinoembryonic antigen level, EHD-extrahepatic disease, POD-progression of disease, RT-radiotherapy, ECOG-performance status, IVC-inferior vena cava, RHV-right hepatic vein, RFA-radiofrequency ablation, LFTs- liver function tests

Table 5 Multivariable analysis of factors associated with overall survival post-radiomebolization

Variable included to MVA	p-value	HR	95%CI
Tumor differentiation level (good/moderate vs. poor)	<0.0001	5.3	2.6-10.7
Sum of largest diameters of two liver target lesions	<0.0001	1.15	1.09-1.21
Number of EHD sites (range, 0-4)	0.016	1.41	1.07-1.87
CEA level at time of RAE (ng/ml)	<0.001	1.00009	1.00006-1.0001
Albumin	0.005	0.46	0.27-0.79
ALT (alanine aminotransferase)	<0.0001	1.02	1.01-1.03
Lymphovascular invasion on pathology of primary (yes/no)	>0.05	Excluded by stepwise forward selection	
Pre-RAE NLR (neutrophil/lymphocyte ratio)	>0.05	Excluded by stepwise forward selection	

EHD-extrahepatic disease; CEA-carcinoembryonic antigen level, RAE-radioembolization

Table 6 Post-radiomebolization toxicities

Grade 1-2 toxicities		
1.	Fatigue/weakness	43/102 (42%)
2.	Abdominal pain/distension	23/102 (23%)
3.	Constipation/diarrhea	14/102 (14%)
4.	Fever	11/102 (11%)
5.	Change in appetite/weight changes	11/102 (11%)
6.	Nausea	10/102 (10%)
7.	Light colored stool/dark urine	10/102 (10%)
8.	Shortness of breath	10/102 (10%)
9.	Ascites	5/102 (5%)
10.	Vomiting	4/102 (4%)
11.	Shoulder/back pain	4/102 (4%)
12.	Hiccups	1/102 (1%)
13.	Portal hypertension	1/102 (1%)
14.	Portal hypertension/ascites in patient with prior oxaliplatin administration	1/102 (1%)
TOTAL		44/102 (43%)
Grade 3-4 toxicities		
1.	Post-radioembolization syndrome (at 1-90 days)	5/102 (5%)
2.	Grade 3 abdominal pain/distension (at 10-12 days)	3/102 (3%)
3.	Grade 3 fevers (at 3 days)	1/102 (1%)
4.	Acute liver failure/ failure to thrive/ grade 3 hyperbilirubinemia (at 14 days)	1/102 (1%)
5.	Grade 3 dyspnea (at 30 days)	1/102 (1%)
6.	Biliary obstruction + Budd-Chiari syndrome+ stop chemotherapy for 6 weeks (at 1-day/60-days)	1/102 (1%)
7.	Biloma requiring multiple drainages, liver abscess, E. Faecium sepsis; patient with liver POD (at 5 days)	1/102 (1%)
8.	Post-mapping brain infarction due anticoagulation break in patient with history of atrial fibrillation. Post-procedure hypertension, recurrent atrial fibrillation, abdominal pain, hypotension, fever, required overnight admission (at 1 day)	1/102 (1%)
TOTAL		14/102 (14%)

One patient was lost to follow-up post procedure; Multiple complications possible per patient; POD-progression of disease

Figure 1 Nomogram for overall survival prediction after radioembolization of colorectal cancer liver metastases. Size - sum of largest diameters of two largest liver lesions in intended-to-treat-region; EHD- number of extrahepatic disease sites; CEA-carcinoembryonic antigen level (ng/ml); Alt - alanine aminotransferase (U/L); differentiation- tumor differentiation level.

Example 1 of nomogram points calculation. The patient presented for radioembolization with following parameters: sum of two largest liver lesions diameters of 11.1 cm, two sites of extrahepatic disease, CEA 765.6 ng/ml, albumin of 2.3 g/dl, ALT of 27 U/L and poor tumor differentiation level. By drawing a straight line from the 11.1 cm point on the Size axis of the nomogram to the Points axis we find that a lesion of 11.1 cm corresponded to 25 points. Repeating the same for the other variables, we got 10 points for two sites of extrahepatic disease, 1 point for CEA of 765.6 ng/ml, 45 points for albumin of 2.3 g/dl points, 9 points for ALT of 27 U/L and 27 points for poor tumor differentiation. Sum of these points was 117 and again drawing a straight line from 117 on the Total Points axis to the 1 Year Survival prediction axis we obtained <10 % as the predicted probability of 1-year survival for this patient. The patient had actual overall survival of 1.9 months.

Example 2 of nomogram points calculation. The patient had following baseline characteristics: sum of two largest liver lesions diameters of 1.8 cm, no extrahepatic disease, CEA 2.9 ng/ml, albumin of 4.5 g/dl, ALT of 34 U/L and moderate tumor differentiation level. By drawing a straight line from the 1.8 cm point on the Size axis of the nomogram to the Points axis we find that a sum of lesions diameters of 1.8 cm corresponded to 4 points. Repeating the same for the other variables, we got 0 points for no extrahepatic disease, 0 points for CEA of 2.9 ng/ml, 9 points for albumin of 4.5 g/dl points, 12 points for ALT of 34 U/L and 0 points for moderate tumor differentiation. Sum of these points was 25 and again drawing a straight line from 25 on the Total Points axis to the 1 Year Survival prediction axis we obtained 90% as the predicted probability of 1-year survival for this patient. The patient had actual overall survival of 60.3 months.

DISCUSSION

This work provided an extensive, comprehensive analysis of imaging, laboratory, pathologic, genetic, primary-disease-related biomarkers, and procedure - related factors as well as prior and post-RAE therapies, associated with overall and liver progression-free survival following RAE of CLMs.

Overall survival prediction nomogram

The developed nomogram included six easy-to-obtain pre-RAE parameters and provided good prediction of patient survival post-RAE, based on internal bootstrap validation result: nomogram showed good discrimination (c-index=0.745) and calibration. One-year overall survival of patients with total nomogram points of <25 vs. >80 was 90% and 10%, respectively.

Existing overall survival prediction nomogram, created by Fendler et al [23] potentially suffered from selection bias due to the inclusion of patients with very limited extrahepatic metastases and did not demonstrate any association of extrahepatic metastases with survival, contradictory to the reported negative impact of extrahepatic disease on patient survival post-RAE [24-26]. Overall 73% of this study patients had extrahepatic metastases at the time of RAE. Recent multicenter randomized phase 3 trials (FOXFIRE, SIRFLOX, and FOXFIRE-Global) showed no survival benefit when combining ⁹⁰Y radioembolization with first-line chemotherapy [13]. According to existing evidence, patients will continue to present for RAE at latest stages of disease, especially when they progress in the liver while receiving second, third or subsequent chemotherapy regimens. RAE is recommended in the chemo-refractory or salvage setting [1]. It is therefore important to identify and describe predictive factors in these settings. An overall survival prognostic score, developed by Damm et al, included heavily pre-treated patients, with a median baseline Karnofsky index of 80% and liver tumor load of 20%. The overall survival post-RAE was 6.7 months. This suggests that radioembolization was a relatively aggressive therapy for this specific compromised population [27]. In our study, only 3% of patients had ECOG grade 2 performance status and only 14% had ≥25% baseline liver involvement by tumor.

All increased metabolic tumor uptake parameters of most metabolically active tumor (SUVmax, SUVpeak, SUVmean, MTV, TLG) within the intended-to-treat region were significantly associated with decreased overall survival. Recent studies confirmed that ¹⁸F-FDG PET/CT is useful to evaluate treatment response and it is an emerging prognostic tool in patients with CLM undergoing RAE, with semi-quantitative factors (as MTV and

TLG) correlating with survival better than RECIST criteria [28,29]. We therefore advocate metabolic imaging to be always performed before RAE. Prior investigations described anatomic biomarkers, such as CLM size, as predictor of decreased survival post-RAE [23, 30-32]. Measuring the sum of two largest lesion diameters is also important for RECIST 1.1 evaluations and was part of our nomogram. Both anatomic (lesion size) or metabolic tumor parameters were statistically significant predictors of overall survival in this study. However, both factors could not be included into the nomogram, because lesion size generally correlates with metabolic uptake. Thus, due to the fact, that ¹⁸F-FDG PET/CT is not always available in other institutions for treatment planning, we chose to include anatomic parameters into the nomogram.

ALT (SGPT, alanine aminotransferase), unlike other routine liver panel enzymes, is predominantly found in the liver and released into the bloodstream as the result of liver injury, thus serves as a fairly specific indicator of liver damage. ALT was the most predictive nomogram factor of decreased survival: ALT level >250 U/L alone corresponded to >80 nomogram points, distinguishing patients with >90% risk for death within 1-year after RAE. Other liver enzymes – aspartate aminotransferase and alkaline phosphatase – were also found to be associated with post-RAE survival. Since we could only include a limited number of factors in the MV analysis and the latter factors are less hepatic function-specific biomarkers compared to ALT, they were not included. Transaminase toxicity was predictive of survival post-RAE in prior studies [23,33], thus it should be emphasized as an important patient selection criterion in patients with CLM. Total bilirubin level was not predictive of survival in our study, most likely due to the strict inclusion criteria of RAE in our center. Only patients with total bilirubin ≤ 1.5 mg/dl were eligible for RAE. Commonly, patients with bilirubin <2 mg/dl are considered eligible for RAE [34].

CEA level differed dramatically in this cohort, with a median of 52 ng/ml, ranging from normal level to >20000 ng/ml, considered as an outlier in our study, that contributed to very high CEA values in the nomogram. Increased CEA level has been associated with poorer survival post-RAE of CLM in multiple studies [4,28,33,35], however, this is influenced by multiple factors, including tumor differentiation level, liver function and the side of primary tumor [35].

The overall survival predictors in this study are similar to a recent study, where higher CEA and AST level, NLR >5, extrahepatic disease, and larger volume of liver metastases were independently associated with increased risk of death on multivariate analysis [36].

Median overall survival in this cohort was 11.3 months post-RAE. This compares favorably

to large retrospective studies with reported median survival of 7.2-10.6 months after radioembolization of CLM, mostly in the salvage setting [37-39]. It should be noted, that RAE in this cohort was administered at a median of 30.9 months from the initial diagnosis of CLM. This reflects that most patients were heavily pre-treated and received multiple prior liver-directed therapies, including resection, HAIP and ablation. Pre-RAE therapies were not associated with overall survival, although, the fact, that most patients received loco-regional therapies pre-RAE might have influenced that. The actual liver function and parameters indicating underlying hepatic toxicity (albumin and ALT level), the metastatic disease volume (liver tumor(s) size, extrahepatic disease extent and CEA level) as well as tumor differentiation were significant predictors of post-RAE overall survival.

All analyzed post - RAE therapies (increased number of systemic chemotherapy lines, HAIP, ablation and bevacizumab) were associated with increased overall survival post-RAE. This result is concordant to prior studies, where RAE did not prohibit re-initiation of systemic chemotherapy, hepatic arterial infusion pump therapy or ablation for CLM that persisted or progressed after initial response to RAE [4, 9, 12, 40-42]. This also demonstrated that overall survival post-RAE cannot be attributed solely to RAE, but rather to the overall management of the disease in the salvage setting. Post-RAE therapies were not included in the 1-year overall survival prediction nomogram. This was necessary to allow us to reach our goal of patient stratification before RAE in this setting.

Patients with KRAS or PI3KCA mutations and left-sided primary tumors showed decreased overall survival following RAE in our study, however, the difference was not statistically significant. Patients with BRAF mutation and right-sided primary tumor showed increased post-RAE survival, but again-not statistically significantly.

Predictors of local tumor progression and liver progression-free survival

Objective response rate of 52% in this study compares favorably with published data of 10-48% response rates, depending on whether the patients received RAE with second line chemotherapy or at the salvage setting [10, 17, 19, 20, 43]. Baseline SUV_{max} was the only significant predictor of liver progression-free survival on MV analysis. There was no significant difference in liver progression-free survival for those, who received resin or glass microspheres. Although the incidence of stasis, resulting in suboptimal radiation dose delivery to tumor increased the risk of local tumor progression, it did not reach statistical significance. PI3KCA mutation was not a significant predictor of LPFS in this cohort, unlike in prior study [44]. This could be related to difference in methodology between studies (response evaluation criteria, evaluation of local tumor progression,

rather than LPFS and analysis of different PI3K mutations, associated with gain of function).

Safety of ⁹⁰Y radioembolization

RAE had acceptable safety profile in this series with incidence of grade 3-4 toxicities of 14%, median overall survival of 11.3 months, no death within 30 days post-procedure and no RAE-related death within 3-months post-treatment.

Two patients in this study developed liver venous occlusion post-RAE: Budd-Chiari syndrome in one patient and right hepatic vein, inferior vena cava thrombus and bilateral pulmonary embolism in second patient. Radiation therapy was shown to cause endothelial activation with subsequent pro-thrombotic response and tissue inflammation with subsequent vein external compression, stasis and thrombus formation [45]. However, the number of patients with these complications was too small to draw meaningful conclusions regarding liver venous occlusion association with RAE.

Study limitations

Study limitations included the single center retrospective study design with its inherited limitations and a relatively short follow-up time. Also, there was a lack of external nomogram validation that preferably would include prospectively recruited patients at multiple centers. Finally, actual radiation dose delivered to the tumor could not be measured in this study due to technical limitations, thus it could not be analyzed as a prognosticator of RAE.

CONCLUSION

The developed nomogram included six pre-RAE parameters and provided good prediction of patient survival post-RAE. Baseline SUVmax was the single significant predictor of liver progression-free survival on multivariate analysis.

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⁹⁰Y Resin Microspheres Radioembolization for Colon Cancer Liver Metastases Using Full- Strength Contrast Material

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ABSTRACT

Objectives

To assess safety and efficacy of ⁹⁰Y resin microspheres administration using undiluted non-ionic contrast material (UDCM) {100% Omnipaque-300 (Iohexol)} in both the “B” and “D” lines.

Materials and methods

We reviewed all colorectal cancer liver metastases patients treated with ⁹⁰Y resin microspheres radioembolization (RE) from 2009 to 2017. As of April 2013, two experienced operators started using UDCM (study group) instead of standard sandwich infusion (control group). Occurrence of myelosuppression (leukopenia, neutropenia, erythrocytopenia or/and thrombocytopenia), stasis, non-target delivery (NTD), median fluoroscopy radiation dose (FRD), median infusion time (IT), liver progression-free (LPFS) and overall survivals (OS) was evaluated. Complications within 6 months post-RE were reported according to CTCAE v3.0 criteria.

Results

Study and control groups comprised 23(28%) and 58(72%) patients, respectively. Median follow-up was 9.1 months. There was no statistically significant difference in myelosuppression incidence within 6 months post-RE between groups. Median FRD and IT for study and control groups were 44.6 vs. 97.35 Gy/cm² ($p=0.048$) and 31 vs. 39 min ($p=0.006$), respectively. A 38% lower stasis incidence in study group was not significant ($p=0.34$). NTD occurred in 1/27 (4%) study vs. 5/73 (7%) control group procedures ($p=1$). Grade 1–2 and grade 3–4 toxicities between study and control group patients were 36% (8/22) vs. 45% (26/58), $p=0.61$ and 9% (2/22) vs. 16% (9/58), $p=0.72$, respectively. There was no difference in LPFS and OS between groups.

Conclusion

Administration of ⁹⁰Y resin microspheres using UDCM in both lines is safe and effective, resulting in lower fluoroscopy radiation dose and shorter infusion time, without evidence of myelosuppression or increased stasis incidence.

INTRODUCTION

⁹⁰Y resin microspheres (SIR-Spheres—Sirtex Medical, Sydney, Australia) radioembolization (RAE) is an FDA approved brachytherapy device, recommended through the National Comprehensive Cancer Network and European Society for Medical oncology guidelines for the treatment of chemo-refractory colorectal cancer liver metastases (CLM) in selected patients with liver-only or liver-dominant disease [1–13]. The manufacturer recommends using a sandwich technique during ⁹⁰Y resin microspheres administration [14, 15]. This technique includes a vehicle {sterile water or 5% dextrose solution (D5W)} to preclude direct contact of iodinated contrast material with the resin microspheres. With the sandwich technique, the contrast agent is never used in the “D” line (authorized user line). Since neither the ⁹⁰Y microspheres nor the vehicle is radiopaque, the sandwich technique does not allow continuous monitoring of the microsphere flow toward the target tumor. This limits the ability to detect microspheres’ stasis or reflux, which can result in non-target delivery with unnecessary toxicity, as well as diminished radioactivity reaching the target tumor. This is particularly important when treating relatively hypovascular tumors such as CLM, where the incidence of stasis may be higher than 30% [16–18].

Although the administration of ⁹⁰Y resin microspheres with contrast agent in the “D” line is not recommended [15], there are only anecdotal and controversial data regarding potential disadvantages of this technique. The main concern of using a contrast agent as the delivery medium during ⁹⁰Y resin microspheres administration includes a theoretical possibility of ⁹⁰Y leaching from the resin microspheres. This could cause systemic non-target radiation delivery [19]. Resin-based yttrium microspheres normally have 0.01–0.4% unbound or unprecipitated ⁹⁰Y [20], with recommended amount of ⁹⁰Y leaching of less than 5% [21]. Another concern is the possibility of microspheres clumping, resulting in microcatheter occlusion. This was observed in vitro in the 1990’s, when resin microspheres were exposed to ionic contrast medium, although the details of that experiment remain unknown. Resin microspheres aggregation did not occur with isotonic solutions of non-ionic contrast agent and 5% dextrose [22].

The safety of a modified ⁹⁰Y microspheres infusion techniques using diluted non-ionic contrast agent in the “B” line-only [14, 22] or in both “B” and “D” lines has been demonstrated [23]. The administration of ⁹⁰Y resin microspheres using 50% non-ionic contrast agent in both lines resulted in lower incidence of stasis, shorter resin microspheres infusion and fluoroscopy times without complications [23].

Fluoroscopic image conspicuity is improved as the opacity degree increases. This is directly

proportional to the concentration of iodinated contrast agent used [24]. Since no adverse event was noted when using diluted contrast material, we started using undiluted contrast medium for ⁹⁰Y resin microspheres administration in 2013. This work was undertaken to specifically address the safety and efficacy of ⁹⁰Y resin microspheres RAE for CLM using undiluted non-ionic contrast material (UDCM) in both “B” and “D” lines.

MATERIALS AND METHODS

IRB waiver of approval was obtained for this retrospective review of our prospectively created and maintained HIPAA registered and compliant CLM RAE database. All patients with CLM treated with ⁹⁰Y resin microspheres RAE from 9/15/2009 to 1/19/2017 were included. Beginning in April 2013, two experienced operators started using 100% nonionic contrast agent {100% Omnipaque-300 (Iohexol 300 mgI/ml, GE Healthcare Inc.)} in both “B” and “D” lines (study group) instead of the standard sandwich infusion technique (control group) for ⁹⁰Y resin microspheres administration. In the study group, intermittent clearance with D5W or sterile water solution was performed from both “B” and “D” lines as needed not unlike any other embolization technique. Standard sandwich technique for microspheres administration was used in the control group per manufacturer’s instructions, which included administration of sterile water or D5W in both “B” and “D” lines with intermittent checking for the progress of radioembolization by using non-ionic contrast agent in “B” line.

Primary study objectives were as follows:

- (1) Comparison of incidence of myelosuppression and lymphopenia within 6 months post-RAE between the groups;
- (2) Comparison of incidence of stasis and/or reflux during RAE between the groups;
- (3) Comparison of non-target microspheres delivery between the groups;
- (4) Comparison of incidence of RAE-related hyperbilirubinemia, side effects and complications within 6 months post-RAE;
- (5) Comparison of ⁹⁰Y infusion time between the groups;
- (6) Comparison of fluoroscopic radiation dose between the groups;
- (7) Comparison of UDCM amount administered between the groups.

Secondary study objectives included:

- (1) Analysis of mean laboratory values changes post- RAE between the groups;
- (2) Liver progression-free survival (LPFS);
- (3) Overall survival (OS).

Definitions of study objectives were presented in **Supplement 1**. All patients were followed at 1–4, 5–8, 9–16 and 17–26 weeks after RAE with clinic visits and laboratory tests to evaluate for possible radiation-induced hepatotoxicity, systemic and any other toxic effect. All laboratory values were recorded by the blinded reader at abovementioned follow-up time points and compared to baseline. In cases of multiple laboratory values within a specific follow-up period available, the value closest to the middle of the specific period was chosen.

Imaging follow-up was obtained at 5–8 weeks and 9–16 weeks post-procedure to assess treatment response and every 3 months thereafter to detect disease progression. Statistical analysis methodology was described in **Supplement 2**.

RESULTS

Eighty-one patients underwent 146 ⁹⁰Y resin microspheres infusions. In 23 (28%) patients, ⁹⁰Y delivery was performed using UDCM (study group), whereas in 58 (72%) patients standard sandwich infusion technique was used (control group). Median follow-up time was 9.1 months. One patient in study group was lost to follow-up. Study and control group demographics and post-RAE therapies were described in **Supplements 3–4**.

Complete Blood Count (CBC) Values Change After Radioembolization: Evidence of Myelosuppression and Lymphopenia

Laboratory values on at least one follow-up time point were available for 20/23 (87%) patients in the study and 56/58 (97%) patients in the control group. On the last follow-up, laboratory values were available for 13/23 (57%) patients in the study and 40/58 (69%) in the control group. Analysis of CBC values at baseline and follow-ups between the study and control groups showed no evidence to support myelosuppression (**Tables 1-2, Figures 1-5**). When comparing study and control groups, the incidence of lymphopenia was statistically significantly lower in the study group at 5–8 weeks post-RAE (p = 0.05).

Detailed description of low CBC values within 6 months post-RAE with related clinical symptoms and treatment in the study group patients was described in **Supplement 5**.

Incidence of Stasis, Catheter Occlusion and Amount of Prescribed Radiation Dose Delivered

Incidence of stasis in study and control groups was 23% (95% CI 10–36%) vs. 28% (95% CI 19–37%). When accounting for multiple infusions per patients using generalized estimated equations test, the study group patients had 38% lower incidence of stasis (HR 0.62,

p = 0.34). The mean percentage of prescribed ⁹⁰Y dose administered was 90% in study group (95% CI 85–95%) versus 85% in control group (95% CI 81–89%), p = 0.21. No catheter occlusion was noted.

Table 1 Incidence of myelosuppression within 6 months after ⁹⁰Y radioembolization

Laboratory value	Control group	Study group	P value
<i>Leucopenia (<4 K/mcl)</i>			
Before treatment	10/57 (17%)	0/22 (0%)	0.06
After 1–4 weeks	11/53 (21%)	1/15 (7%)	0.28
After 5–8 weeks	15/54 (28%)	3/17 (18%)	0.53
After 9–16 weeks	16/49 (33%)	3/14 (21%)	0.52
After 17–26 weeks	10/40 (25%)	3/13 (23%)	1
<i>Neutropenia (<1.5 K/mcl)</i>			
Before treatment	2/57 (4%)	0/22 (0%)	1
After 1–4 weeks	1/53 (2%)	0/15 (0%)	1
After 5–8 weeks	2/54 (4%)	0/17 (0%)	1
After 9–16 weeks	5/49 (10%)	0/14 (0%)	0.17
After 17–26 weeks	2/40 (5%)	3/13 (23%)	0.09
<i>Erythrocytopenia (<4.2 M/mcl)</i>			
Before treatment	31/57 (54%)	15/22 (68%)	0.32
After 1–4 weeks	30/53 (57%)	11/15 (73%)	0.37
After 5–8 weeks	29/54 (54%)	10/17 (59%)	0.78
After 9–16 weeks	23/49 (47%)	10/14 (71%)	0.14
After 17–26 weeks	24/40 (60%)	8/13 (62%)	1
<i>Thrombocytopenia (<160 K/mcl)</i>			
Before treatment	24/57 (42%)	8/22 (36%)	0.08
After 1–4 weeks	20/53 (38%)	8/15 (53%)	0.37
After 5–8 weeks	28/54 (52%)	5/17 (29%)	0.16
After 9–16 weeks	25/49 (51%)	9/14 (64%)	0.54
After 17–26 weeks	21/40 (53%)	9/13 (69%)	0.35
<i>Lymphocytopenia (<0.5 K/mcl)</i>			
Before treatment	3/55 (5%)	3/20 (15%)	0.33
After 1–4 weeks	15/50 (30%)	4/16 (25%)	1
After 5–8 weeks	16/50 (32%)	1/16 (6%)	0.05
After 9–16 weeks	10/47 (21%)	3/13 (23%)	1
After 17–26 weeks	8/38 (21%)	0/13 (0%)	0.17

Table 2 Complete blood count value changes after RAE

Laboratory value	Coefficient*	P value	95% CI
WBC (K/mcl) Diff between infusion groups	0.02	0.98	[− 1.59; 1.63]
ANC (K/mcl) Diff between infusion groups	− 0.4	0.95	[− 1.46; 1.37]
RBC (M/mcl) Diff between infusion groups	0.11	0.17	[− 1.46; 1.37]
PLT (K/mcl) Diff between infusion groups	− 10.21	0.45	[− 36.41; 16.0]
ALC (K/mcl) Diff between infusion groups	0.14	0.11	[− 0.03; 30]

Analysis was made using multilevel mixed-effects linear regression model
Diff—difference; WBC—white blood cell count, ANC—absolute neutrophil count, RBC—red blood cell count, PLT—platelet count, ALC—absolute lymphocyte count. There was no statistically significant difference between study and control groups complete blood count changes over 6 months period.*Negative coefficients reflect lower mean values in study group during follow-up period, positive coefficients—higher mean values in study group

Figure 1 Mean white blood cell count (WBC) values within 6 months post-radiomebolization (accounted for multiple treatment sessions per patient). The figure demonstrates that there was no statistically significant difference in mean white blood cell count between study and control groups (p = 0.98)

Figure 2 Mean absolute neutrophil count (ANC) values within 6 months post-radiomebolization. The figure demonstrates that there was no statistically significant difference between study and control groups (p = 0.95)

Figure 3 Mean red blood cell count (RBC) values within 6 months post-radiation therapy. The figure demonstrates that there was no statistically significant difference between study and control groups ($p = 0.17$)

Figure 4 Mean platelet count (PLT) values within 6 months post-radiation therapy. The figure demonstrates that there was no statistically significant difference between study and control groups ($p = 0.45$)

Figure 5 Mean absolute lymphocyte count (ALC) values within 6 months post-radiation therapy. The figure demonstrates that there was no statistically significant difference between study and control groups ($p = 0.11$)

Median Fluoroscopy Radiation Dose, Microspheres Infusion Time and Amount of Used UDCM
Median microsphere infusion time was 31 vs. 39 min for the study vs. control groups ($p = 0.006$). A total of 71 single-infusion procedures were identified and used for the median fluoroscopy radiation dose and median amount of administered UDCM analyses; 8/71 (11%) infusions were excluded from the analysis as they required additional vascular embolization prior to RAE. After exclusion, 12 procedures in the study and 51 in the control group were analyzed.

Median single-infusion RAE fluoroscopy radiation dose for the study and control groups was 44.6 Gy/cm² (range, 19.4–221.8 Gy/cm²) and 97.35 Gy/cm² (range, 23.2–398.2 Gy/cm²), respectively, $p = 0.048$. There was no statistically significant difference in mean patients BMI values between study (26.6) and control group (28.4), $p = 0.3$. Median amount of UDCM administered in the study and control groups was exactly the same: 150 ml (range, 101–200 ml) and 150 ml (range, 60–275 ml), respectively, $p = 0.72$ (Table 3).

Table 3 Comparison of time from resin microspheres infusion start to post-implantation vial radioactivity measurement, fluoroscopy radiation doses and amount on contrast medium (Omnipaque-300) administered between study and control groups

Parameter	Study group	Control group*
Resin microspheres infusion time {from infusion start to post-implantation vial radioactivity measurement (for single-infusion procedures)}		
Number of patients	12	37
Median	31 min	39 min
Range	22–50 min	20–110 min
<i>P</i> value	0.0058	
Fluoroscopy radiation dose (Gy/cm2, for single-infusion procedures)		
Number of patients	12	46
Median	44.6	97.35
Range	19.4–221.8 Gy/cm2	23.23–398.16 Gy/cm2
<i>P</i> value	0.048	
Amount of Omnipaque administered (ml, for single-infusion procedures)		
Number of patients	12	47
Median	150 ml	150 ml
Range 60–275 ml	101–200 ml	60–275 ml
<i>P</i> value	0.72	

Bold values are statistically significant

*Analyzed parameters data were not available per reports for all control group patients. The table demonstrated statistically significantly shorter resin microspheres infusion time ($p = 0.0058$) and lower fluoroscopy radiation dose in study group ($p = 0.048$), compared to control group. There was no statistically significant difference between groups regarding amount of contrast medium (Omnipaque) administered.

Incidence of Reflux and Evidence of Non-target Delivery on Bremsstrahlung SPECT/CT Imaging

Reflux was not observed in the study group. It was recorded in 3/58 (5%) of infusions in the control group. The incidence of non-target ^{90}Y delivery on Bremsstrahlung SPECT/CT between study and control groups was 1/27 (4%, 95% CI 0–11%) vs. 5/73 (7%, 95% CI 1–13%), $p = 1$. In the study group, tracer uptake along the distribution of the falciform artery was recorded. The vessel was identified in pretreatment mapping, but could not be embolized. Ice packs were placed on the skin during ^{90}Y microspheres delivery; however, activity in the distribution of this vessel was detected in the Bremsstrahlung SPECT/CT scan [25]. The patient remained asymptomatic and without skin changes during follow-up.

Side Effects and Complications after ^{90}Y Radioembolization

Side effects during ^{90}Y microspheres infusion were observed only in the control group (in 6/58 (9%) of patients), which included pain, hypersensitivity reaction (flushing and swelling) and arterial hypertension. There were no side effects in the study group. There was no difference in incidence of hyperbilirubinemia, grade 1–2 and grade 3–4 toxicities (Tables 4, 5).

Table 4 Grade 1–2 toxicities

Complication*	Study group	Control group
Fatigue/weakness	5/22 (23%)	26/58 (45%)
Abdominal pain/distension	3/22 (14%)	17/58 (29%)
Shortness of breath	1/22 (5%)	9/58 (16%)
Fever	1/22 (5%)	9/58 (16%)
Change in appetite/weight changes	0	8/58 (14%)
Nausea	1/22 (5%)	7/58 (12%)
Vomiting	0	4/58 (7%)
Ascites	0	5/58 (9%)
Constipation/diarrhoea	0	13/58 (45%)
Light coloured stool/dark urine	0	9/58 (16%)
Hiccups	0	1/58 (2%)
Portal hypertension	1/22 (5%)	0
Total patients number	8/22 (36%)	26/58 (45%)

*Some of the patient might have developed multiple complications

Table 5 Grade 3–4 toxicities

Complication	Days post-RE	Study group	Control group
Post-RE radioembolization syndrome	1–90 days	1/22 (5%)	4/58 (7%)
Grade 3 abdominal pain/distension	10–12 days	1/22 (5%)	2/58 (3%)
Grade 3 fevers	3 days	0	1/58 (2%)
Acute liver failure/failure to thrive/grade 3 hyperbilirubinemia	14 days	0	1/58 (2%)
Grade 3 dyspnoea	30 days	0	1/58 (2%)
Bile duct obstruction + Budd-Chiari syndrome + stop chemotherapy for 6 weeks	1 day/60 days	1/22 (5%)	0
Total patients number		2/22 (9%)	9/58 (16%)

*Some of the patient might have developed multiple complications. RE-radioembolization

Median Liver PFS and OS

Median liver PFS for study and control groups was 4.13 vs. 3.97 months (HR = 1.29, $p = 0.38$) (Fig. 6). OS for study and control groups was 11.6 months vs. 9 months ($p = 0.74$, HR = 0.9) (Fig. 7).

Figure 6 Liver progression-free survival (PFS) association by infusion technique. The figure demonstrated that there was no statistically significant difference in liver PFS between study and control groups ($p = 0.38$)

Figure 7 Overall survival (OS) association with infusion technique. The figure demonstrated that there was no statistically significant difference in OS between study group (simultaneous 100% contrast medium infusion) and control group (standard sandwich technique infusion), $p = 0.74$

DISCUSSION

This study demonstrated no indirect evidence of ⁹⁰Y leaching when using UDCM for ⁹⁰Y resin microspheres administration in both “B” and “D” lines. This was indicated by no difference in complete blood count values at baseline and follow-ups between the study and control groups. The comparison with the control group was used as reference to anticipated complete blood count changes post-RAE, such as thrombocytopenia and lymphopenia [26–28]. No abnormal β-emission was detected on Bremsstrahlung SPECT/CT in the study group, which further supported the lack of ⁹⁰Y leaching in the study. There was no difference in peri- or post-procedural toxicity, hepatic progression-free and overall survival between the groups. These findings indicated that no additive toxicity occurred during direct infusion of resin microspheres using UDCM. Chao et al., similarly, reported no complications when infusing ⁹⁰Y resin microspheres with 50% non-ionic contrast medium in saline [23].

Statistically significantly lower median fluoroscopy radiation dose was recorded in the study group, compared to control (44.6 vs. 97.4 Gy/cm², $p = 0.048$), accounting for patients’ BMI. The amount of contrast agent used was similar between the groups. A significantly shorter median resin microspheres infusion time in the study group may have attributed to the lower fluoroscopy radiation dose and the same amount of contrast agent used between groups. This is concordant with reported findings by Chao et al. (7 min infusion time for the 50% of Isovue vs. 22 min for the standard sandwich technique) [23]. A 38% reduction in the incidence of stasis in the study group did not reach statistical significance in our study. However, when using 50% of concentration non-ionic contrast medium, a significant decrease in the incidence of stasis was documented [23]. Reflux never occurred during UDCM infusion in our study, compared to three cases in the control group. Non-target delivery occurred in 5/73 (7%) of infusions in the control group compared to 1/27 (4%) in the study group (all asymptomatic).

No gastrointestinal ulceration was noted, comparing favorably to historical data. Gastrointestinal ulceration is the most frequent major complication, reported in 0–20% of RAEs with a median incidence of 8% when using advanced antireflux protective techniques and in 6% of cases requiring surgical ulcer management [29]. ⁹⁰Y administration using UDCM was as effective as sandwich technique in terms of liver progression-free and overall survival.

Limitations of the study include its single-center, retrospective nature and the relatively small number of patients. The lack of pathologic assessment such as bone marrow biopsy

at different time points after RAE to detect early microscopic bone marrow morphologic changes was another study limitation. Direct ⁹⁰Y leaching detection should be performed in blood or urine samples in certified radioactive material laboratories, according to radiation safety standards [21]. The lack of these assessments was limitations of this study. Leaching and radiotoxicity were assessed only indirectly, through post-RAE serial complete blood count, Bremsstrahlung SPECT/CT as well as laboratory and clinical toxicity evaluations. The fact, that ⁹⁰Y Bremsstrahlung SPECT/CT has low quantitative accuracy and that it was only done at one-time point (within hours of RAE, according to routine practice), limits the potential for leaching detection [30, 31]. Considering that the half-life of ⁹⁰Y is 2.7 days, ideally such study should be performed in several time points within 11 days after RAE to detect all emitted β -radiation in both target and non-target organs. However, such information would have little if any impact on clinical patient management due to the absence of symptoms and laboratory values, indicating myelosuppression and radiotoxicity. Further prospective studies could address these limitations and optimize the direct administration of ⁹⁰Y resin microspheres with non-ionic contrast medium.

CONCLUSION

Despite the limitations, the study met its goal and demonstrated that direct ⁹⁰Y resin microspheres infusion with undiluted non-ionic contrast medium was safe and effective. Significant reduction in ⁹⁰Y resin microspheres infusion time and fluoroscopic radiation exposure were documented.

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SUPPLEMENTARY MATERIAL

Supplement 1 Definitions of primary and secondary study objectives

	Primary study objectives and definitions
Incidence of myelosuppression and lymphopenia	Myelosuppression was defined as occurrence of leukopenia, neutropenia, erythrocytopenia and/or thrombocytopenia within 6 months post-RAE. These parameters were chosen based on bone marrow and lymphocytes sensitivity to radiation with toxic absorbed dose of approximately 2 Gy.
Non-target microspheres delivery	Non-target delivery was determined as extrahepatic or non-target intrahepatic tracer activity detected on Bremsstrahlung SPECT/CT imaging post-RAE.
Incidence of RAE-related hyperbilirubinemia	RAE-related hyperbilirubinemia was defined as elevation of total plasma bilirubin for at least 1 mg/dl from the norm within 3 months post-RAE, not resolved within 1 month, with no evidence of liver disease progression, biliary dilatation or another hepatic pathology.
Side effects and complications	Complications severity was recorded according to CTCAE v3.0 criteria within 6 months post-RAE.
Median resin microspheres infusion time	It was calculated after review of the timed ⁹⁰ Y vial radioactivity measurement records, documented immediately prior (from infusion start) and after implantation by the radiation safety officer. Only single-infusion RAE procedures were included for the assessment of this factor. RAEs requiring coil-embolization were excluded from analysis.
Fluoroscopy radiation dose	Fluoroscopy radiation dose was analysed taking into consideration patient's BMI. Only single-infusion RAE procedures were included for the assessment of this factor. RAEs requiring coil-embolization were excluded from analysis.
Amount of UDCM administered	Amount of UDCM administered during all RAE procedure was recorded in ml. Only single dose RAE procedures were included for the assessment of this factor. RAEs requiring coil-embolization were excluded from analysis.
Secondary study objectives and definitions	
Mean laboratory values comparison between groups	For patients who underwent two RAE sessions, blood count values before and after each RAE session were recorded.
Liver progression-free survival (LPFS)	LPFS was defined as the time from initial RAE to documented liver progression (in the treated region or outside treated region after RAE) or until the last imaging follow-up using EORTC and/or RECIST 1.1 criteria, depending on imaging availability. In cases of differing responses between the criteria, the concordance between both modalities imaging findings was used for defining LPFS.
Overall survival (OS)	OS was defined as the time from initial RAE to patient death or last follow-up.

RAE- radioembolization, UDCM- undiluted contrast medium

Supplement 2 Overview of statistical analysis methods used in the study

Kaplan Meier method	Method was used to estimate patients' overall and liver progression-free survivals.
Cox regression analysis	Analysis was used to assess patients' overall and liver progression-free survival (LPFS) association with infusion technique.
Multilevel mixed effects linear regression model	Model was used to evaluate whether there was a statistically significant difference in mean blood count values between treatment groups during follow-up period. This statistical test was chosen as it contains both fixed effects and random effects for evaluation of repeated measurements on different follow-up points, presence of multiple radioembolization (RAE) sessions per patient and superiority of handling missing values over ANOVA statistical test.
Generalized estimated equation test	Test was used to evaluate difference in occurrence of stasis and radiation dose delivery between the two patients' groups. This test was chosen as it can handle unmeasured dependence between variables (presence of multiple variables at the same or different time points per patient, due to multiple infusions during one RAE session or due to several RAE sessions).
Fisher exact test	Test was used for the analysis of categorical variables.
Mann-Whitney test	Test was used to analyse the difference between two groups regarding not normally distributed continuous variables.
Unpaired t-test	Test was used to analyse normally distributed variables.
Other	Median follow-up time was calculated for the patients who were alive on last follow-up. Normal distribution of variables was assessed using Shapiro-Wilk test as well as by evaluating the histograms of the variables, comparing means and medians, skewness and kurtosis of the histogram. Statistical analysis was performed using STATA 12.1 software. A p-value <0.05 was considered significant.

Supplement 3 Comparison of study and control groups

Parameter	Study group	Control group	P-value
Number of patients	23 (28%)	58 (72%)	-
Number of procedures	27	73	-
Number of infusions	39	107	-
Mean age (years)	64 ± 12.8	56.6 ± 13	0.047
Gender			-
Male	14/23 (61%)	41/58 (71%)	
Female	9/23 (39%)	17/58 (29%)	
SUV _{max} before procedure (median, range) *	14 (6.8-30.5)	9.3 (3.3-28.6)	0.04
Tumor involvement			
Unilobar [‡]	1/23 (4%)	13/58 (22%)	0.11
Unilobar post hepatectomy	3/23 (13%)	7/58 (12%)	1
Bilobar	19/23 (83%)	38/58 (66%)	0.18
Prescribed radiation dose (mCi, mean ± SD)	36.2 ± 12.9	41.1 ± 14.6	
Delivered radiation dose (mCi, mean ± SD)	30.4 ± 12.8	36 ± 15.2	
CEA level before procedure (median, range)	16.3 (5.5-11723)	79.5 (1.1-23938)	0.016
Synchronous liver metastases on initial diagnosis	20/23 (87%)	41/58 (71%)	0.25
Lymph nodes involvement on initial diagnosis	9/13 (69%)	40/57 (71%)	1
Lymphovascular invasion of primary tumor	8/11 (73%)	27/49 (55%)	0.33
Tumor differentiation level			
Good to moderate	16/21 (76%)	46/57 (81%)	0.75
Moderate to poor	5/21 (24%)	11/57 (19%)	0.75
Prior liver surgery	14/23 (61%)	50/57 (88%)	0.01
Prior hepatic artery infusion chemotherapy	13/23 (57%)	30/57 (53%)	0.81

*SUV-standard uptake value; mean SUV_{max} of 1-5 most metabolically active liver tumours was measured; CEA-carcinoembryonic antigen level; Study group patients were significantly older and had higher baseline SUV_{max} values. The control group patients, on the other hand, had statistically significantly higher baseline CEA level and higher incidence of prior liver surgery for metastatic disease.

Supplement 4 Incidence of hepatic and systemic chemotherapy regimens received post-RAE between the groups

	Study group	Control group*	P-value
Post-RAE hepatic artery infusion chemotherapy	1/23 (4%)	15/58 (26%)	0.03
No post-RAE systemic chemotherapy	5/23 (22%)	17/57 (30%)	0.58
1 post-RAE systemic chemotherapy regimen	12/23 (52%)	17/57 (30%)	0.07
2 post-RAE systemic chemotherapy regimens	4/23 (17%)	9/57 (16%)	1
≥ 3 post-RAE systemic chemotherapy regimens	2/23 (9%)	10/57 (18%)	0.49

*The data of one patient about systemic therapy was not available. RAE-radioembolization. The table demonstrated that control group patients had higher incidence of post-RAE hepatic artery infusion chemotherapy, compared to the study group. There was no statistically significant difference in systemic chemotherapy regimens administered post-RAE between the groups

Supplement 5 Occurrence of low blood count values at any recorded time point within 6 months post-RAE with related clinical symptoms and treatment in study group patients

Parameter (n=21)	Incidence
Erythrocytopenia (<4.2 M/mcl)	17 (81%)
Fatigue, weakness, dizziness, reduced performance status	15 (71%)
Shortness of breath	6 (29%)
Required treatment with <i>iron sucrose 100 mg IVPB or ferrous gluconate 324 mg p/os</i>	5 (24%)
Patients also had disease progression; poor per oral uptake or myelosuppression likely as systemic chemotherapy side effect	16 (76%)
Thrombocytopenia (<160 K/mcl)	11 (52%)
Bleeding	3 (14%)
Bruising	0
Required treatment	1 (5%)
Symptoms could be attributed to other factors (bevacizumab administration, anticoagulation therapy, high INR, comorbidities - hemorrhoids/chronic anal canal irritation)	3 (14%)
Leucopenia (<4 K/mcl) and/or neutropenia (<1.5 K/mcl)	7 (33%)
Bacterial infections (urinary tract infection, 6 months post-RAE)	1 (5%)
Leucopenia required treatment with bone marrow stimulants (<i>pegfilgrastim 6 mg s/c or filgrastim 480 mcg s/c</i>)	3 (14%)
Required break from systemic chemotherapy due low blood count values (at 4-6 months post-RAE, break was for 1-2 weeks)	4 (19%)
Normal laboratory values	2 (10%)
No laboratory values data available as patients were lost to follow-up	2 (10%)

Radiation Segmentectomy for Hepatic Metastases with ^{90}Y Glass-Based Microspheres: Technical Considerations, Correlations to Dosimetry and Preliminary Results

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ABSTRACT

Objectives

To evaluate safety and efficacy of ablative-dose ⁹⁰Y glass-based microspheres radiation segmentectomy (RS) in patients with limited metastatic liver disease not amenable to surgery or percutaneous ablation.

Materials and methods

Patients with ≤3 tumors treated with RS from 6/2015-12/2017 were included. Tumor response, local tumor progression (LTP) and LTP-free survival (LTPFS) were defined using Choi and RECIST 1.1 criteria. Toxicities were evaluated using modified SIR criteria.

Results

Ten patients with 14 tumors underwent 12 procedures. Median tumor size was 3 cm (range, 1.4-5.6). Median follow-up was 8.8 months (range, 1.6-14.7). Response rates per Choi and RECIST 1.1 criteria were 8/8 (100%) and 4/9 (44%), respectively. Target tumor LTP rate was 1/14 (7%) resulting in 1-year LTPFS of 89% (95% CI, 43-98%). New tumors occurred after 1/12 (8%) procedures. Intra-patient dosimetry varied among partition model, MIRD, ^{99m}Tc-MAA and Bremsstrahlung-based approaches with median tumor radiation dose of 650 Gy, 293 Gy, 202 Gy and 112 Gy, respectively. Median minimum tumor radiation dose was 67 Gy (range, 28-378) based on Bremsstrahlung SPECT/CT. A higher segment disease-progression rate was associated with lower radiation doses (p=0.036, OR=0.96). One major complication was recorded in a patient post-Whipple who suffered anaphylactic reaction to prophylactic cefotetan and liver abscess in the RS region 6.5 months post-procedure. All patients were alive on last follow-up.

Conclusion

RS of ≤3 hepatic segments can safely provide good local tumor control in selected patients with limited metastatic liver disease and treatment options. Optimal dosimetry methodology requires further investigation.

INTRODUCTION

Radiation segmentectomy (RS) is an intra-arterial therapy that selectively delivers very high ablative radiation dose (> 190 Gy) to liver segments containing tumor [1-3]. This technique is intended to achieve complete tumor eradication in selected patients with limited liver tumor burden that cannot be treated by surgery or ablation [1, 2, 4].

RS has been successfully used for the treatment of selected patients with localized hepatocellular carcinoma (HCC) that could not be resected or percutaneously ablated [1, 2, 4-6]. RS enabled to achieve significantly better local tumor control compared to other intra-arterial therapies (transarterial chemoembolization) [7-9]. RS resulted in >90% necrosis rates, with complete necrosis rate of 52% [2], demonstrating outcomes similar to those of other local curative treatments [10].

Radiation segmentectomy allows the creation of treatment margins around the target tumor, similarly to surgical resection, percutaneous ablation or stereotactic ablative radiotherapy. This is the result of treating the entire segment containing the tumor (rather than superselective tumor targeting) and the tumor penetration by the β-emission (~1 cm) around each microsphere loaded into the tumor and surrounding capillaries [11].

To date, most reports of ablative dose radioembolization involve the delivery of ⁹⁰Y glass-based microspheres [1, 2]. Due to the high radioactivity per sphere, ⁹⁰Y glass-based microspheres deliver extremely high radiation dose into the targeted tumor(s) with relatively small number of spheres and minimal risk of stasis or occlusion even in relatively hypovascular tumors [2].

Worldwide secondary liver malignancies are more prevalent than primary liver tumors [12] with local therapy demonstrating potential for prolonged survival for this patient population [13, 14]. There is very limited data on RS role as a local potentially curative therapy in patients with limited hepatic metastases [15].

This work was conducted to assess the feasibility, safety and efficacy of radiation segmentectomy in the setting of limited metastatic liver disease in patients who could not undergo surgery or percutaneous ablation.

MATERIALS AND METHODS

Study population

Internal review board approval was obtained for this retrospective cohort study of ⁹⁰Y RS for liver metastases. Informed consent was not required for this type of study. All patients signed clinical informed consent.

All patients treated with RS for liver metastases between 6/2015 and 12/2017 were eligible for inclusion in the study.

Inclusion and exclusion criteria and rationale for radiation segmentectomy

Patients were eligible for RS if they had up to 3 unresectable liver metastases, not amenable to percutaneous ablation with sufficient ablation margins due to the following reasons: ≥ 3 cm tumor size, challenging tumor location near major hepatic structures or increased risk of adjacent organ damage. The patients also needed to meet standard ⁹⁰Y radioembolization eligibility criteria. RS was preferred to stereotactic ablative radiotherapy either by the patients (to avoid multiple radiation sessions) or by the treating physician (due to the challenging tumor position, requiring fiducial placement or near an organ at risk for collateral radiation injury) [16].

Study exclusion criteria and pre-procedural work-up were analogic to ⁹⁰Y radioembolization and are described in **Table 1**.

Study objectives and definitions

Primary study objective was to assess the feasibility and efficacy of ⁹⁰Y RS in patients with limited metastatic disease (objective response rate, local tumor and liver progression-free survivals).

Objective response rate (defined as complete and partial response rate) was assessed by an experienced radiologist (A.Bendet, faculty body imaging, 9 years of experience) based on CT imaging using Choi and RECIST 1.1 criteria (**Supplement 1**). Choi criteria were chosen as they have shown to correlate with overall survival following ⁹⁰Y radioembolization [17-19]. Tumor response rates were evaluated at first and second imaging follow-up time points after RS (at 4-8 and 12-16 weeks, respectively). Tumor attenuation was measured on portal venous phase with ROI comprising the tumor. In case of discordant findings, Choi criteria were considered superior to RECIST 1.1 [20].

Table 1 Radiation segmentectomy inclusion and exclusion criteria, pre-procedure work-up and angiographic mapping.

Parameter	Description
Inclusion criteria	Radiation segmentectomy specific: Up to 3 hepatic metastases Ineligibility for liver surgery Ineligibility for curative image-guided percutaneous ablation with margins (due to tumor abutment of a major vessel and/or bile duct; increased risk of diaphragmatic injury (in subcapsular dome lesions) or surrounding organ damage, that could not be protected by hydrodissection; relatively large tumor size (>3 cm) that would not allow the creation of sufficient minimal ablation margins of at least 5 mm) Local tumor progression post-ablation with suspicion of micrometastatic spread in the same hepatic segment, but with no evidence of distant liver or other disease Standard as for any ⁹⁰ Y radioembolization treatment: Histologically confirmed primary tumor No or stable extra-hepatic disease Age ≥ 18 years Eastern Cooperative Oncology Group (ECOG) performance status 0-2 Adequate blood cell counts (WBC>1.5×10 ⁹ /L, platelet count >50×10 ⁹ /L) Adequate renal function (creatinine < 1.5 mg/dL) Total bilirubin level ≤ 1.5 mg/dL
Exclusion criteria (analogic to radioembolization)	Prior hepatic radiotherapy Evidence of severe cirrhosis Severe portal hypertension Uncorrectable flow to the gastrointestinal tract and/or >20% shunting to the lungs, as determined by ^{99m} Tc-MAA hepatic arterial perfusion scintigram (mapping)
Pre-procedural work-up	All patients were evaluated at a clinic visit within 30-days before RS. Past medical history was reviewed, physical examination was performed and relevant baseline laboratory values were evaluated Pre-procedural baseline imaging with liver dynamic (ideally triphasic) CT or contrast-enhanced MRI and/or ¹⁸ F-FDG PET/CT was available/ obtained within 30-days from RS for accurate re-staging of disease
Angiographic mapping	All patients underwent angiographic evaluation and ^{99m} Tc-MAA mapping prior to RS During arteriography, hepatic arterial anatomy and tumor vascular supply were assessed Extrahepatic vessels with hepatofugal flow within 3 cm from the desired point of ⁹⁰ Y administration were prophylactically coil-embolized to prevent inadvertent delivery of ⁹⁰ Y in extra-hepatic sites Once the desired location(s) of RS administration(s) was determined, a total of 4-5 mCi of ^{99m} Tc-MAA were injected at desired sites of ⁹⁰ Y arterial infusion and subsequent planar scintigraphy and SPECT/CT imaging were performed to calculate the lung shunt fraction and to detect extrahepatic activity RS was delivered approximately two weeks after mapping angiograph, with no radiation activity adjustments

Local tumor progression (LTP) was defined as progression of the target tumor and within 1 cm area around it (accounting for maximal β-emission penetration depth) [11]. Occurrence of new metastases within the treated segment was reported separately.

Secondary study objective was to assess the safety of RS. Toxicities were described within 6-months post-treatment according to modified SIR criteria [21, 22] with side effects reported separately. Side effects were defined as expected, undesired and

frequent consequences of the procedure that were self-limiting without requirement of admission or change in care management [22].

Methods to estimate the delivered radiation dose

Ablative radiation dose (>190 Gy) was intended to be delivered in the target tumor and cause complete tumor destruction [2]. This was achieved via the intra-arterial delivery of ⁹⁰Y glass-based microspheres (*TheraSphere*; MDS Nordion, Ottawa, Ontario, Canada) super-selectively within the tumor-containing liver segment(s).

To measure radiation dose delivered to the tumor, volumetric segmentations of regions of interest (ROI) of the target tumors and the intended-to-treat Couinaud liver segments were performed on pre-treatment diagnostic contrast-enhanced CT scans (obtained within 6-weeks from RS) using Hermes Hybrid Viewer software (*Hermes Medical Solutions, Stockholm, Sweden*).

Radiation dose delivered to the tumor was estimated using three different methods (**Table 2**):

- 1) The manufacturer specified/simplified dose formula that is based on the Medical Internal Radiation Dose (MIRD) approach, taking into account lung shunt fraction and residual vial radiation activity [23]. This formula does not take into account preferential blood flow to the tumor during RS and assumes uniform microspheres distribution within the treated region;
- 2) Image-based dosimetry approaches, that take into account non-uniform particles distribution. These included ^{99m}Tc-MAA SPECT/CT-based and Bremsstrahlung SPECT/CT-based dosimetry approaches. Imaging-based dosimetry methods were applied only if rigid imaging co-registration was possible to account for differences in patient positioning and respiratory motion. This was feasible in 4/10 (40%) of the study patients.
- 3) Partition model-based ^{99m}Tc-MAA SPECT predictive dosimetry. This model is more accurate and personalized but more complex than semi-empirical methods [24]. It is based on three compartments dosimetry (tumor, normal liver and lung) with deposited activity determined based on ^{99m}Tc-MAA SPECT/CT.

Statistical analysis

The median follow-up period was calculated for the patients who were alive on last follow-up. Survivals (overall, liver and extrahepatic disease progression-free) were estimated using Kaplan-Meier methodology. Statistical analysis was performed using STATA 11.0 statistical software (*StataCorp LLC, USA*). $P < 0.05$ was considered significant.

Table 2 Calculation of radiation dose delivered to segment/tumor

Method	Description
MIRD approach-based dosimetry	<p>Radiation dose to the target segment was calculated using the following formula (assuming uniform particle distribution between a tumor and uninvolved liver parenchyma within a treated segment):</p> $D(\text{segment}) = 50 \frac{\text{Gy} \cdot \text{kg}}{\text{GBq}} \times A \times (1 - LSF) \times \frac{(1 - R)}{M_s}$ <p>Here D is the absorbed radiation dose (Gy); A is the vial radioactivity (GBq); LSF is the lung shunt fraction; R is the residual activity (GBq); M is the segment mass (kg) which is calculated by: $M_s = \text{segment volume (cm}^3) \times 1.03 \text{ kg/1000 cm}^3$. Tumor and target segment volumes were evaluated by performing volumetric segmentation using <i>Hermes</i> Software.</p>
^{99m} Tc-MAA SPECT/CT and Bremsstrahlung SPECT/CT	<p>Tumor and segment regions of interest (ROI) were delineated on contrast - enhanced CT images</p> <p>These images were co-registered by rigid registration (translation and rotation) using <i>Hermes Hybrid Viewer</i> software (<i>Hermes Medical Solutions, Stockholm, Sweden</i>) software to CT images acquired at the same time and coaxially with ^{99m}Tc-MAA and ⁹⁰Y Bremsstrahlung images</p> <p>Total summed activity in the SPECT images was equated with total therapeutic activity administered to the segment less the lung shunt activity</p> <p>The fraction of total imaged ^{99m}Tc-MAA or ⁹⁰Y Bremsstrahlung activity in each voxel was used to extrapolate the activity concentration (Bq/g) due to microspheres in each voxel. A ⁹⁰Y dose constant of 49.7 Gy·kg/GBq was used to estimate dose assuming total local absorption in each voxel</p>
Partition-model based dosimetry	<p>Radiation dose delivered to the tumor was calculated using the formula:</p> $D(\text{tumor}) = \frac{A_0 \times 49.7 \frac{\text{Gy} \cdot \text{kg}}{\text{GBq}} \times T/N \times (1 - LSF)}{(V_T \times T/N + V_N) \times 1.03 \times 10^{-3} \frac{\text{kg}}{\text{mL}}}$ $D(\text{normal tissue}) = \frac{A_0 \times 49.7 \frac{\text{Gy} \cdot \text{kg}}{\text{GBq}} \times (1 - LSF)}{T/N \times (\frac{V_N}{T/N} + V_T) \times 1.03 \times 10^{-3} \frac{\text{kg}}{\text{mL}}}$ <p>Here A_0 is the actual administered activity measured in GBq; T/N is the tumor-to-normal liver activity concentration ratio, based on the ^{99m}Tc-MAA uptake values within a treated segment; LSF is the lung shunt fraction; V_T is the tumor volume in mL; and V_N is the volume of the normal liver parenchyma in mL.</p>

RESULTS

Patient, tumor and treatment characteristics

We treated 10 patients with 14 tumors 12 RS sessions. Incidence of mono-, bi- and tri-segmentectomies (anterior sector + Segment 3 or 4) was: 4/10 (40%), 4/10 (40%) and 2/10 (20%). Total of 3/10 of the patients had more than one tumor located in separate lobes; in 2/3 of these cases RS was completed in 2 separate sessions (5-10 weeks apart). The entire prescribed radioactivity was delivered in all cases with no stasis in any of the RS sessions. Detailed patient, tumor and treatment characteristics are depicted in **Table 3**. Representative RS case is depicted in **Figure 1**.

Figure 1

A-C, Pre-treatment ¹⁸F-FDG PET/CT showed FDG-avid liver metastasis, $SUV_{max}=8.6$, SUV_{mean} of background liver is 2.4 in patient with colorectal cancer;

D, The fused image of CT angiography (CTA) of Segment 5 branch and CTA of Segment 8 branch;

E-F, Fusion of pre-treatment liver ¹⁸F-FDG PET/CT scan (showing the FDG uptake by the tumor) with the liver CTA of S5 and S8 branches. The fused images demonstrated that Segment 5 branch almost entirely supplied the tumor;

G, Segmentation of the tumor and the normal liver parenchyma supplied by Segment 5 branch.

H, Segmentation of the tumor and the normal liver parenchyma supplied by Segment 8 branch. Tumor volume planned to be covered by Segment 5 injection was 107 cm³ (74%). Tumor volume planned to be covered by Segment 8 injection was 38 cm³ (26%). Segment 5 branch perfused liver volume - 286 cm³, Segment 8 branch perfused liver volume - 156 cm³. Total liver volume planned to irradiate during radiation segmentectomy was 442 cm³ (33% of total liver volume);

I-K, Bremsstrahlung SPECT/CT showed deposition of ⁹⁰Y with the delineated metabolic tumor volume, defined on ¹⁸F-FDG PET/CT;

L-N, Complete metabolic resolution of tumor FDG-uptake on first follow-up;

O-Q, Local tumor progression on second follow-up ¹⁸F-FDG PET/CT with metabolic tumor volume, defined on ¹⁸F-FDG PET/CT before treatment is marked in blue;

R-T, Correlation of area of local tumor progression with distribution and deposition of ⁹⁰Y particles as seen on Bremsstrahlung SPECT/CT.

Table 3 Patient, tumor and treatment characteristics

Parameter	Result
Number of patients	10
Number of tumours	14
Number of procedures	12
Origin of metastases:	
colorectal	2
breast	1
ovarian	1
non-small cell lung cancer	1
pancreatic	1
gallbladder	1
gastric	1
ampullary	1
gastro-oesophageal junction	1
Patients age, mean	68.1±13.6 years
Gender	60% woman
Median follow-up, range	8.8 months (1.6 - 14.7)
Reason for radiation segmentectomy	
Lesion too large to ablate	8/14 (57%)
Abutment of major liver vascular and biliary structures	2/14 (14%)
Subcapsular location with increased risk of diaphragmatic injury	2/14 (14%)
Increased risk of extrahepatic structures injury (heart, phrenic nerve, stomach, superior mesenteric and gastroduodenal arteries)	2/14 (14%)
Prior liver-directed therapies	
Yes (thermal ablation, liver resection, liver bland embolization)	4/10 (40%)
No	6/10 (60%)
Number of treated segments	
One	4/10 (40%)
Two	4/10 (40%)
Three (Segments 5,8 + Segment 3 or Segments 5,8 + Segment 4)	2/10 (20%)
Number of tumours treated per patient	1-3 tumours
Number of ⁹⁰ Y infusions	
One*	9/14 (64%)
Two (tumours were supplied by two hepatic artery branches)	5/14 (36%)
Median tumor size, range**	3 cm (1.4 - 5.6)
Baseline extrahepatic disease	
Yes	2/10 (20%)
No	8/10 (80%)

*In one patient two tumours in the anterior sector were supplied by a single hepatic artery branch and treated in one hepatic artery infusion.** Radiation segmentectomy of 1.4 cm lesion was favoured to thermal ablation (due to abutment of central biliary duct) and to irreversible electroporation (due to the physician's preference)

Response evaluations: first and second imaging assessments after RS

Eight/10 (80%) of patients were evaluated by triphasic CT scan and all demonstrated partial (n=7) or complete response (n=1) according to Choi criteria, resulting in 100% objective response rate on first and second imaging follow-up (at 4-8 and 12-16 weeks after RS, respectively). One patient with only MRI available at baseline had complete response on the first imaging 4-months post-RS (based on RECIST 1.1). One patient had only ¹⁸F-FDG PET/CT imaging available post-RS, showing stable disease (14% decrease in

SUV_{max} based on EORTC criteria). Objective response rate based by RECIST 1.1 criteria was 4/9 (44%).

LTP rate and LTPFS

One-year LTPFS (for target tumors) was 89% (95%CI, 43%-98%) with median LTPFS not reached (**Figure 2**).

Figure 2 Local tumor progression-free survival (LTPFS) after radiation segmentectomy. Target tumor LTP rate was 7% with 1-year LTPFS of 89%

There was only one LTP at 4.9 months post-RS in a patient with colorectal liver metastasis (**Figure 1**). This was a marginal recurrence of the largest tumor in this cohort (>5 cm in size). Only 35% of this tumor received the intended radiation dose > 200 Gy. A minimum tumor radiation dose of 100 Gy was calculated based on ^{99m}Tc-MAA SPECT/CT. A relatively poor coverage of the tumor was shown in post-RS Bremsstrahlung imaging (**Figure 1 I-K**) and corresponded to the area of LTP (**Figure 1 O-Q**). The same patient developed disease progression in the liver beyond the treated segments. Additional locoregional therapies were considered technically challenging due to recurrent tumor location, patient's age, comorbidities and worsening performance status. Thus the patient received palliative oral systemic chemotherapy only.

In another patient, a new metastasis distant to the target tumor, but within the treated segment was detected 9.1 months post-RS. This new tumor was treated with MW

ablation. This patient had prior history of multiple liver-directed therapies in other liver segments than the one treated with RS.

Dosimetry

Median radiation dose delivered to treated segment(s), tumor(s) and lungs, total treated tumor volume and percentage of irradiated liver are described in **Table 4**.

There were large intra-patient dosimetry distribution variations among the MIRD, partition model, ^{99m}Tc-MAA SPECT/CT and Bremsstrahlung SPECT/CT-based dosimetry, with the latter demonstrating the lowest absorbed radiation doses.

Median radiation doses delivered to the tumor based on partition model, MIRD approach, ^{99m}Tc-MAA and Bremsstrahlung SPECT/CT were 650 Gy, 293 Gy, 202 Gy and 112 Gy, respectively. Median minimum tumor radiation dose was 54 Gy (range, 0-100 Gy, based on ^{99m}Tc-MAA SPECT/CT) and 67 Gy (range, 28-378 Gy, based on Bremsstrahlung SPECT/CT). Median radiation doses delivered to the target segments were 227 Gy, 293 Gy, 98 Gy and 47 Gy, respectively (**Table 4**).

Dose-response correlation

A relatively higher disease progression rate in the treated segment (of the target tumor or occurrence of new tumors distant from the target tumor) was significantly associated with lower radiation dose delivered to that segment, according to the MIRD approach-based dosimetry (p=0.036, OR=0.96). The correlation of the absorbed radiation dose in the treated segment (based on MIRD approach) with the corresponding segment progression-free survival was not significant (p=0.3, OR=0.98).

Distant intrahepatic disease progression

4/10 (40%) patients developed disease progression in the liver, outside the RS field. Median untreated liver progression-free survival was 4.9 months (95% CI, 2.1-NR).

Toxicity

Side effects were reported in half of the procedures (**Table 5**). All side effects were self-limiting without requirement for admission or change in care management.

Minor complications occurred after 1/12 (8%) (95% CI, 0-23%) of RS procedures. This involved abdominal pain, fever, hypertension and atrial fibrillation (in a patient with history of atrial fibrillation). This required overnight observation and was successfully managed without further sequelae or additional treatment.

Table 4 Radiation segmentectomy dosimetry values (to tumor/segment) based on different dosimetry approaches

Pt. Nr.	Tumor Size (cm)	Total tumor burden (cm ³)	Treated segment volume (cm ³)	Total liver volume (cm ³)	Tumor location	LTP tumor	POD segment	LTPFS in months	Bremsstrahlung SPECT/CT-based dosimetry (Gy)	^{99m} Tc-MAA SPECT/CT-based dosimetry (Gy)	Partition model -based dosimetry (Gy)	MIRD approach-based dosimetry (Gy)
1*	3-8	No contrast-enhanced CT available	S4		No	No	2.1	-	-	-	-	-
1*	3-9	for accurate measurements	S5/S8		No	No	2.1	-	-	-	-	-
2	1.4*	7.2	527.6	1208	S5/S8	No	14.5	-	-	-	-	247
1.9					No	No	14.5	-	-	-	-	
2	1.4				S3	No	12.3	-	-	-	-	429
3	3	3	346.7	1469	S7	No	7.2	562/378	380/54	215/95	97/12	284
4	5.6	65.7	691.7	1480	S4+S8	Yes	4.9	99/80	52/5	189/100	99/0	206
5	1.5	4.6	336	1053	S2	No	12.6	-	-	-	-	1303
5	1.6				S7	Yes	9.1	-	-	-	-	163
6	3	5	303.4	2204	S6	No	7.3	-	-	-	-	63.4
7	1.7	4.1	173.1	1112	S2-3	No	8.8	125/54	34/2	333/13	106/0	223
8	4	19.2	240.2	926	S7	No	1.6	-	-	-	-	1086
9	4.2	61.4	620	2010	S7-8	No	2.7	-	-	-	-	303
10	5.4	43.2	271.1	1097	S8	No	1.5	63/28	42/6	43/0	22/0	293
Median radiation dose delivered								112	47	202	98	293
Median % of irradiated liver										26%		
Median radiation activity prescribed										1.86 GBq		
Median treated tumor volume										4.6 cm ³		
Median radiation dose to the lungs										2.9 Gy		

Medical Internal Radiation Dose (MIRD) approach does not take into account preferential blood flow to the tumor during RS, thus tumor and uninvolved liver absorbed radiation doses in the treated segment were considered to be the same. *Estimation of MIRD-approached-based dosimetry was not possible for patient Nr.1, because he had only non-contrast-enhanced CT available at baseline, thus it was not possible to perform liver segments delineation. Pt - patient, LTP - local tumor progression, POD - progression of disease, LTPFS - local tumor progression-free survival, min.- minimum, S-segment

Table 5 Side effects following radiation segmentectomy

Side effects	Incidence
Pronounced fatigue	4/12 (33%)
Abdominal pain/distension	3/12 (25%)
Nausea	1/12 (8%)
Dyspnea	1/12 (8%)
Weight loss (≥10 pounds)	1/12 (8%)
Elevation of hemidiaphragm including phrenic artery, resolved on its own	1/12 (8%)
Total patients number	6/12 (50%)*

*Multiple side effects could have been reported per procedure

Major complications occurred after 1/12 (8%) (95%CI, 0-23%) of RS procedures in a high-risk patient with history of Whipple procedure 4-years prior to RS. This patient developed anaphylaxis to prophylactic cefotetan. The RS was aborted and performed a month later, using premedication with clindamycin, gentamycin and dexamethasone. The patient did not receive additional antibiotics after RS. One month after RS he underwent MW ablation for a liver tumor outside the RS field that was complicated by perihepatic abscess, requiring percutaneous drainage. The same patient presented 5-months after RS with bilomas within the RS region, complicated by polymicrobial liver abscess, requiring 9-days of hospitalization for abscess aspiration and intravenous antibiotics with no further sequelae.

DISCUSSION

Technical considerations

In this study we described our initial experience with RS in patients with liver metastases. RS was utilized for selected patients with oligometastatic disease and limited treatment options. This included patients not amenable to resection or percutaneous ablation. The main RS treatment intent was local cure, similarly to ablative external radiation therapy [25] or ablation [26]. During RS a target ablative radiation dose of >190 Gy was administered superselectively into the tumor containing liver segments. The choice of this radiation dose was based on published data for RS in the patients with HCC, which reported a correlation of delivered radiation dose to the level of necrosis in explanted tumors [2].

Even though currently RS has been reported only for the treatment of up to two liver segments, we described successful RS for up to three segments (in two sessions). We intentionally used glass-based instead of resin microspheres during RS to enable

maximal radiation dose delivery with the smallest possible number of spheres and risk of stasis [12, 27-30].

Efficacy

Despite the heterogeneous population treated in this cohort, encouraging local tumor control was achieved. The overall 100% objective response rate by Choi criteria compared favorably to 81% response rate reported after RS in HCC patients [1]. The LTP rate of 7% and resulting 1-year LTPFS of 89% of the target tumors need to be assessed in the context of patients with advanced and refractory metastatic disease that had very limited if any local curative treatment options.

The single marginal LTP occurred in the largest tumor within the cohort (>5 cm in size), that only partially received the intended >200 Gy radiation dose in 35% of the target tumor volume. The same tumor received a minimum tumor radiation dose as low as 100 Gy. Of interest the area of LTP corresponded with area of predicted lower radiation dose by ^{99m}Tc MAA SPECT method and the actual lower dose exposure documented in the post-RS Bremsstrahlung SPECT. This is similar to prior research, where incomplete tumor targeting was associated with worse local tumor control following ⁹⁰Y radioembolization [31]. These findings indicating areas of technical weaknesses that can be improved for the optimization of this technique and the sufficient radiation dose delivery to target tumor and surrounding parenchyma.

Safety

Self-limiting side effects were noted after a half of RS procedures and were similar to known side effects of ⁹⁰Y radioembolization (weakness, nausea, abdominal distention, weight loss and transient dyspnea). None of these required admission or medication [29, 32]. Major complication was noted in a single patient, who was high-risk in developing complications: it is well known that patients with Whipple or prior sphincterotomy and in general any biliary intervention are high risk for liver abscess formation after any liver-directed therapies [33-36]. It is therefore recommended that they also be considered as high risk for radioembolization and be protected with biliary secreted antibiotics in the peri- and post-procedure period. All patients were alive on last follow-up without evidence of radiation-related toxicity. Similarly, Riaz et al. reported favorable adverse event profile following RS for HCC patients [1]. This suggests that RS is safe as expected since the non-exposed liver remains fully functional.

Dosimetry

We reported large variation in estimated absorbed radiation doses among different

dosimetry assessment methods used.

The partition model-based dosimetry theoretically should have provided the most accurate tumor radiation dose values amongst the three methods employed in this study. It accounts for a preferential flow of microspheres to tumor and for the entire delivered radiation activity. However, it also has several limitations: it assumes, that radiation dose is homogeneously distributed in each compartment (tumor, uninvolved liver parenchyma and the lungs) [37, 38], which is incorrect; and it is based on the distribution of ^{99m}Tc-MAA, rather than ⁹⁰Y particles [39-42].

Bremsstrahlung SPECT/CT dose estimates might be unreliable due to the lack of consensus on the correct settings for energy windows and corrections [43]. The MIRD-based segment dosimetry estimation is also not optimal as it assumes uniform distribution of radiation activity within the tumor and the non-involved liver parenchyma (tumor-to-normal liver ratio equal to 1), that is not accurate [44].

The discrepancy among the methods is concordant with prior data indicating, that current dosimetry calculators are not optimal and represent gross oversimplifications of tumor architecture and radiobiology. Alternatively, three-dimensional voxel-based dosimetry using ⁹⁰Y PET/CT was found to be beneficial, detecting associations of tumor response, progression-free, overall survival and toxicity with the delivered ⁹⁰Y dose [31]. However, it cannot be used for treatment planning and dose delivery predictions. An optimal radiation activity calculation methodology for RS must be applicable to treatment planning, accounting for microspheres' number and distribution as well as tumor type and characteristics (vasculature, perfusion and genetic factors). Radiology-pathology correlations with dosimetry are very much warranted in an effort to better understand and optimize radioembolization as a treatment for cancer.

Dose-response correlations

Despite the small number of patients included in the study, we found a significant correlation between the absorbed radiation dose in the treated segment (based on MIRD dosimetry) and the incidence of disease progression rates, implying greater tumor control with increased radiation dose to the target segment. Subsequent correlation of increased radiation dose absorbed in the treated segment with segment progression-free survival was not significant. While the disease progression rate result is promising, progression-free survival is generally considered a better indicator of local tumor control than disease progression rate. The lack of significant correlation between radiation dose delivered to the segment and segment progression-free survival in this

study is most likely the result of the small cohort and the pathologic heterogeneity of the treated metastases.

Study limitations

This study has several limitations including the heterogeneous patient and tumor characteristics, the retrospective single-center nature, the small sample size, the relatively short follow-up time and the lack of uniform follow-up imaging. These limitations are inherent to the limited population of patients with metastatic disease that were candidates and received RS to date.

The initial experience with RS for hepatic metastases described in this short report is encouraging and sets the stage for further investigation regarding RS as a potential alternative local curative treatment for hepatic metastases. Well-designed prospective investigations with pathologic validation of response and correlations to dosimetry are very much warranted to assess radiation segmentectomy in the treatment of metastatic liver disease.

CONCLUSION

This study provided the data on initial single-center experience with radiation segmentectomy in selected patients with limited hepatic metastases that could not be treated with resection or ablation. Specifically, the study demonstrated that radiation segmentectomy of up to three hepatic segments is feasible and safe providing good local tumor control in patients with limited liver metastatic disease and poor if any treatment options.

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SUPPLEMENTARY MATERIAL

Supplement 1 Response evaluation criteria used in the study

Response Category	RECIST 1.1 Guidelines	Choi Criteria
Partial response	≥ 30% decrease in sum of longest tumor diameters.	≥ 15% decrease in tumor attenuation (HU) or ≥ 10% decrease in tumor size.
Stable disease	No partial response or progressive disease.	No partial response or progressive disease.
Progressive disease	> 20% increase in sum of longest tumor diameters or development of new tumors.	Has ≥ 10% increase in tumor size, but does not meet criteria for partial response as measured by change in tumor attenuation or development of new tumors.

PART 2

Management of Colorectal
Lung Metastases In
Interventional
Oncology Setting

Image-Guided Thermal Ablation for the Treatment of Pulmonary Malignancies

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ABSTRACT

Objective

Image-guided thermal ablation is a minimally invasive treatment option for patients with primary and secondary pulmonary malignancies. Modalities include radiofrequency ablation, microwave ablation and cryoablation.

Conclusion

Although no large randomized studies exist comparing ablation to surgery or radiotherapy, numerous studies have reported safety and efficacy for the treatment of both primary and metastatic disease in select patients. Future studies will refine patient selection, procedural technique, and assessment for local recurrence and will evaluate long-term survival.

A variety of image-guided thermal ablation techniques exist for patients with non-small cell lung carcinoma (NSCLC) and oligometastatic disease. Many of these patients are not surgical candidates, so thermal ablation techniques—including radiofrequency ablation (RFA), microwave ablation (MWA), and cryoablation—have been explored, showing safety, efficacy, and good local disease control while preserving the lung parenchyma [1–8]. For patients with stage I or II NSCLC, surgical resection provides the best curative option, with 5-year survival rates of 50–75% [9]. However, only one-third of patients may meet the criteria for lobar or sublobar resection [10]. For the remaining patients, ablative therapies have proved useful [3, 11–14]. Additionally, the lungs are the second most common site of metastatic disease [15]. In selected patients with a limited number of tumors that can be ablated with adequate margins or those who present with residual or recurrent disease after having undergone other treatments, percutaneous thermal ablation plays a role in disease management. Over the past 2 decades, ablation has played an important role in the treatment of both primary and secondary pulmonary malignancies, providing an effective therapy, which can also provide potential cure in select cases.

MECHANISM OF ACTION AND LOCAL EFFICACY

The unique characteristics of pulmonary parenchyma facilitate thermal ablation, including heat insulation and low electrical conductivity. These characteristics permit a larger volume of tissue to be ablated for a given energy than in other tissues in the body [16]. With RFA, an electrode from a generator causes frictional heating, elevating tissue temperature to 60–100°C. This creates a necrotic zone covering both the tumor and margin of normal parenchyma [17]. However, this thermal energy can be limited by the heat-sink effect of adjacent blood vessels and airways [1]. Several groups have reported that the presence of vessels or bronchi greater than 3 mm in diameter within the ablation zone is predictors of incomplete local treatment [18, 19]. Pathologic analyses of 354 NSCLC cases (adenocarcinoma and squamous cell carcinoma) have revealed that 8 and 6 mm margins, respectively, are needed to cover 95% of microscopic disease extension [20]. Thus to obtain adequate margins, the ablation zone must exceed the tumor size [21]. RFA therefore performs best for lesions smaller than 2 cm, with rates of complete ablation ranging from 78% to 96% with a mean follow-up of 1 year [3, 14, 18, 22, 23]. Lower success rates are seen with tumors 2–3 cm in diameter [3, 18, 22, 23]. More specifically, a ratio of RFA-induced ground-glass opacity (GGO) to tumor area of greater than 4 (bidimensional area on axial images) is correlated with a significantly higher rate of complete ablation than a ratio of less than or equal to 4 [3].

MWA uses microwaves to cause friction between water molecules, generating hyperthermia [24]. Unlike RFA, during which only one probe is activated at a time, MWA enables simultaneous energy delivery with multiple probes, thus permitting larger ablation zones than RFA. In animal studies, investigators have reported lung ablation zones as large as 54.8 ± 8.5 mm (mean $\pm$ SD) [25]. Clinically, Wolf et al. [4] reported MWA results in 50 patients with pulmonary tumors up to 5 cm. The authors reported an overall recurrence rate of 26% and a tumor size of larger than 3 cm being predictive of recurrent disease.

Cryoablation uses compressed argon gas to generate subzero temperatures with ice-ball formation. When temperatures are less than -40°C , protein denaturation, cell rupture, and ischemia occur [26]. Unlike heat-based ablation, cryoablation does not create GGO intra-procedurally; instead, the ice ball is used to estimate the ablated margin. Hinshaw et al. [27] examined the temperature isotherms and associated ablation zone size seen with cryoablation in an in vivo porcine lung model. They identified the -20°C isotherm as the zone of coagulative necrosis, with a mean ablation zone diameter of 2.4 ± 0.2 cm [27]. Most ablation protocols call for three freeze-thaw cycles to achieve tissue necrosis [27, 28].

Irreversible electroporation, which uses electrical pulses to generate high electrical fields (1500 V/cm^2), was developed as a non-thermal ablation technique. This technique causes cellular apoptosis by creating cell membrane pores and resultant cell lysis. However, in the multicenter phase II trial of 23 patients with metastatic disease, Rieke et al. [29] reported local progression in 61% of treated patients. They postulated that the high local recurrence was likely because of conductivity differences between the tumor tissue and normal lung parenchyma. Given these results, irreversible electroporation requires refinement before becoming an effective ablation modality for pulmonary malignancies.

IMAGING AND RESPONSE

CT is the preferred image guidance modality for thermal ablation because it provides excellent contrast between the tumor tissue and normal aerated lung. CT provides multiplanar imaging, which facilitates accurate and quick probe placement [30]. In fact, operators who have access to multiplanar imaging have been shown to better distinguish between margin- and lesion-centered probe placement than operators who have access to axial images alone [31]. Cone-beam CT has been used for lung ablation because it facilitates ablation approaches from any angle; however, it lacks real-time imaging capability. This can be an issue in the setting of moving target lesions [32].

CT is also the modality of choice for follow-up after ablation. After ablation, the targeted lesion is replaced by a central area of increased radiographic density that is surrounded by GGO [11], which may overestimate the actual pathologic margins of RFA [33] and cryoablation [28]. An ablation margin surrounding the target lesion of less than 4.5 mm or an incomplete margin has been correlated with local tumor progression [34]. GGO margins of less than 3 mm have been associated with tumor progression as well [35]. During the initial post-ablation period (< 2 months), this dense opacification and surrounding GGO serve as the new “baseline” post-ablation image [21, 36]. Any increase in the size of this lesion on follow-up should be considered local progression.

The evolution of the imaging appearance of the ablation zone varies depending on the thermal ablation modality. Palussière et al. [37] described the involution pattern seen after RFA of 350 treated lesions with CT follow-up to 12 months. Although they reported five different imaging patterns, they concluded that none of these patterns can be used to exclude local tumor progression. RFA-treated lesions show a relatively slow rate of involution, with a 40% decrease in size at 15 months after treatment [38]. Similar post-ablation imaging findings have been described after MWA [4] (**Figure 1**). Cryoablated lesions, however, show faster involution on CT follow-up so that local tumor progression can be visualized as early as 6 months after treatment [39]. CT enhancement patterns after both RFA and cryoablation have not shown correlation with local progression [6, 39]. CT is therefore primarily used to examine morphologic changes to the ablation zone. However, detecting local progression at follow-up using CT alone remains difficult. Beland et al. [40] found that in 79 patients with NSCLC treated using RFA, local progression was seen in only 1.5% at 6 months, increasing to 10.1% at 1 year and 28% at 2 years. De Baère et al. [13] retrospectively examined the records and images of 566 patients with metastatic disease treated with RFA and reported rates of local tumor progression of 10.4% at 1 year and 18.1% at 4 years.

To overcome the limitations of CT’s morphologic assessment of local recurrence, PET/CT follow-up has been explored (**Table 1**). Yoo et al. [41] examined the role of PET/CT in 30 patients with stage I NSCLC treated with RFA. They reported that imaging 6 months after RFA more accurately reflected outcomes at 1 year than imaging performed immediately after RFA [41]. Suzawa et al. [33] studied the utility of PET/CT in the follow-up of 143 patients treated with RFA. Local tumor progression was seen in 20.4% of tumors with a median follow-up of 24 months, and PET’s diagnostic performance exceeded that of CT at all follow-up imaging time points. However, for up to 3 months after ablation, PET/CT can be confounded by inflammatory changes in both the treated tissues and mediastinum [40]. Split-dose PET/CT has been developed to aid in target localization and evaluation of treatment effectiveness intraprocedurally [42,43] (**Figures 2-3**).

Figure 1 Successful microwave ablation (MWA) of recurrent non-small cell lung carcinoma (NSCLC) metastasis in the left lower lobel with gradual constriction of ablation zone

This case illustrated value of locoregional therapy in general and ablation specifically in treatment of primary lung cancer with recurrent metastatic nodules. Over course of treatment, patient had minimal and stable pulmonary symptoms. In this 72-year old man, initial diagnosis in 2008 was right upper lobe lung adenocarcinoma, stage IB. Patient underwent right upper lobectomy and right lower lobe wedge resection with tumor-free margins for moderately differentiated adenocarcinoma with micropapillary (60%), papillary (30%) and lepidic (10%) components. Patient received no adjuvant chemotherapy and there was no evidence of disease for 20 months. In 2010, imaging detected new clustering of right lower lobe nodules, which were biopsy-proven adenocarcinoma and were morphologically similar to primary tumor. There was no evidence of disease elsewhere. Because of undetermined staging of the disease (metastatic vs second primary tumor), no systematic therapy was used and patient was treated with image-guided radiation therapy. In 2012, imaging showed left lung nodule, and patient was diagnosed with stage IV disease treated with MWA. After MWA, new left upper lobe nodule was treated with wedge resection in January 2013. Subsequent recurrences in two right lower lobe metastases in February 2013 and right lower lobe in May 2014 were treated with MWA. Patient's disease was stable until December 2015 when chest CT revealed increasing left lower lobe nodule, recurrent tumor 3 years after MWA, but not in

area of prior MWA.

A, CT scan obtained before MWA shows 0.9 × 0.9 cm left lower lobe lung metastasis (arrow)

B, CT scan obtained during MWA. Metastasis was treated in three overlapping ablations.

C, CT scan obtained immediately after MWA shows ablation defect (arrow) that is 2.5 × 1.8 cm. Margins were assessed as 5 mm and extend to aorta.

D-F, Follow-up CT scans obtained 11 weeks (**D**), 7 months (**E**), and 1 year (**F**) after MWA show expected gradual constriction of ablation zone (arrows) and no evidence of local recurrence. Patient remained without disease until February 2017 when he developed bilateral lung nodules with associated rib destruction and increased pleural thickening consistent with multifocal progression of disease. Patient is currently undergoing systemic therapy for disease management.

Table 1 Modification of the Response Evaluation Criteria in Solid Tumours (RECIST) as presented by Herrera et al. [96]^a

Response	CT Mass Size (RECIST)	CT Mass Quality	PET ^b
Complete (2 of the criteria)	Lesion disappearance (scar) or <25% of original size	Cyst cavity formation, low density	SUV<2.5
Partial (1 of the criteria)	>30% Decrease in sum LD of target lesions	Mass central necrosis or central cavity with liquid density	Decreased SUV or area of FDG uptake
Stable lesion (1 of the criteria)	<30% Decrease in sum LD of target lesions	Mass solid appearance, no central necrosis or cavity	Unchanged SUV or area of FDG uptake
Progression (2 of the criteria)	Increase >20% in sum LD of target lesions	Solid mass, invasion adjacent structures	Higher SUV or larger area of FDG uptake

Note-Modified from the RECIST criteria [97,98]. SUV=standardized uptake value. Sum LD=sum of largest diameters of all target lesions

^aReprinted with permission of Elsevier from the Journal of Thoracic and Cardiovascular Surgery (volume 125, Herrera LJ, Fernando HC, Perry Y, et al. Radiofrequency ablation of pulmonary malignant tumours in nonsurgical candidates, pages 929-937, Copyright 2003) [96]

^bPET scan was used selectively in lesions with unclear response by CT imaging.

^cTumours treated with radiofrequency ablation

Figure 2 Successful microwave ablation (MWA) of recurrent biopsy-proven non-small cell lung carcinoma (NSCLC) in 83-year-old woman

Initial diagnosis in May 2007 was stage IA bronchoalveolar adenocarcinoma in right upper lobe. Wedge resection of left upper and lower lobes was performed, and malignancy was pathologically proven only in left upper lobe. Left lower lobe FDG-avid nodule remained in situ after resection. This nodule had interval enlargement and was found to be positive for adenocarcinoma in November 2007 at biopsy. This nodule was treated with radiofrequency ablation in March 2008, with no viable Ki-67-positive tumor cells detected on tissue adherent to electrodes [90]. In November 2011 patient returned with new biopsy-proven NSCLC nodule in left lower lobe. This nodule was treated with MWA.

A, Cross-sectional CT scan shows 2,8 cm recurrent NSCLC lesion (arrow) in left lower lobe.

B, Pre-treatment split-dose ^{18}F -FDG PET/CT scan shows FDG-avid lesion (arrow) with maximum standardized uptake value of 5.9. Split-dose ^{18}F -FDG PET/CT is technique for PET/CT-guided ablation that permits both target localization and evaluation of treatment effectiveness. During procedure, standard administered diagnostic FDG activity dose of approximately 12 mCi [444 MBq] is administered in two aliquots: 4-mCi [148 MBq] target dose or imaging dose administered 30-60 minutes before ablation and 8-mCi [296 MBq] treatment efficacy dose administered immediately after ablation. Images are obtained 30 minutes later.

C, CT scan obtained during MWA shows microwave electrode (arrow) in tumor: two overlapping ablations of 8 minutes each were performed at 10-25 W.

D, CT scan obtained immediately after MWA shows ablation zone. All margins except medial margin are more than 5 mm. Smaller medial margin extends to aorta.

E, Split dose ^{18}F -FDG PET/CT scan obtained immediately after MWA shows no residual FDG avidity in the area (arrow).

F, ^{18}F -FDG PET/CT scan obtained 6 months after MWA shows expected constriction of ablated zone (arrow) and no FDG avidity.

G and **H**, FDG PET/CT scan (**G**) and corresponding CT scan (**H**) obtained 1 year after MWA show further constriction of ablation zone (arrows).

I and **J**, FDG PET/CT scan (**I**) and corresponding CT scan (**J**) obtained 2 years after MWA show expected evolution of ablation zone (arrows) with no evidence of local recurrence.

Figure 3—Successful microwave ablation (MWA) of lung metastases from colorectal carcinoma in 37-year-old man

The patient had a history of ulcerative colitis and underwent proctocolectomy and formation of J-pouch in 1996. In June 2010, patient was diagnosed with stage I mucinous adenocarcinoma of rectum and received adjuvant chemotherapy (folic acid, 5-fluorouracil, oxaliplatin) and chemoradiotherapy. In April 2012, patient developed right middle lobe lung metastasis and underwent right middle lobe wedge resection. In February 2013 when patient was no longer receiving chemotherapy, follow-up imaging showed significant progression of disease in left lung with two growing nodules in left lower lobe and left upper lobe. Both lesions underwent MWA with at least 5-mm ablation margins. Tissue from ablation electrodes showed no viable tumor cells [90]. We present imaging of one of two ablated lesions.

- A**, Pretreatment cross-sectional CT scan shows 8 × 10 mm medial left upper lobe lung metastasis (*arrow*).
- B**, Fluorine-18-FDG PET/CT scan shows mildly FDG-avid lesion (*arrow*).
- C**, CT scan obtained during MWA shows microwave electrode in tumor. Two overlapping ablations, 45 W for 10 minutes and 65 W for 5 minutes, were performed.
- D**, CT scan obtained immediately after ablation shows ablation zone (*arrow*) of 28 × 30 × 30 mm with minimal ablation margin of more than 10 mm.
- E**, Split-dose ¹⁸F-FDG PET/CT scan obtained after second dose shows no uptake in ablated zone (*arrow*); maximum standardized uptake value (SUV_{max}) is 1.0. Histopathologic analysis of tissue from ablation

electrodes showed no viable tumor cells [90]. Split-dose ¹⁸FDG PET/CT is technique for PET/CT-guided ablation that permits both target localization and evaluation of treatment effectiveness. During procedure, standard administered diagnostic FDG activity dose of approximately 12 mCi [444 MBq] is administered in two aliquots: 4-mCi [148-MBq] target dose or imaging dose administered 30–60 minutes before ablation and 8-mCi [296-MBq] treatment efficacy dose administered immediately after ablation. Images are obtained 30 minutes later.

F, ¹⁸FDG PET/CT scan obtained 5 weeks after MWA shows hypermetabolic rim of cavitated ablation zone (*arrow*). Ablation zone is 2.9 × 4.1 cm with SUV_{max} of 5.5. Follow-up imaging finding of hypermetabolic rim of cavitated ablation zone was characterized as expected post-ablation change rather than as residual or recurrent disease. Cavitated ablation zone with hypermetabolic rim can erroneously be interpreted as evidence of local tumor progression. Sequential imaging follow-up with standardized uptake value readings is helpful to detect gradual resolution. In cases of focal SUV increase in ablation zone and whenever in doubt, short-interval PET or biopsy is recommended with aim of repeat treatment.

G, ¹⁸FDG PET/CT scan obtained 4 months after MWA shows typical collapse and constriction of cavitated ablation zone (*arrow*), which is 1.6 × 1 cm, and decreased FDG avidity of ablation zone to SUV_{max} of 4.7.

H, ¹⁸FDG PET/CT scan obtained 7 months after MWA shows no FDG uptake in ablated area (*arrow*).

I, CT scan obtained 1 year after MWA shows constricted ablation zone (*arrow*).

J and **K**, CT scans obtained 2 years (**J**) and 4 years (**K**) after MWA show ablation zone (*arrows*).

L, ¹⁸FDG PET/CT scan obtained 4 years after ablation shows no FDG uptake in ablated area (*arrow*). After ablation of left lung metastases, patient developed right lung metastasis, which was also treated by MWA. In November 2014, patient developed pleural metastases and pleural-based metastases, which were treated with three regimens of systemic chemotherapy. Patient was alive at last follow-up in 2017.

CLINICAL OUTCOMES

Non-Small Cell Lung Carcinoma

An early study by Simon et al. [44] reported a median overall survival (OS) of 29 months (95% CI, 20–38 months) in 75 patients with NSCLC, with 1- and 5-year survival rates of 78% and 27%. They found improved survival in patients with lower stage disease and lesions less than 3 cm in diameter [44]. Ambrogi et al. [45] and Huang et al. [46] reported similar 5-year survival rates of 25% in patients with stage I NSCLC. Huang et al. reported a local progression rate of 23.7%, with a significantly increased rate of local progression in patients with lesions larger than 4 cm. More recent studies have reported improved survival, which is likely a combination of multiple factors, including technical refinements, better patient selection, and the use of targeted systemic therapies [30]. Palussière et al. [37] reported a 5-year OS rate of 58.1% and disease-free survival rate of 27.9% in 87 patients with NSCLC after thermal ablation. On multivariate analysis, tumor size larger than 2 cm was an

independent prognostic factor for disease-free survival [37]. Dupuy et al. [47] reported the outcomes of the American College of Surgeons Oncology Group trial of 51 patients with stage IA NSCLC tumors less than 3 cm in diameter. These authors reported 1- and 2-year OS rates of 86.3% and 69.8%, with 2-year survival rates increasing to 83% for patients with lesions less than 2 cm [47]. Similar results were seen by Hiraki et al. [48] and Liu et al. [49] in patients with stage I NSCLC. Both groups reported 1-year OS rates ranging from 90% to 94% and 3-year OS rates ranging from 74% to 79%. In addition to baseline tumor characteristics, patient comorbidities are predictive of survival. In 82 patients with NSCLC treated with RFA, Simon et al. [50] reported that 40 patients died; however, only 19 patients died due to disease progression. On multivariate Cox regression analyses, the Charlson comorbidity index (CCI), a measure of comorbidities, was strongly predictive of OS. A CCI of greater than 5 (mean OS, 10.43 months) was associated with significantly increased mortality versus a score of 1–2 (mean OS, 55.5 months) or 3–4 (mean OS, 36.62 months). No significant difference in survival was seen between CCI scores of 1–2 and 3–4 [50].

Long-term data after MWA for the treatment of NSCLC are limited. Wolf et al. [4] reported outcomes after MWA of NSCLC in 30 patients. With a mean follow-up of 10 months, Wolf et al. found a local recurrence rate of 26%, which was significantly increased in lesions larger than 3 cm on logistic regression analysis. OS rates ranged from 65% at 1 year to 45% at 3 years, which were not associated with tumor size [4]. Lu et al. [51] reported 1- and 3-year OS rates of 75% and 29.2% after MWA in 48 patients with NSCLC of various stages (I–IV). A significantly increased risk of local progression was seen for lesions larger than 4 cm. Belfiore et al. [52] reported 1- and 3-year cancer-specific survival (CSS) of 69% and 49% after MWA in 44 patients with lung cancer of various disease stages. A formal survival analysis was omitted due to cohort heterogeneity. In 47 patients with stage I NSCLC treated with MWA, Yang et al. [53] reported local control rates of 96% and 48% at 1 and 5 years after MWA. Median CSS and OS were 47.4 and 33.8 months, with significantly improved survival in patients with lesions less than 3.5 cm. Zheng et al. [54] studied outcomes in 183 patients (138 of whom had primary lung cancer) treated with MWA. The local progression rate was 19.1%, with an increased risk of progression seen in patients with lesions larger than 3 cm and in the setting of emphysema on multivariate analysis [54]. The authors reported a median progression-free survival (PFS) and CSS of 16.5 and 29.0 months. Tumor stage and diameter greater than 3 cm were independent risk factors for CSS on multivariate analysis. A recent retrospective study by Healey et al. [55] examined outcomes of 108 patients (82 NSCLCs) who underwent MWA with a median follow-up of 14.1 months. The authors found significantly higher rates of technical success with lesions less than 3 cm in diameter. The median time to tumor recurrence was 62 months, with recurrence rates ranging from 22% at 1 year to 44% at 3 years. Significantly lower rates

of recurrence were seen with lesions less than 3 cm. The median OS was 27.1 months, with 1- and 3-year OS rates of 78% and 39%.

Although the long-term studies on cryoablation of NSCLC are limited, the initial studies have yielded promising results. Yamauchi et al. [56] used cryoablation to treat 34 NSCLC stage I tumors and reported a median survival of 68 months and a 2-year OS rate of 88%; these results are comparable to results seen with RFA. Moore et al. [57] reported a 5-year OS rate of 67.8% and a local recurrence rate of 14.9% in 45 patients with T1 NSCLC. A recent study by McDevitt et al. [58] of 25 patients with NSCLC found a median OS of 43 months (95% CI, 30–57 months) with a median PFS of 15 months (95% CI, 8.7–20 months).

Thermal ablation has a role in the setting of advanced disease or as salvage therapy. Kodama et al. [59] examined RFA of 51 recurrent NSCLCs that were initially treated with surgery and reported a 1-year survival rate of 97.7% and a 5-year survival rate of 55.7%. The authors found that tumor size less than 3 cm predicts prognosis, with 1- and 3-year survival rates of 100% and 79.8% for tumors greater than 3 cm versus 83.3% and 31.3% for smaller tumors [59]. In patients with stage III or IV NSCLC, Lee et al. [60] found longer median OS in patients treated with RFA and chemotherapy ($n = 24$) than in those treated with chemotherapy alone ($n = 18$) (42 vs 29 months, respectively; $p < 0.03$). Ablation has also been used in patients with a solitary lung after pneumonectomy, a population with few treatment options for new or recurrent disease and limited pulmonary reserve. Hess et al. [12] and Sofocleous et al. [61] have shown acceptable morbidity and safety of ablation in treating these patients. Sofocleous et al. [61] caution that post-ablation pneumonitis may be a concern in these patients and may be mitigated with periprocedural steroid administration.

Metastatic Disease

Thermal ablation plays a role in the management of metastatic disease in selected patients with limited disease burden that can be ablated with margins. In general, this group includes patients with up to four lesions per lung and with lesions smaller than 3.5 cm [6,62–65]. Given the clinical course of metastatic disease, the therapies should be repeatable and associated with limited effects on pulmonary function [5, 63, 66]. The Radiofrequency Ablation of Pulmonary Tumors Response Evaluation (RAPTURE) trial in 53 patients with metastatic colorectal carcinoma (CRC) reported 1- and 2-year OS rates of 89% and 66% [14]. De Baère et al. [13] reported the largest series of pulmonary metastases (566 patients with 1037 metastases) treated with RFA. The authors reported a median OS of 62 months and 1- and 5-year OS rates of 92.4% and 51.5% for the entire cohort. On multivariate analysis, the location of the primary tumor, disease-free interval, tumor

size greater than 2 cm, and presence of more than three metastases were associated with OS. Several studies have reported similar 1- and 3-year OS rates [67, 68]. Most series evaluating RFA for metastatic disease report local progression rates of 10–30%, especially for lesions larger than 3 cm [14, 18, 63, 69–71]. Omae et al. [72] reported long-term follow-up in 123 patients with lung oligometastases treated with RFA. The authors found a 5-year OS rate and recurrence-free survival rate of 62% and 25% [72].

MWA has also been explored for the treatment of pulmonary metastatic disease. Vogl et al. [5] reported outcomes of MWA in 80 patients with metastatic disease. The authors found a rate of local recurrence of 26%, with treatment success significantly related to tumor size less than 3 cm and to peripheral lesions rather than central lesions. The 1- and 2-year survival rates were 91.3% and 75%. In a follow-up study in 57 patients with 91 metastatic lesions [73], local progression was seen in 33% of patients, with a median time to local progression of 22.6 ± 12.4 months. On regression analysis, the shape of the primary lesion and energy deployed per unit of tumor volume (< 26.7 J/mm³) were associated with disease progression. In a more recent comparison study, Vogl et al. [74] examined the role of MWA ($n = 47$ patients) and RFA ($n = 41$ patients) in the treatment of CRC metastases. These authors reported significantly improved local control rates with MWA over RFA and no significant difference in OS or PFS [74]. However, these studies did not perform histopathologic analysis of ablation zones, via biopsy or resection, to validate technical success.

Cryoablation has also been shown to be safe and effective in the treatment of pulmonary metastases, although survival data are limited [75]. Yamauchi et al. [76] reported a local progression rate of 26% with significantly improved PFS with tumors less than 15 mm in 24 patients with metastatic CRC treated with cryoablation. The 1- and 3-year OS rates were 91% and 59.6% and the 1- and 3-year PFS rates were 90.8% and 59%. McDevitt et al. [58] found a mean time to local progression of 10 months, with a median OS of 22 months across tumor types treated with cryoablation. A tumor diameter of greater than 3 cm was associated with local progression. Early results from the Evaluating Cryoablation of Metastatic Lung/Pleura Tumors in Patients—Safety and Efficacy (ECLIPSE) trial [77] of 40 patients with 60 lesions are currently being analyzed. The multicenter prospective cohort includes patients with colon (40%), renal (23%), and sarcoma (8%) primaries. The authors report a local control rate at 1 year of 94.2% and a 1-year OS rate of 97.5%. The investigators concluded that these initial results compare favorably with those of other ablation modalities including RFA and MWA [77]. Taken in conjunction with the results of other studies, these results indicate that thermal ablation performs best in tumors less than 3 cm, similar to findings seen with NSCLC.

COMPARATIVE STUDIES

There are limited comparative studies of thermal ablation with other treatment modalities, including surgical resection and stereotactic beam RT. Kim et al. [78] compared the outcomes of patients with stage I NSCLC treated with RFA ($n = 8$) versus those treated with surgical resection ($n = 14$). Although the rates of local recurrence were higher in the patients treated with RFA, OS was similar for the two groups [78]. Lee et al. [60] compared survival in patients with stage I and II NSCLC who were treated with RFA ($n = 16$) versus those who were treated with surgery ($n = 13$). Although the patients in the RFA group were significantly older than those in the surgery group, there was no significant difference in OS between the RFA and surgery groups (28.2 and 33.8 months, respectively; $p = 0.43$) [60]. Zemlyak et al. [79] studied 64 patients with biopsy-proven stage I NSCLC unfit for standard resection. The patients underwent sublobar resection ($n = 25$), RFA ($n = 12$), or cryoablation ($n = 27$). No significant difference in 3-year OS (sublobar resection, 87.1%; RFA, 87.5%; cryoablation, 77%) or in 3-year CSS (sublobar resection, 90.6%; RFA, 97.5%; cryoablation, 90.2%) was seen.

Using the database from the National Cancer Institute's Surveillance, Epidemiology, and End Results program, Kwan et al. [80] examined survival in 1897 patients with early-stage NSCLC who underwent surgical resection or ablation. After propensity score matching was performed, OS and CSS were not significantly different. Alexander et al. [81] compared 56 patients with stage I NSCLC treated with RFA and 28 patients with stage I NSCLC treated with sublobar resection. The 1-, 2-, and 3-year survival rates were 100%, 95%, and 83%, respectively, for the patients who underwent surgery and 91%, 73%, and 55% for those who underwent RFA; there was a significant increase in survival in patients who underwent resection compared with those who underwent RFA [81].

There are limited data comparing ablation with stereotactic beam RT in the treatment of NSCLC. Ochiai et al. [82] compared outcomes after RFA ($n = 48$) and stereotactic beam RT ($n = 47$) in patients with solitary tumors less than 5 cm. The authors reported similar 3-year local control and OS rates between the two modalities: 9.6% and 86.4% for RFA and 7.0% and 79.6% for stereotactic beam RT, with no significant difference between the treatments. However, less than half the patients who underwent stereotactic beam RT had pathologically proven NSCLC [82]. In a pooled analysis of 31 stereotactic beam RT ($n = 2767$ patients) and 18 RFA ($n = 328$ patients) studies, Bilal et al. [83] reported that stereotactic beam RT showed lower local progression rates than RFA (3.5–14.5% vs 23.7–43%). OS rates were similar between the two treatments, but 5-year OS rates favored stereotactic beam RT over RFA (47% vs 20.1–27%) [83].

In the treatment of patients with metastatic disease, RFA compares favorably with surgical resection with reported 5-year OS rates of 27–70% [84–86]. Large studies detailing the outcomes of stereotactic beam RT in patients with metastatic disease are limited. Fode and Hoyer [87] examined 321 patients with oligometastatic disease treated with stereotactic beam RT. The authors found a median OS of 2.4 years (95% CI, 2.3–2.7 years), with 1- and 5-year OS rates of 80% and 23%. In both primary disease and metastatic disease and unlike surgical resection or stereotactic beam RT, thermal ablation techniques can be repeated with limited changes to pulmonary function [5, 47]. This capability is of particular benefit in the setting of recurrent or residual disease.

FUTURE DIRECTIONS

Local recurrence remains a limitation of ablative therapy. Several predictors of local recurrence have been reported including tumor size and ablation margin [13, 18, 34]. There has been interest in developing additional biomarkers of disease local recurrence and improved predictors of response. In lung cancer specifically, several oncogenic mutations have been associated with prognosis [88, 89]. Sofocleous et al. [90] reported the utility of Ki-67 protein as a biomarker for response after RFA in 47 treated tumors, both primary and metastatic. Ki-67-positive tumor cells were an independent marker of local tumor progression and shorter PFS and CSS. Ziv et al. [91] reported that *KRAS* mutation status of an ablated lesion was a significant predictor of local recurrence that was independent of tumor size or ablation margin in 54 patients with primary adenocarcinoma. Conversely, Wei et al. [92] reported that *EGFR*-positive status did not adversely affect PFS or OS in 61 patients with stage IIIB or IV NSCLC treated with MWA.

The role of inflammatory cytokines and immune markers for determining prognosis in patients with lung cancer is also being explored. RFA-mediated tumor necrosis can stimulate an immune response [93]. Schneider et al. [93] examined the impact of RFA on the profile of serum inflammatory factors and immune suppressive cells in ablation in 12 patients. In patients with disease recurrence, the investigators found elevated levels of tumor necrosis factor- α , chemokine (CC motif) ligand-2, and chemokine ligand-4 and increased nitric oxide production in circulating myeloid-derived suppressor cells. The authors concluded that these factors may serve as early indicators of incomplete ablation of NSCLC.

CONCLUSION

Thermal ablation has shown safety and efficacy in the treatment of both primary and secondary lung malignancies in nonsurgical candidates. In NSCLC, after propensity score matching was performed, 2-year OS survival rates match those of surgery and stereotactic beam RT [47, 94]. Ablation also plays a role in metastatic disease, showing safety and efficacy. Across ablation modalities, lesion size is the main determinant of treatment success and survival. Furthermore, local progression remains a limitation for these therapies. Development of new tissue and corresponding surrogate image biomarkers for patient risk stratification and earlier detection of recurrence is needed. Further refinements of ablation technique including the intra-procedural development of tissue confirmation of complete tumor ablation with margins can improve local tumor control and significantly lower recurrence rates. Although ongoing prospective clinical trials comparing the efficacy of thermal ablation, stereotactic beam RT, and surgery are unlikely to mature, they could define the role of these therapies and improve patient selection for each treatment [77, 95].

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Microwave Ablation in the Management of Colorectal Cancer Pulmonary Metastases

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ABSTRACT

Purpose

To review outcomes following microwave ablation (MWA) of colorectal cancer pulmonary metastases and assess predictors of oncologic outcomes.

Methods

Technical success, primary and secondary technique efficacy rates were evaluated for 50 patients with 90 colorectal cancer pulmonary metastases at immediate, 4-8 weeks post-MWA and subsequent follow-up CT and/or ¹⁸F-FDG PET/CT. Local Tumor Progression (LTP) rate, LTP-free survival (LTPFS), cancer-specific and overall survivals were assessed. Complications were recorded according to SIR classification.

Results

Median follow-up was 25.6 months. Median tumor size was 1 cm (0.3-3.2cm). Technical success, primary and secondary technique efficacy rates were 99%, 90% and 92%, respectively. LTP rate was 10%. One-, 2- and 3-year LTPFS was: 93%, 86% and 86%, respectively with median LTPFS not reached. Median overall survival was 58.6 months, median cancer-specific survival (CSS) was not reached. One-, 2- and 3-year overall and cancer-specific survivals were 94% and 98%, 82% and 90%, 61% and 70%, respectively. On univariate analysis, minimal ablation margin (p<0.001) and tumor size (p=0.001) predicted LTPFS; with no LTP for minimal margin ≥ 5mm and/or tumor size < 1cm. Pleural-based metastases were associated with increased LTP risk (p=0.002, SHR=7.7). Pre-MWA CEA level >10 ng/ml (p=0.046) and ≥3 prior chemotherapy lines predicted decreased CSS (p=0.02). There was no 90-day death. Major complications rate was 13%.

Conclusions

MWA with minimal ablation margin ≥ 5 mm is essential for local control of colorectal cancer pulmonary metastases. Pleural-based metastases and larger tumor size were associated with higher risk of LTP. CEA level and pre-MWA chemotherapy impacted CSS.

INTRODUCTION

Approximately 5% of men and 4% of women develop colorectal cancer (CRC) during their lifetime, with 20% of patients having distant metastases at initial diagnosis [1, 2]. Lung is a second most common metastatic site with incidence of 10%-15% [3, 4]. Five-year survival of patients with distant disease is roughly 12% [5]. Complete metastatectomy and/or ablation increase 5-year survival to 27-68% [6-9]. However, only minority of patients with CRC pulmonary metastases is surgical candidates due to comorbidities or compromised pulmonary function [10]. In addition, lung metastasectomy recurrences are common (20-68%) and subsequent surgery is challenging due to limited pulmonary reserve [11-14]. Key ablation advantages compared to metastasectomy include possibility to spare pulmonary parenchyma, lung function and retreatment of new and recurrent metastases, which is often required in pulmonary metastases management [15-25]. Ablation is commonly used in the treatment of patients with limited number of relatively small tumors. Preferably <3 tumors in each hemithorax with no, limited or at least controlled extrapulmonary disease are generally accepted pulmonary ablation eligibility criteria [26-29].

Microwave ablation (MWA) has at least theoretical potential to overcome known limitations of radiofrequency ablation (RFA) [20, 21, 25-28, 30, 31], such as the diminished thermal conductivity of aerated lung and the “heat sink phenomenon” (due to flow in nearby vessels or the airway) that can impact the ability to create large and more uniform ablation zones with adequate margins in shorter time as demonstrated in animal studies [32-35]. Consequently, higher rates of complete ablation and sustained tumor control could be expected when using MWA [33-35].

This study assessed oncologic outcomes and complications of MWA in the management of patients with colorectal pulmonary metastases as well as factors affecting these outcomes.

METHODS

Study population

IRB waiver of approval was obtained for this retrospective review of our prospectively created and maintained HIPAA registered and compliant lung tumor ablation database. All patients with colorectal pulmonary metastases undergoing image-guided MWA between March 2011 and May 2016 were included in the study.

MWA inclusion criteria were: limited number of metastases (up to 6) in each hemithorax and relatively small tumor size (up to 3.5 cm) with no, limited or at least controlled extrapulmonary disease. Central tumor location was not an exclusion criterion if ablation could be performed safely without risk of damaging adjacent structures. The decision to treat the metastasis with ablation was made after multidisciplinary discussion.

Ablation procedure, imaging follow-up and definitions

Operators' experience, pre-ablation imaging and biopsy timing, image guidance, percutaneous entry route, MWA system and electrode choice, prophylactic antibiotics, anesthesia type, bilateral lung metastases and pneumothorax management, thermal monitoring, immediate post-procedure imaging, minimal ablation margin measurement (**Figure 1**) and imaging follow-up are described in **Table 1**. All study definitions are described in **Table 2**.

All patients with LTP were assessed for repeat thermal ablation eligibility.

Figure 1 Minimal ablation margin measurement.

A, Pre-ablation measurements: measurement (1) = 34 mm; measurement (2) = 14mm; measurement (3) = 8mm; measurement (4) = 50mm.

B, Post-ablation measurements: measurement (1) = 19mm; measurement (2) = 12mm; measurement (3) = 3mm; measurement (4) = 37 mm. After subtracting corresponding measurements at each location (1-4) the respective ablation margins were 15 mm, 2 mm, 5 mm and 13 mm. Therefore, minimal ablation margin for this ablation zone was 2 mm (insufficient).

C, Minimal ablation margin scheme.

Table 1 Ablation procedure descriptions. MWA-microwave ablation

Parameter	Description
Operator's experience	Majority of tumours (64%) were treated by two very experienced operators in lung ablation. Both operators started to perform lung thermal ablation (RFA) since year 1999, with MWA introduction since the year 2009. Importantly, since the year 2014 all the lung lesions have been treated solely with MW ablation in our institution, contributing to increased experience in this technique for all the operators
Lesion biopsy timing	It was chosen based on the need to know tumor pathology in disease management discussions (such as in patients with history of smoking second primary tumor was a reasonable possibility), as well as based on technical factors (such as the feasibility to biopsy the tumor without significant risk for bleeding that could obscure the target for MW ablation)
Pre-procedure imaging	All patients underwent pre-ablation cross-sectional CT and/or ¹⁸ F-FDG PET/CT for tumor assessment, restaging and pre-procedural planning
Intra-procedural image guidance	Included conventional CT in all patients, with additional CT fluoroscopy and/or split-dose ¹⁸ F-FDG PET/CT [39] at operator's discretion
Percutaneous entry route	Chosen based on tumor size, location and proximity to adjacent structures
MW system/ electrode number	Based on operator's preference. Ablation protocol was completed according to each manufacturer recommendations for the desired ablation size
Prophylactic antibiotics	Cefazolin (1 g IV x 1) or, in case of severe allergy, Clindamycin (900 mg IV x 1) combined with Gentamicin (1.5 mg/kg IV x 1) were administered once within 1 hour before the procedure
Anaesthesia type	All MWAs were performed under general anaesthesia
Number of ablation sessions	In case of single lung involvement, MWA was completed in a single session. In bilateral tumours, contralateral lung MWA was performed at least 3 weeks later to allow recovery of the initially treated lung. In cases of persistent symptoms/persistent pneumothorax, contralateral ablation was delayed until symptoms resolution
Thermal monitoring	Used with thermometer tip positioned at: (1) desired ablation margin; (2) at structure that needed be protected from the heat (chest wall, pleural surface); and (3) in the ablation zone to confirm lethal temperatures
Immediate post-procedure imaging	Non-contrast-enhanced CT scan was obtained to depict the ablation zone as an area of ground glass opacity covering the target tumor with a minimal ablation margin of at least 5 mm uniformly around target metastasis
Minimal ablation margin (MM) measurement	It was measured on immediate post-procedure non-contrast-enhanced CT (Figure 1). MM was defined as the shortest distance between the ablated metastasis and the edge of the ablation zone. In confluent ablation zones and cases of bleeding obscuring the ablation zone the MM was not measured
Detection and management of pneumothorax	After ablation, chest X-rays were obtained for at least 2 hours to detect pneumothorax prior to patients' release from the post-anaesthesia care unit. Asymptomatic patients without pneumothorax and with no intravenous analgesia requirement were discharged home on the same day. Patients with small asymptomatic pneumothoraces were admitted for overnight observation. Patients with larger, enlarging and/or symptomatic pneumothoraces were treated with thoracostomy and admitted to the hospital
Imaging follow-up	First follow-up CT and ¹⁸ F-FDG PET/CT were performed at 4-8 weeks and served as the new baseline for future evaluations. Subsequent imaging follow-up was performed approximately every 3 months thereafter

Table 2 Study definitions

Term	Definition
Technical success rate	Percentage of target tumours, successfully treated per ablation protocol, resulting in the creation of an ablation zone covering the target tumor, depicted on the immediate post-ablation imaging and on first follow-up imaging (at 4-8 weeks post-MWA), which served as the new baseline for future comparisons
Residual tumor	Enlargement of the ablation zone or nodular enhancement/ increased focal FDG uptake ($SUV_{max} \geq 2.5$) at or within 1 cm from the ablation zone on first post MWA imaging (at 4-8 weeks)
Local tumor progression	Enlargement of the ablation zone or nodular enhancement/ increased focal FDG uptake ($SUV_{max} \geq 2.5$) at or within 1 cm from the ablation zone. LTP was defined at the earliest on the second imaging (at 9-16 weeks) post-MWA for those tumours successfully ablated as depicted at the first (4-8 weeks) post MWA imaging
Primary technique efficacy rate	Percentage of target tumours successfully eradicated following the initial MWA during the entire study follow-up period [40]
LTP-free survival (LTPFS)	Time period, calculated from the ablation date until LTP or until the last available CT and/or ^{18}F -FDG PET/CT
Secondary technique efficacy rate	Percentage of target tumours successfully eradicated following repeat ablation(s) to treat residual disease or LTP
Assisted LTPFS	Cumulative time interval from the initial MWA until the latest follow-up, including all ablations to treat the initial tumor and all subsequent LTP(s).
Side effects	Side effects included expected, undesired consequences of MWA that did not lead to unexpected increase of level of care
Minor complications	Minor complications included events that did not require intervention or required only nominal therapy
Minor complications	Major complications required intervention, resulted in prolonged hospitalization (>48 hours) or had permanent sequelae

MWA- microwave ablation, LTP-local tumor progression

Study objectives

Primary objectives included technical success, primary and secondary technique efficacy rates, LTP rate, LTP-free survival (LTPFS), assisted LTPFS, overall survival (OS) and cancer- specific survival as well as identification of factors, associated with LTPFS and cancer-specific survival.

Secondary study objectives included assessment of side effects and complication according to SIR classification [27, 39].

Factors affecting oncologic outcomes

Tumor-related (tumor size and location) and procedure-related factors (minimal ablation margin) were analyzed as potential predictors of LTPFS.

Patient-related factors (lungs as the first metastatic disease site) and prior therapies (prior lung or liver surgery, prior chemotherapy ± target therapy lines) were analyzed as potential predictors of cancer-specific survival.

Statistical analysis

Statistical analysis methodology is described in Table 3.

Table 3 Statistical analysis methods used in the study

Kaplan Meier method	Used to evaluate LTPFS, overall and cancer-specific survivals
Compete risk model, adjusted for clustering (tumor-based)	Analysed LTPFS predictors (tumor size, minimal margin size and location) to account for multiple patients that underwent ablation for more than one tumor. Death was considered a competing event in this analysis
Fisher exact test	Used to analyse categorical variables
Other	Sample proportion confidence intervals were calculated using Wilson method with continuity correction
Software used	STATA 12.1
Significance level	P<0.05 was considered significant

RESULTS

Patient Population

Fifty patients with 90 colorectal lung metastases were treated in 60 MWA sessions. Twenty-eight (56%) of patients were women and 22 (44%) were men with a mean age of 58.5 ± 13.2 years. Median follow-up for survivors was 25.6 months (range: 12.8-80.6 months), 29/50 (58%) of patients were followed for more than two years (Figures 2-3). At the time of initial diagnosis 21/50 (42%) of the patients had AJCC stage IV disease. Thirteen out of fifty (26%) of patients underwent MWA for disease progression after lung metastasectomy. Patient and tumor characteristics, biopsy timing as well as pre-MWA therapies are described in Tables 4-5.

Technical Parameters and Technical Success Rate

Six out of fifty (12%) of patients received MWA in two separate sessions to treat bilateral lung metastases, with one patient requiring contralateral ablation delay for a week to allow persistent asymptomatic pneumothorax resolution. Ablation technical parameters are depicted in Table 6.

Technical success rate was 89/90 (99%): 1/90 (1%) of ablated tumors (3.2 cm in size and pleural-based) maintained focal metabolic uptake on first post-MWA ^{18}F -FDG PET/CT scan, consistent with residual tumor.

Figure 2 Lung MWA ablation zone changes in 72-year old woman with metastatic colorectal cancer over 28 months follow - up period on cross-sectional CT, showing gradual constriction of ablation zone and no evidence of local tumor progression.

After initial diagnosis, the patient underwent right hemicolectomy, adjuvant chemotherapy with 5-FU and leucovorin and was off-treatment with no evidence of disease for 18 months.

A, Pre-ablation enlarging lung nodule (from 0.9 cm to 1.6 cm) with rising CEA (from 5.8 ng/ml to 11.6 ng/ml): lesion was considered metastatic, not biopsy-proven. Due to significant comorbidities (end-stage kidney insufficiency, coronary artery disease, diabetes, arterial hypertension and history of stroke) lung ablation was preferred to surgery.

B, Immediate post-MWA CT with ablation zone as ground-glass opacity measuring 3.2 × 3.0 cm.

C, Follow - up scan at 5 weeks, which served as a new baseline for future comparisons.

D, Follow - up scan at 17 weeks.

E, Follow - up scan at 15.5 months;

F, Follow-up scan at 28 months with constricted ablation zone and no evidence of local tumor progression. The patient was off-treatment after MWA with no evidence of disease elsewhere for 2 years, when the patient developed solitary biopsy proven liver metastasis, treated with liver segmentectomy. The patient then was off - treatment with no evidence of disease elsewhere throughout the last follow-up.

Figure 3 Real time ¹⁸F-FDG PET/CT - guided lung MWA with ablation zone constriction and decreased metabolic uptake over 28 months follow-up period (imaging of the same patient as in the **Figure 1**).

A, Pre-ablation split-dose ¹⁸F-FDG PET/CT scan* with FDG - avid left upper lobe lung metastasis.

B, Immediate post-ablation ¹⁸F-FDG PET/CT scan with no metabolic uptake in the ablation zone.

C, ¹⁸F-FDG PET/CT scan 4 weeks after ablation.

D, ¹⁸F-FDG PET/CT scan 17 weeks post- ablation.

E, ¹⁸F-FDG PET/CT scan 15.5 months after ablation.

F, ¹⁸F-FDG PET/CT scan 23 months after ablation with constricted ablation zone, no metabolic uptake and no evidence of local tumor progression.

*Split - dose ¹⁸F-FDG PET/CT is a technique for PET/CT-guided ablation that permits both target localization and evaluation of treatment effectiveness. During the procedure, the standard administered diagnostic FDG activity dose of approximately 12 mCi (444 MBq) is administered in two aliquots: a 4-mCi (148-MBq) target/imaging dose administered 30-60 minutes before ablation and an 8-mCi (296-MBq) treatment efficacy dose administered immediately after the ablation with images obtained 30 minutes later [43].

Table 4 Patient Characteristics

Parameter	Incidence
Number of patients	50
Number of treated lesions	90
Number of ablations	60
Lesion size (median, cm)	1 cm (range, 0.3-3.2 cm)
Time from primary diagnosis to lung metastases (median, in months)	27.9 (range, 12.1-141.2)
Time from lung metastases diagnosis to MWA (median, in months)	9.4 (range, 0.4-106.9)
Time from lung resection to MWA (median, in months)	25.5 (range, 1.9-153.2)
Target tumor biopsy	
Performed within 2-6 weeks pre-MW ablation	5/90 (6%)
Performed in the same setting with MW ablation	5/90 (6%)
Not performed	80/90 (78%)
Number of tumours ablated per procedure	
Median	1 (range, 1-6)
1 lesion	40 (67%)
2 lesions	16 (27%)
3 lesions	6 (10%)
>3 lesions	2 (3%)
AJCC stage at initial diagnosis	
I	2 (4%)
II	9 (18%)
III	18 (36%)
IV	21 (42%)
Liver metastases at initial diagnosis	
Yes	19 (38%)
No	31 (62%)
Pulmonary progression outside ablation zone post-MWA (in same and/or contralateral lung)	
Yes	9 (18%)
No	41 (82%)
Extrapulmonary progression of disease after MWA	
Yes	32 (64%)
No	18 (36%)

Table 5 Pre-MWA therapies received

Pre-MWA therapy	Incidence
Prior lung surgery	
Yes	13 (26%)
No	37 (74%)
Prior lung ablation	
Yes	16 (32%)
No	34 (68%)
Multiple prior ablations (range, 2-8)	3 (6%)
Prior chemotherapy / target therapy received	
Median chemotherapy/target therapy lines received	2
1 line	16 (32%)
2 lines	21 (42%)
≥3 lines	13 (26%)
Prior hepatic artery infusion pump therapy	
Yes	28 (56%)
No	22 (44%)

Table 5 continued.

Pre-MWA therapy	Incidence
Prior primary tumor resection	
Yes	47 (94%)
No	3 (6%)
Prior liver resection	
Yes	31 (62%)
No	19 (38%)
Prior liver ablation	
Yes	16 (32%)
No	34 (68%)
Other prior therapies for metastatic disease (radiotherapy, resection or ablation of other tumor sites, radioembolization, intraperitoneal chemotherapy)	
Yes	16 (32%)
No	34 (68%)
Received only 1 line of systemic chemotherapy + primary tumor resection ± chemoradiotherapy and no other treatments before MWA	
Yes	7 (14%)
No	43 (86%)

Primary Technique Efficacy Rate, LTP Rate and LTPFS

Median tumor size was 1 cm (range 0.3 – 3.2 cm). Primary technique efficacy rate was 81/90 (90%). Nine tumors progressed after MWA resulting in LTP rate of 9/90 (10%) during the entire study follow-up. LTP occurred 3.9-21.8 months after the initial MWA. One-, 2- and 3-year LTPFS were: 93, 86 and 86%, respectively. Median time to LTP was not reached (Table 7).

LTP occurred at ablation margin or directly adjacent to the ablation zone in 6/9 (66%) LTPs. LTP within the ablation zone occurred in 3/9 (33%) of ablations, all detected on CT imaging: one stable in size cavitary ablation zone became filled in, forming spiculated mass with pleural tethering, micronodularities and peribronchial thickening; another ablation zone showed considerable increase in solid component centrally; third ablation zone demonstrated gradual increase in size.

New focal FDG-avidity within the ablation zone consistent with LTP occurred in 4/9 (44%) LTPs, with SUV_{max} ranging from 3.8 to 7.1. In all these cases chest CT imaging also demonstrated suspicious increased ablation zone or focal nodularity adjacent to it.

Minimal Ablation Margin

Median minimal ablation margin size was 5 mm (range 0 - 19 mm). Measurement of the minimal margin was feasible in 86/90 (96%) ablations. In 4/90 (4%) ablations it could not be calculated due to bleeding obscuring the ablation zone (in 2%) or confluent ablation zones (in 2%). Minimal margin of at least 5 mm was achieved in 48/86 (56%) of measurable ablation zones. Fourteen out of eighty-six (16%) of metastases were pleural-based and minimal margin was considered 0 mm. Minimal margin size is described in Table 6.

Table 6 Ablation technical parameters

Parameter	Incidence
Median time of ablation per target tumor	10 min (range, 2-30 min)
Median power of ablation per target tumor	59W (20-140 W)
Thermal monitoring (in ablation zone center ± periphery)	43/60 (46%) of ablations
MWA system used	
NeuWave, (NeuWave, Madison, WI)	82 (91%)
Medwaves, (Medwaves, San Diego, Calif)	3 (3%)
Emprint (Medtronic, Minneapolis, MN)	3 (3%)
Microsulis Medical (Microsulis Medical Ltd, UK)	1 (1%)
Amica Microwave (HealthTronics)	1 (1%)
Number of electrodes used	
1 electrode	73 (81%)
2 electrodes	11 (12%)
4 electrodes (for ablation of six lesions during procedure)	6 (7%)
Image guidance	
Conventional CT-only	34 (38%)
Additional CT fluoroscopy	46 (51%)
Additional split-dose PET/CT* + CT fluoroscopy	10 (11%)
Patient positioning	
Prone	34 (38%)
Lateral	25 (28%)
Supine	20 (22%)
Modified prone/lateral/supine	11 (12%)
Approach	
Posterior	24 (27%)
Posterolateral	19 (21%)
Anterolateral	19 (21%)
Anterior	14 (16%)
Lateral	13 (14%)
Minimal ablation margin	
0mm (pleural-based metastases)	14/90 (16%)
0mm (non-pleural based metastases)	3/90 (3%)
1-4 mm	21/90 (23%)
5-9 mm	37/90 (41%)
≥10 mm	11/90 (12%)
Not measurable	4/90 (4%)
Number of overlapping ablations	
One	21 (23%)
Two	33 (37%)
Three-four	33 (37%)
Unclear	3 (3%)

*Split - dose ¹⁸F-FDG PET/CT is a technique for PET/CT-guided ablation that permits target tumor localization and evaluation of treatment effectiveness. With this technique, standard diagnostic FDG activity dose of approximately 12 mCi (444 MBq) is administered in two aliquots: a 4-mCi (148-MBq) target/imaging dose is administered 30-60 minutes before the ablation followed by an 8-mCi (296-MBq) administered immediately after the ablation with images obtained 30 minutes later. The higher dose overcomes background signal of the first lower dose and allows assessment of metabolic activity of the ablation zone and detection of residual hypermetabolic signal representing untreated residual tumor

Table 7 Local tumor control, prognosticators of local tumor progression-free survival (LTPFS) and description of lung progression-free survival (PFS)

Parameter	Value
Lung PFS (in same and/or contralateral lung)	
Median (inside and outside ablation zone)	8.8 months (95%CI, 7-12.7)
Median (outside ablation zone-only)	10 months
1-year lung PFS	40% (95%CI, 27-53%)
2- and 3- year lung PFS	15% (95%CI, 7-27%)
Local tumor control	
Local tumor progression (LTP) rate	9/90 (10%), 95%CI, 5-19%
Median LTPFS	Not reached
1-year LTPFS	93% (95% CI, 85-97%)
2- and 3-year LTPFS	86% (95% CI, 75-93%)
Prognosticators of LTPFS	
Minimal ablation margin size	p<0.001, SHR=0.18, 95% CI, 0.08-0.42
LTP rate for ablations with 0 mm margin	6/17 (35%, 95% CI, 12-58%)
LTP rate for ablations with 1-4 mm margin	3/21 (14%, 95% CI, 0-29%)
LTP rate for ablations with ≥ 5 mm margin	0/48 (0%)
Cumulative 1-year LTP hazard for non-PB with margin<5mm	14% (95% CI, 4-43%)
Cumulative 2-year LTP hazard for non-PB with margin <5mm	23% (95%CI, 8-64%)
Cumulative 2-year LTP hazard for non-PB with margin ≥5mm	0%
Tumor location (pleural-based (PB) vs. non-PB)	p=0.002, SHR=7.7
Cumulative 1-year LTP hazard for PB metastases	25% (95%CI, 8-77%)
Cumulative 2-year LTP hazard for PB metastases	47% (95%CI, 19-100%)
Cumulative 1-year LTP hazard of non-PB metastases	4% (95%CI, 1-13%)
Cumulative 2-year LTP hazard of non-PB metastases	7% (95%CI, 3-22%)
Tumor size	p=0.001, SHR=5.38, 95% CI=1.9-15
LTP rate for tumours ≥ 1 cm in size	19% (95% CI, 8%-30%)
LTP rate for tumours <1 cm in size	0/43 (0%)
LTP rate for tumours ≥ 1 cm with MM < 5mm	41% (95% CI, 20%-62%)
LTP rate for tumours ≥ 1 cm with MM ≥ 5mm	0/25(0%)

SHR- sub-hazard ratio

Prognosticators of LTPFS in Univariate Analysis

Minimal ablation margin size. LTPFS was statistically significantly associated with minimal margin size (p<0.001) (**Table 7**). LTP was observed only for tumors ablated with minimal margin <5 mm, with LTP rate of 24% (**Table 7**).

Tumor location (pleural vs. non-pleural-based). Pleural-based metastases had 7.7 times higher LTP risk compared to non-pleural-based metastases (p=0.002). One and two-year cumulative LTP hazard for non-pleural vs. pleural-based metastases was 4% and 7% versus 25% and 47%, respectively (**Table 7, Figure 4**). When analyzing non-pleural based metastases alone, the minimal ablation margin retained significance as a predictor of LTP on univariate analysis (p<0.001) (**Table 7, Figure 5**).

Tumor size. LTPFS was statistically significantly associated with tumor size (p=0.001): LTP was only observed after MWA of tumors ≥ 1 cm, with LTP rate of 19% (**Table 7**). LTP rate of

tumors >1 cm in size was 41% when minimal margin was <5 mm compared to 0% when minimal margin was ≥ 5 mm ($p=0.0004$, **Figure 6**).

Figure 4 Cumulative (Cum.) local tumor progression (LTP) hazard of non-pleural-based and pleural-based colorectal cancer pulmonary metastases (CPM). The figure demonstrated more than 7 times increased LTP hazard for pleural-based metastases, compared to non-pleural-based.

Figure 5 Cumulative (Cum.) local tumor progression (LTP) hazard of non-pleural-based colorectal cancer pulmonary metastases (CPM) treated with <5 mm and ≥ 5 mm minimal ablation margin (MM). There was no LTP in non-pleural metastases, treated with ≥ 5 mm MM, compared to 23% 2-year cumulative LTP hazard for metastases treated with <5 mm MM.

Figure 6 Local tumor progression-free survival (LTPFS) association with metastasis size and minimal ablation margin

Overall and Cancer-Specific survival

Median OS was 58.6 months, and median cancer-specific survival was not reached (**Table 7**). Median OS for the patients without LTP was 45.2 months, and not reached for patients with LTP (HR=0.63, $p=0.54$).

Three out of sixteen (19%) of deaths was not cancer-related. They included sepsis and multi-organ failure in a patient with retroperitoneal abscess (4.7 months post-MWA), respiratory failure due to pneumonia (18 months post-MWA) and death of other cause 11 months post-MWA, with no evidence of oncologic disease in one patient (negative whole body ^{18}F -FDG PET/CT 2 months before death). One out of sixteen (6%) of patients was lost to follow-up 13 months before death.

Management of LTP and Assisted LTPFS

Repeat MWA was offered in 2/9 (22%) LTPs and one residual tumor. Assisted LTPFS was not reached. Repeat MWA for residual tumor increased local tumor control with MWA from 1.5 to 23.7 months in one patient (after one repeat MWA; however, patient had subsequent LTP which was aggressively re-treated with RFA using 3 electrodes and 4 overlapping ablations), from 8.83 months to 75.5 months in second patient (two additional MWAs, no further LTP) and from 3.9 to 19.37 months in third patient (single additional MWA, no further LTP). Resulting secondary technique efficacy rate, accounting for all repeat MWAs was 83/90 (92%). LTPs in the rest of patients were managed with: systemic chemotherapy in 4/9 (44%), lung resection in 1/9 (11%) and lung radiotherapy in 1/9 (11%).

Post-ablation Patient Management, Lung and Extrapulmonary Disease Progression

Six out of fifty (12%) of patients had no lung progression (inside and/or outside the ablation zone). Lung progression outside ablation zone was ablated in 14/41 (34%) of patients. Median overall lung progression-free survival was 8.8 months (Table 7, Figure 7).

Figure 7 Overall lung progression free-survival (PFS, inside and/or outside the ablation zone)

Thirty-two out of fifty (64%) patients had extra-pulmonary disease progression post-MWA (with pulmonary progression in 29/32 (91%), and without in 3/32 (9%) patients).

Three out of fifty (6%) of patients were disease-free post-lung ablation and were off-treatment for 25 months, 65.4 months and 74.9 months. Post-MWA therapies are presented in Table 8.

Cancer-Specific Survival Prognosticators

Pre-MWACEA level >10 ng/ml (p=0.046, Table 9, Figure 8) and ≥3 pre-MWA chemotherapy ± target therapy lines were associated with cancer-specific survival on univariate analysis (p=0.02, Table 9, Figure 9).

Prior lung or liver resection and lung as the first site of metastatic disease were not associated with cancer-specific survival (Table 9).

Small number of deaths and intermediate follow-up time precluded multivariate analysis of any predictors.

Table 8 Post-microwave ablation (MWA) therapies received

Post-MWA therapy	Incidence
Systemic chemotherapy	
Yes. Number of regimens received:	37 (74%)
1 regimen	12/37 (32%)
2 regimens	12/37 (32%)
≥3 regimens	13/37 (35%)
No	13 (26%)
Target therapy (EGFR inhibitors/antibody, anti-VEGF, tyrosine kinase inhibitors)	
Yes	29 (58%)
No	21 (42%)
Lung ablation	
Yes	19 (38%)
No	31 (62%)
Lung resection	
Yes	5 (10%)
No	45 (90%)
Other therapies (radiotherapy, resection or ablation of the other tumor sites, radioembolization, hepatic artery infusion pump therapy, immunotherapy)	
Yes	28 (56%)
No	22 (44%)
Patients off-treatment after MWA due to no evidence of disease, low volume of disease or due side effects/comorbidities	
Yes	5 (10%)
No	45 (90%)

Table 9 Overall survival, cancer-specific survival and prognosticators of them

Overall survival (OS)	
Median OS	58.6 months (95% CI, 28.2-NR)
1-year OS	94% (95% CI, 83-98%)
2-year OS	82% (95% CI, 67-91%)
3-year OS	61% (95% CI, 42-75%)
Cancer-specific survival (CSS)	
Median CSS	Not reached
1-year CSS	98% (95%CI, 86-100%)
2-year CSS	90% (95% CI, 74-96%)
3-year CSS	70% (95% CI, 49-83%)
Prognosticators of shorter CSS	
Pre-MWA CEA level >10 ng/ml	p=0.046*, HR=3.53, 95%CI, 1.02-12.2
≥3 chemotherapy ± target therapy regimens	p=0.019*, HR=3.92, 95% CI, 1.3-12.3
Prior lung resection	p=0.1, HR=0.27
Prior liver resection	p=0.43, HR=0.62
Lung as a first site of metastatic disease	p=1, HR=1

CEA-carcinoembryonic antigen level, HR-hazard ratio, CI-confidence interval, *statistically significant values

Figure 8 Cancer-specific survival (CSS) association with pre-MWA carcinoembryonic antigen (CEA) level

Figure 9 Cancer-specific survival (CSS) association with number of pre-MWA chemotherapy lines

Side Effects and Complications

Incidence of side effects was 12/60 (20%). Minor complications rate was 23/60 (38%) and included pneumothorax, requiring thoracostomy. Major complications rate was 8/60 (13%); 75% of major complications included pneumothoraces requiring prolonged hospitalization (**Table 10**).

Table 10 Side effects, minor and major complications following lung MW ablation.

Adverse event	Incidence
Side effects (asymptomatic pneumothoraces, no treatment)	12/60 (20%)
Minor complications (pneumothoraces, requiring thoracostomy), overall incidence	23/60 (38%)
Moderate pneumothoraces	12/23 (52%)
Enlarging (hemo)pneumothoraces	4/23 (17%)
Large pneumothoraces	1/23 (4%)
Small recurrent/circumferential/symptomatic pneumothorax or small pneumothorax with persistent air leak/ small pleural effusion/pneumomediastinum	5/23 (22%)
Small asymptomatic non-circumferential pneumothorax, no admission	1/23 (4%)
Median length of stay of patients with pneumothorax	1 day (range, 0-7)
Major complications, overall incidence	8/60 (13%)
Thoracostomy, requiring prolonged hospitalization (3-7 days) for persistent air leak, desaturation, severe pain or intra-parenchymal bleeding with large hemopneumothorax; Aspergilloma formation in the ablation zone cavity 2 months after MWA. This became chronic pulmonary aspergillosis requiring hospitalization for 2 days with prolonged treatment with voriconazole (6 weeks 200 mg p/os every 12 hours and subsequent 6 weeks of 100-400 mg IVPB every 12 hours);	6/60 (10%)
Pleuritic pain 12 days after MWA with underlying pneumonia, empyema, bronchopleural fistula and dehydration requiring hospitalization for 10 days with intravenous antibiotics (combination of piperacillin and tazobactam), infusion therapy and analgesics (fentanyl and morphine). After discussion with thoracic surgery service, the underlying bronchopleural fistula was successfully managed with prolonged thoracostomy for 5 months in the outpatient setting without further sequelae.	1/60 (2%)
Deaths within 90 days post- MWA	0/60 (0%)

MWA-microwave ablation; IVPB-piggy bag (short-term or secondary infusion)

DISCUSSION

The LTP rate of 10 % in this cohort compared favorably to reported 12-26% LTP-rates of prior pulmonary tumors MWA series [33-35, 37]. This may be attributed to the relatively small tumor size and the creation of minimal margin ≥ 5 mm in large number of patients (56%). We found strong association between tumor size ($p=0.001$), minimal ablation margin ($p<0.001$), lesion location ($p=0.002$) and LTP. Small LTP number precluded multivariate analysis.

All LTPs occurred in tumors ≥ 1 cm, ablated with minimal margin < 5 mm, with 41% LTP rate for tumors with both these factors ($p=0.0004$). This observation supports the value of the minimal margin as independent predictor of LTP [7, 22, 31, 38, 39]. Tumor size remains a limiting factor for the widespread use of ablation regardless of energy used [23, 40-42].

Pleural-based tumors had more than seven times higher LTP risk. Minimal ablation margin remained significant predictor of LTP for non-pleural-based metastases. One-, 2- and 3-year survival rates of 94, 84 and 60% compared favorably to reported ranges

of 84-95, 56-72 and 35-65, respectively [43].

LTP did not affect overall survival ($p=0.54$). The majority of patients received systemic chemotherapy and/or targeted therapy post-MWA; more than a third of patients had subsequent lung ablation or lung resection for progression. Therefore, overall survival could not be solely attributed to lung ablation, but rather to the overall therapeutic management of oligometastatic disease. Local therapy for pulmonary metastases significantly prolonged 3-year survival in patients receiving adjuvant radiotherapy or ablation, compared to those treated with chemotherapy alone (88 vs. 33%, respectively) [44].

Pre-MWA CEA level and number of prior chemotherapy and target therapy regimens predicted cancer-specific survival. CEA association with survival can be explained by CEA circulating cancer cell death inhibition and activation of cell adhesion-related molecules [45] that has been reported after metastasectomy of CRC lung metastases [46,47].

Thoracostomy rate of 38% is higher than reported after RFA (13 – 33%) [43]. This may be related to our clinical protocol of thoracostomy for any circumferential pneumothorax even in asymptomatic patients. The rate of moderate/large or enlarging pneumothorax was 28%, requiring prolonged hospitalization in 10% of procedures. The overall major complication rate of 13% is comparable to the 20% rate in prior lung MWA series [48,49]. Approximately a third of patients underwent MWA for progression of disease after lung metastasectomy and only 11% of the tumors were biopsy-proven, since radiological diagnosis of lung metastases is generally reliable [50].

There currently is an ongoing debate on the impact of local therapy and pulmonary metastasectomy on survival in this population. Most of the evidence supporting complete removal of pulmonary metastases originated from surgical series of well-selected patients with favorable characteristics (a few or small size metastases) without any comparison to patients that were not resected [47,51]. The lack of randomized data and comparative studies make conclusions about the impact of resection and locoregional therapies difficult [51]. Lung metastasectomy can improve survival; however, recurrence rates are high with repeat thoracotomy being associated with higher morbidity, whereas lobectomy offers no survival benefit when compared to limited sub-lobar or wedge resections [51]. Therefore, ablation could be advocated to be a preferable local therapy for small tumors, which can be ablated with sufficient margins.

The study had several limitations including its retrospective nature, the small number of patients and the intermediate length of follow-up, precluding long-term estimations. Another limitation is the lack of pathologic complete ablation confirmation, a common limitation of interventional oncology therapies. The impact of MWA device choice on local tumor control was limited since 91% of all tumors were ablated using NeuWave device. Known genetic signatures and predictive biomarkers were not available for the entire cohort of patients and could not be assessed as potential factors impacting outcomes [39, 52-55].

To summarize, this work indicated the efficacy of MWA that compared favorably to prior results of thermal ablation in terms of local tumor control, local progression-free survival and overall survival. Factors associated with LTPFS and cancer-specific survival were identified and described. Further validation is certainly needed in larger studies with longer follow-up to better define the role of MWA in the management of CRC metastatic disease.

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A grayscale background image of a microplate, showing a grid of circular wells. The wells are arranged in a hexagonal pattern, with some wells containing a dark substance. The image is slightly blurred and has a soft, ethereal quality.

PART 3

General discussion,
valorization and summary

General Discussion,
Future Perspectives and
Conclusion

GENERAL DISCUSSION

In this thesis, we identified factors that can **improve patient selection** and **modify treatment approach** in order to **increase local tumor control** and **reduce morbidity** following lung and liver thermal ablation as well as ^{90}Y radioembolization for patients with metastatic CRC.

In our literature review on liver-directed therapies for the patients with metastatic CRC, we discussed the role of interventional oncology (IO) procedures among other local and systemic therapies. Hepatectomy, which is considered the gold standard treatment for CRC liver and lung metastases, is no longer the only potentially curative treatment: thermal ablation **can result in local cure** in well selected patients that can undergo ablation with sufficient minimal ablation margins [1, 2]. Interventional oncologists/radiologists strive to achieve oncological outcomes similar to those achieved with resection, establishing the terms “resectable” and “ablatable” as synonyms [3-5] for selected patients with small CRC metastases.

Minimal ablation margin is a key modifiable procedure factor of liver [6, 7] and lung [8] thermal ablations. As CRC liver metastases were found to have distinct histological patterns, which impact prognosis [9, 10], it is important to ablate the area around the tumor to eradicate all viable tumor cells. In case insufficient minimal ablation margin is detected on immediate post-ablation scan, it may still be corrected with an immediate on-site additional ablation creating a larger ablation zone. In addition, a patient with an insufficient minimal ablation margin (< 5 mm) may be handled by the medical oncologist and benefit from adjuvant chemotherapy after ablation.

Despite significant progress achieved in creating methods to assess the minimal ablation margin size, these still have limitations. Common limitations include an inadequate description of the methodology, lack of accountancy for non-ellipsoid tumor geometry or eccentric ablation zone, as well as lack of availability of imaging registration software [11-14]. In this thesis we utilized a manual minimal ablation margin assessment method using **anatomical landmarks** on pre- and post-ablation CT [6] that can be universally reproducible and do not require dedicated software. We also validated the correlation of minimal margin with local tumor progression [6, 7] and showed that a minimal ablation margin of > 10 mm was associated with **no LTP** within the median study follow-up of 31 months.

Incidence of **biliary complications** following liver thermal ablation has been reported

to be within a range of 0.1-12% [15-18]. In our study, biliary complications were the **most common type of major complication** following liver thermal ablation. To the best of our knowledge, factors contributing to biliary complications have not been fully investigated. Although prior biliary interventions, proximity to major biliary structures and history of bilioenteric anastomoses are known risk factors for biliary complications a detailed analysis that can predispose to biliary and other major complications has been lacking [19].

We showed that several **easy-to-obtain pre-treatment parameters** could help to detect those patients with an increased risk of post-ablation biliary complications. The main biliary complication risk factor in our cohort was a history of **prior hepatic artery infusion (HAI) chemotherapy** carrying 100% sensitivity in predicting biliary complications. Additional risk factors included pre-existing biliary dilatation and bevacizumab administration within 1-month prior to ablation. Notably, our study showed that even though a minimal ablation margin of > 10 mm is associated with the best local tumor control, it might also **contribute to the risk for biliary complications** in specific **high-risk** patient cohorts. Thus by modifying the size of minimal ablation margin, we can actually decrease the number of biliary complications in these selected groups.

The trade-off between local tumor control and safety is arbitrary. The question of what is the acceptable local tumor control and complications rate is a subject for discussion and may end up being customized for each patient based on the long-term management goals (that greatly depend on extent of extrahepatic disease) as well as on the molecular profile of the specific disease.

There is no increased concern for biliary complications in HAI-naïve patients. These patients were safely ablated with > 10 mm margins without added morbidity in our study. An important challenge is to define the optimal ablation margin for the high-risk patients **with prior HAI therapy**. A reasonable option for safe and effective treatment of the high-risk patients with prior HAI therapy may be the creation of a **6-10 mm minimal ablation margin**. Compared to the patients, ablated with > 10 mm minimal margin, those ablated with 6-10 mm minimal margins had significantly lower major biliary complications rate (4% vs. 31%) and a rather “acceptable” than “optimal” local tumor control rate (76% vs. 100%). A 24% local tumor progression rate was deemed acceptable for these high-risk patients as they can be salvaged with re-ablation and other local therapies together with adjuvant systemic therapies or additional HAI chemotherapy. Further improvement of local tumor control in these patients can be achieved with

tissue confirmation of complete tumor necrosis through core biopsy of ablation zone center and a margin. A tumor-negative biopsy of the ablation zone combined with 5 mm minimal ablation margins offers 97% local tumor progression-free survival at a median 30 month follow-up [20]. Identification of viable tumor in biopsy could prompt re-ablation, adjuvant therapies and/or closer imaging follow-up. Such precaution is especially important for the high-risk group of patients with history of HAI, prior bevacizumab exposure, pre-existing biliary dilatation or biloma (on CT imaging) where the ideal minimal ablation margin would further add to the risks for biliary complication.

Although many studies have addressed the role of **⁹⁰Y radiation segmentectomy** for hepatocellular carcinoma these data are scarce for liver metastatic disease. **⁹⁰Y radiation segmentectomy** is an important new treatment option for the patients without **curative treatment alternatives** and **not eligible for liver resection or ablation**. Our preliminary findings suggest that for this patient population radiation segmentectomy of ≤ 3 liver segments is safe and enables to achieve high tumor response rates and local tumor control. However, optimal dosimetry methodology for this procedure requires further investigation.

We were able to design a nomogram prognostic of overall survival, which can aid in improving patient selection for **⁹⁰Y radioembolization** in the **salvage setting** to avoid unnecessary morbidity [21]. Our nomogram includes **six easy-to-obtain parameters**, widely available in an electronic patient record system. These factors include parameters related to tumor burden (metastatic liver tumor size, presence of extrahepatic disease and CEA level), tumor differentiation level as well as biochemical parameters reflecting liver damage and synthetic function. It provides good discrimination of the patients' 1-year survival. For the patients with a $\leq 10\%$ predicted chance of 1-year survival, it is important to discuss the treatment risks and benefits with the patient to have realistic survival expectations and **potentially consider other treatment options**. Internal validation showed that the nomogram had good discrimination and calibration.

Realistic, unbiased outcome scores can be useful for both the patients and healthcare providers. Such a nomogram can be employed during an initial clinic visit prior to a formal pre-procedural evaluation. This nomogram can be readily converted to an easily accessible computer-based algorithm, which quickly provides information about estimated individual patient risk. However, additional interpretative safeguards should be included in such computer-based algorithm, stating that the nomogram still requires external validation. This would prevent discouraging complex patients and their providers from considering radioembolization.

We evaluated the value of a **modified infusion technique** for **⁹⁰Y radioembolization** [22]. **⁹⁰Y resin microspheres** are the **most commonly used** radioembolization microspheres type for CRC liver metastases. Due to the high number of resin microspheres infused during the procedure, more uniform tumor coverage can be achieved compared to glass-based **⁹⁰Y microspheres**. The main disadvantage of infusing high number of microspheres is the occurrence of **stasis**. Stasis has been reported in $> 30\%$ of infusions for the treatment of CRC liver metastases [21, 22]. It can lead to **non-target radiation delivery**, with consequent development of gastrointestinal ulceration as well as inadequate radiation exposure of the target tumor.

We proposed a modified **⁹⁰Y resin microspheres infusion technique**, which includes administering undiluted contrast medium in both "B" and "D" infusion lines. It enables better real-time monitoring of administration of resin microspheres (compared to the standard sandwich technique) and better detection of flow reduction to minimize the risk of stasis. Our research demonstrated that the modified infusion technique is **safe**, with no evidence of radiation leaching or increased microspheres clotting. Even though the incidence of stasis was not significantly reduced, the modified infusion technique enabled shortening of resin microspheres infusion time, resulting in significant **reduction of fluoroscopy radiation dose**.

In **CRC lung metastases** over the last two decades, numerous studies had reported safety, good local disease control and lung parenchyma preservation following thermal ablation for unresectable oligometastatic patients [23-25]. Ablation of lung metastases has an important role for patients with limited disease, which can be ablated **with sufficient minimal ablation margins (≥ 5 mm)** as well as for those who present with **residual or recurrent** disease after having undergone other local treatments. Despite the relative lack of comparative studies of thermal lung ablation with other local treatments such as radiation treatment for metastatic disease, existing evidence shows that thermal ablation compares favorably with surgical resection. Unlike surgical resection or stereotactic beam radiotherapy, thermal ablation **can be repeated with minimal if any impact on pulmonary function**. This is of particular benefit in the setting of recurrent or residual disease in a population where future metastases and need for repeated local therapy is rather the rule than the exception.

Our literature review showed that local disease progression remains a limitation of ablative therapy. Across ablation modalities, tumor size is the primary determinant of treatment success as it dictates the ability for sufficient minimal ablation margin creation. Development of new tissue and corresponding surrogate image biomarkers

for patients risk stratification and earlier detection of local tumor progression is needed. These developments along with evolution of technology may allow the application of local thermal ablation in a larger patient population.

There is limited clinical data on **lung MW ablation** especially for metastatic disease of CRC origin. MW ablation has at least theoretical potential to overcome known limitations of RF ablation. These include diminished thermal conductivity of aerated lung and “heat sink phenomenon” that can impact the ability to create large and uniform ablation zones. Thus higher rates of complete ablation and sustained tumor control could be expected when using MW ablation.

Currently there is a lack of homogeneous patient population research to see what MW ablation has to offer for the patients with CRC lung metastases. Our study is one of the most robust studies wherein. We showed that MW ablation for CRC lung metastases is safe and efficient. We identified factors related to local tumor control and showed that minimal ablation margin of ≥ 5 mm is **critical** for local tumor control following lung ablation, similarly to liver ablation. Pleural-based metastases and larger tumor size were associated with higher risk of local tumor progression. We also identified that known factors such as increased CEA levels and an increased prior number of chemotherapy regimens (likely reflecting more advanced disease stage) negatively impacted cancer-specific survival.

9

FUTURE PERSPECTIVES

To date the evidence regarding whether increased local tumor control after interventional treatment of metastatic disease translates into increased overall survival is lacking. As IO techniques strive to take additional roles in the management of metastatic CRC, substantial prospective trial-based evidence is warranted. Although prospective clinical trials comparing the efficacy of thermal ablation, image guided beam radiotherapy and surgery are challenging to set up, they could define the role of these therapies and improve patient selection for each treatment. It may be as important to design trials to assess the potential synergistic role of local therapies’ in combination with systemic options in an effort to prolong patients’ survival while maintaining the best possible quality of life.

With immunotherapy increasingly applied for stage IV disease, understanding the abscopal effect of IO treatments in patients treated with immunotherapy is of high

importance. This includes investigation of its role in tumor priming, immunomodulation and selective immunotherapy delivery. Such research will expand the role of IO and local therapies in general in the patient population with diffuse metastatic disease that in the end have no local options.

CONCLUSION

Interventional oncology has an expanding role in the local treatment of the patients with oligometastatic CRC. Understanding the role of IO therapies in the multidisciplinary spectrum of local therapies is crucial. In this thesis, we identified factors that can help to **improve local tumor control and reduce the incidence of complications** following lung and liver thermal ablations as well as ⁹⁰Y radioembolization for patients with CRC liver metastases. We showed the importance of minimal ablation margin of at least 5 mm for good local tumor control following thermal ablation. We identified relevant factors associated with biliary complications following liver thermal ablation. Obtaining a >10 mm minimal ablation margin enabled durable liver tumor eradication in patients without biliary complications risk. However for the high-risk patients with a history of HAI therapy a 6-10 mm minimal margin is ideal to balance between an acceptable risk of morbidity and good local control. We developed a prognostic nomogram aimed to improve the selection of patients undergoing ⁹⁰Y radiomebolization in the advanced, chemorefractory salvage setting. This nomogram may be useful during pre-treatment patient assessment to obtain a realistic estimation of patients’ survival, but further external validation is warranted before it can be implemented in routine clinical practice. We evaluated a modified resin microspheres infusion technique during ⁹⁰Y radioembolization which was demonstrated to be safe and to reduce infusion time and fluoroscopy radiation dose. Radiation segmentectomy was demonstrated to be safe, enabled to achieve high tumor response and local tumor control rate for the patients with liver metastatic disease and limited treatment options. Larger prospective studies defining the role of radiation segmentectomy for metastatic CRC patients are required.

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Summary

Chapter 2. Liver-directed and systemic therapies for colorectal cancer liver metastases

This literature review provided an overview on epidemiology, predisposing factors, pathology, diagnosis, approved/ recommended liver-directed and systemic therapies for metastatic CRC as well as it defined the role of interventional oncology in treatment of CRC liver metastases. The review also discussed standard of care as well as emerging interventional oncology procedures to treat metastatic CRC, new treatment modalities on the pipeline and key driving mutations which are important for better patient selection.

Chapter 3. Factors associated with local tumor control and complications after thermal ablation for colorectal cancer liver metastases: a 15-years retrospective cohort study

In our research we identified the factors associated with biliary complications - the most common type of major complications following liver thermal ablation in our study. We noted the strong association between post-ablation biliary complications with prior HAI therapy as well as with additional biliary complication predictors, such as pre-existing biliary dilatation, bevacizumab administration and minimum ablation margin size, which to the best of our knowledge, have not been described before. Our study provided recommendation to withhold bevacizumab within one month to thermal ablation, similarly to the precautions to the surgery [1].

Also, our study was one of the few studies documenting the importance of minimum ablation margin for a long-term tumor control by thermal ablation [2-9]. This study also supported the findings of our prior research group study that was limited on RFA, identifying minimal ablation margin size, increased tumor size and no history of prior hepatectomy as independent predictors of better LTPFS on multivariate analysis. We noted, that the best oncological outcomes were achieved for the patients treated with >10 mm minimal ablation margins with no case of LTP recorded. In our study we analyzed the risks of creating a >10 mm minimal ablation margin for two patient populations: patients with HAI history and HAI-naïve.

Chapter 4. Factors Affecting Oncologic Outcomes of ⁹⁰Y Radioembolization of Heavily Pre-Treated Patients with Colon Cancer Liver Metastases

The developed nomogram included six easy-to-obtain pre-treatment parameters (sum of largest diameters of two largest liver lesions in intended to-treat-region, number of extrahepatic disease sites, CEA level, alanine aminotransferase, tumor differentiation and albumin levels) and provided good prediction of patient survival post-radioembolization. Baseline metabolic FDG-uptake parameter (SUV_{max}) was the single significant predictor of liver progression-free survival on multivariate analysis.

Chapter 5. ⁹⁰Y Resin Microspheres Radioembolization for Colon Cancer Liver Metastases Using Full-Strength Contrast Material

Administration of ⁹⁰Y resin microspheres using undiluted contrast medium in both “B” and “D” infusion lines was demonstrated to be safe and effective, resulting in lower fluoroscopy radiation dose and shorter infusion time, without evidence of myelosuppression or increased stasis incidence.

Chapter 6. Radiation Segmentectomy for Hepatic Metastases with ⁹⁰Y Glass-Based Microspheres: Technical Considerations, Correlations to Dosimetry and Preliminary Results

In this small retrospective study we described our initial experience with radiation segmentectomy in selected patients with limited metastatic liver disease that was not amenable to resection or percutaneous ablation. The study assessed the feasibility of treating up to three liver metastases using ⁹⁰Y radiation segmentectomy with local curative intent similar to ablative external radiation therapy or curative percutaneous ablation [10,11]. We demonstrated, that radiation segmentectomy of ≤3 hepatic segments can safely provide good local tumor control in selected patients with limited metastatic liver disease and treatment options.

Chapter 7. Image-Guided Thermal Ablation for the Treatment of Pulmonary Malignancies

This literature review provided an overview on a variety of image-guided thermal ablation techniques for patients with oligometastatic lung disease and non-small cell lung carcinoma.

Chapter 8. Microwave Ablation in the Management of Colorectal Cancer Pulmonary Metastases

In this study we indicated, that the efficacy of MW ablation compared favorably to prior results of thermal ablation in terms of local tumor control, local progression-free and overall survivals [12-15].

Factors associated with local tumor progression-free survival and cancer-specific survival were identified and described. Firstly, we found strong association between tumor size and local tumor progression (LTP) and strong inverse association of LTP with minimal ablation margin, with all LTPs occurring in tumors ≥ 1 cm, ablated with minimal margin of < 5 mm. This observation supports the value of the minimal ablation margin as independent predictor of LTP as reported previously [2, 4, 16-18]. Also, this finding supports the fact, that tumor size remains a limiting factor for the widespread use of ablation regardless of energy used [19-22]. Pleural-based tumors had more than seven times the risk for LTP when compared to non-pleural-based metastases. Also, we found that increased CEA level and increased number of pre-MW ablation chemotherapy

lines negatively impacted cancer-specific survival. Further validation of study results is certainly needed in larger studies with longer follow-up to better define the role of MW ablation in the management of CRC metastatic disease.

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Valorization

Colorectal cancer (CRC) is one of the deadliest cancers, with metastatic disease being the most common cause of death in these patients [1]. Netherlands is among top ten countries in the world with the highest CRC prevalence [2]. On a daily basis around 37 patients receive CRC diagnosis and 14 patients die from CRC in the Netherlands [3]. The incidence of CRC is expected to rise even further because of the implementation of nationwide screening program [4] growing incidence in rectal cancer among young patients [5-7] and ageing population.

To date, the awareness of general population, patients and referring physicians about the field of interventional oncology and what it has to offer for the patients with CRC is low [8]. Thus active participation of those in the field is crucial to help to educate the public about many potential benefits interventional radiology may offer.

RELEVANCE

With this thesis, we aimed to provide an overview about the expanding role of interventional oncology in the management of the patients with metastatic CRC. We provided the data on oncological outcomes following the most common as well as emerging interventional oncology procedures. These procedures included thermal ablation (in the liver and lungs) and ^{90}Y radioembolization approaches. Notably, we analyzed predictive and prognostic factors for local tumor control, safety and survival following these therapies.

The research presented in this thesis was performed within the collaborative research project between the Netherlands Cancer Institute and Memorial Sloan Kettering Cancer Center (New York, USA). Memorial Sloan Kettering Cancer Center performs one of the largest numbers of interventional oncology procedures in the world, which enables to conduct large scale laboratory and clinical research. This collaboration was formed in order to profit from the expertise which is present there in the area of most modern minimally invasive approaches for the treatment of metastatic colorectal cancer and transfer this knowledge to the Netherlands.

TARGET POPULATION

This thesis has a wide target population. It includes **interventional radiologists** who are utilizing these procedures in their daily practice and who could benefit from applying

the techniques described here to achieve better tumor control, increase procedure safety and improve patient selection. It is also very important to increase awareness about interventional radiology procedures among **medical oncologists** and **other medical specialists** involved in the management of the patients with metastatic colorectal cancer so that the patients could be more often referred to interventional radiology. Minimally invasive procedures have many advantages over traditional treatments, including lower morbidity and mortality, also sometimes representing the patients an only viable treatment option.

Colorectal cancer patients with metastatic disease could benefit from this thesis in multiple ways. Currently there is a lack of awareness among the patients about interventional radiology [8]. This may result in patients favoring traditional therapies over unfamiliar minimally invasive procedures despite lower complication rates, faster recovery time and a better quality of life. There is evidence that the patients referred for an interventional radiology procedure largely do not know very much if anything about the field, even if they had undergone an interventional radiology procedure in the past [8]. Efforts to increase public awareness about this field could improve patient access to these procedures and empower patients with the information they need to make the best healthcare decisions themselves.

The patients with **other types of oligometastatic cancer** also could benefit from our research as the interventional radiology procedures we described are used for multiple types of oligometastatic cancer.

Researchers, conducting clinical and fundamental research in interventional radiology, colorectal cancer as well as in other local therapies could also find this thesis useful. Multidisciplinary and combinational treatments are very important to maximize treatment outcomes in the patients with metastatic CRC.

INNOVATION AND FUTURE

The results of this thesis demonstrated that it is possible to achieve **better local tumor control** with thermal ablation while creating a sufficient minimal ablation margin [9]. We also **identified complications risk factors** following thermal ablation and provided recommendation on how to approach high-risk patients [10]. In terms of ^{90}Y radioembolization approaches, we developed a prognostic tool aimed **at improving patient selection** [11] as well as proposed a modified ^{90}Y resin microspheres infusion

technique to **improve the procedure safety** [12]. We also **filled in the knowledge gap** on radiation segmentectomy for the patients with liver metastatic disease and limited treatment options, demonstrating that it has a potential to safely achieve high tumor response and local tumor control rate.

Currently minimal ablation margin assessment is not performed universally and uniformly among interventional radiologists immediately post-procedure. Ablative dose radioembolization approaches, such as radiation segmentectomy are emerging, but are also not yet utilized in multiple centers due to the limited evidence available to date. There is a lack of prognostic tools for physicians to use during pre-procedure patient visit to help decision-making. Our research tried to address all these limitations; however larger prospective trials, aiming at externally validating our retrospective study results are warranted.

In addition, despite expanding evidence regarding the value of interventional oncology procedures to provide local disease control, data on the effect of these procedures on patients' overall survival is lacking. Prospective studies comparing different locoregional modalities to surgery are also limited. Future research should also focus on the identification of the patients with curable oligometastatic CRC disease, systemic effects of interventional radiology procedures and immunomodulation. As interventional oncology techniques strive to take additional roles in the management of the patients with metastatic CRC, progress will ultimately depend on the ability to produce substantial prospective trial-based evidence.

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List of publications

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Curriculum Vitae

Ieva Kurilova was born on 6th December 1991 in Vilnius, Lithuania. In 2010-2016 she studied Medicine in the Vilnius University, where besides medical studies she was conducting the clinical research in the areas of lung cancer and gastric neuroendocrine tumors. After graduating medical school Ieva became research fellow in the Radiology department of Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, working on imaging in immunotherapy.

In December 2016 Ieva became a PhD student in the Radiology Department of NKI-AVL, working under the supervision of Prof. Regina G.H. Beets-Tan. Majority of the PhD research she conducted within the collaborative research project in Memorial Sloan Kettering Cancer Center, New York, USA, where she worked under supervision of Prof. Dr. Constantinos T. Sofocleous.

Ieva has presented her PhD research results in the largest Radiology/ Interventional Radiology congresses, including Radiology Society of Northern America (RSNA), World Congress of Interventional Oncology (WCIO), Society of Interventional Radiology (SIR) and Cardiovascular and Interventional Radiology Society of Europe (CIRSE). Ieva has also been a European Research Seed Grant winner (2020), WCIO Fellow and Resident-in-training Scholarship winner (2018) as well as Rolf W. Günter Foundation Young Radiologist's Travel Grant winner (2018). Ieva is also a member of good standing of ESR, CIRSE, ESOI and ARRS radiological societies. She is also a reviewer for the journals in the area of interventional radiology, such as Cardiovascular and Interventional Radiology journal (CVIR) and Journal of Vascular and Interventional Radiology (JVIR).

Currently, besides conducting clinical research, Ieva is actively assisting in setting up prospective clinical trials in the area of metastatic colorectal cancer treatment in interventional radiology setting, development of novel imaging biomarkers as well as student supervision in the Netherlands Cancer Institute.