

Long-Term Survival Following Ablation of Colorectal Liver Metastases

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Abstract: Introduction: Ablation of colorectal liver metastases (CRLM) in highly selected patients is an option with curative potential. Patient selection and the ablative technique have continued to improve over the years. This study assessed the trends in long-term survival after ablation of CRLM. Methods: We conducted a register-based cohort study of all patients with CRLM referred to ablative treatment by the multidisciplinary team for hepatic diseases at our institution between 2000 and 2014. Patient data used to calculate estimates of survival was retrieved using national registries. Patients were divided into three subgroups according to time of ablation (2000-2004; 2005-2009, and 2010-2014). Survival was defined as the time from the first ablation procedure until death, censoring or end of the follow-up period (December 31, 2015). Results: 741 CRLM ablations were performed in 444 patients. The estimated 5-year survival from first ablation procedure was for 2000-2004: 18.9% (95% CI: 10.7-28.8%); 2005-2009: 31.1% (95% CI: 24.3-38.2%); and 2010-2014: 53.3% (95% CI: 44.3-61.5%). Log rank test showed a statistically significant difference in the survival between the three subgroups ($p < 0.001$). Conclusion: Survival rates improved from 2000 to 2014 probably owing to multiple factors, including advances in ablation procedures, oncological therapy, and optimized patient selection.

Keywords: Survival, Ablation, Radiofrequency/RFA, Microwave/MWA, Colorectal Cancer, Liver Metastases

1. Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide, affecting approximately 4300 persons in Denmark each year. About 20-25% of patients with CRC have liver metastases at the time of diagnosis and further 20% will subsequently develop liver metastases [1, 2]. Survival for untreated liver metastases is historically reported with a median of 6-15 months.

Surgical resection still offers the best treatment in order to cure patients with colorectal liver metastases (CRLM), with reported five-year survival rates ranging from 25-58%, depending on selection criteria [2-6]. Approximately 80% of patients are not candidates for surgery due to extensive disease or reduced performance status [7-9]. Ablation, either radio-frequency ablation (RFA) or micro-wave ablation (MWA), has

emerged as an alternative treatment option. Ablation is less invasive than surgery, resulting in fewer major complications and thus a more acceptable choice of treatment for patients unfit for major liver surgery. Ablation can also be combined with hepatic resection, thereby expanding the group of patients offered possible curative treatment [10, 11]. Some studies with short follow-up time indicate that the overall survival and progression-free survival following ablation approach that of surgery in carefully selected patients [12, 13].

The aim of this study was to assess the trends in long-term survival after ablation of CRLM.

2. Methods

2.1. Setting and Study Population

Using a local procedure registry, we assembled an initial

cohort of all patients treated with ablation at our institution (percutaneously, open or in combination with surgery) between January 2000 and December 2014, regardless of the diagnosis. Using the civil registration number, which is a unique identification number assigned to all Danish residents at birth or immigration, individual-level data was linked with several national registries [14]. Our initial cohort treated with ablation was cross-linked with *The Danish Cancer Registry* [15]. This enabled us to identify all patients with CRC in our initial cohort of ablated patients. Thus, our final cohort consisted of all patients undergoing ablation for CRLM in the defined study period.

Table 1. Estimated median survival rates (%) and corresponding 95% CIs in 444 patients treated with ablation for CRLM.

Year	1-year	2-year	3-year	4-year	5-year	10-year	Median, years
2000-2004	84.1 (73.1-90.8)	63.8 (51.3-73.9)	31.9 (21.3-42.9)	21.7 (12.9-32.0)	18.9 (10.7-28.8)	10.1 (4.5-18.6)	2.44 (2.00-2.81)
2005-2009	85.6 (79.3-90.1)	68.3 (60.6-74.7)	52.7 (44.9-59.9)	37.7 (30.4-45.0)	31.1 (24.3-38.2)	18.9 (12.2-26.6)	3.30 (2.55-3.62)
2010-2014	90.4 (85.5-93.7)	71.3 (64.3-77.2)	61.5 (53.7-68.4)	56.5 (48.1-64.0)	53.3 (44.3-61.5)	-	-

2.3. Multidisciplinary Team Conferences

Since 2000, we have conducted multidisciplinary team (MDT) conferences to evaluate all patients with liver tumors referred from secondary level hospitals in Western Denmark or a department at our institution. At the MDT conferences, all patients were evaluated, and an individual treatment plan for each patient was assembled. In CRLM, surgery is always the primary choice of treatment unless the patient is considered inoperable or unresectable. Only when patients are unfit for major surgery, ablation treatment or oncological therapies are considered as treatment options.

All patients in the present study were selected for ablation according to the Danish National Guidelines (see Information Box).

2.4. Ablative Procedures

Ablations were performed percutaneously, open or in combination with surgery. Patients were treated with the Covidien Cool Tip™ system, the Covidien Emprint™ MWA system or AngioDynamics RITA® system. Small metastases were treated with a 3 cm single electrode, while larger metastases (>1.5 cm) were treated with a clustered electrode.

In general, the clustered electrode was preferred in tumors ≥1.5 cm in diameter because it produces a necrosis of approximately 4 cm in diameter, thereby ensuring an ablation margin of >5 mm when treating tumors up to 3 cm. In recent years, MWA has been preferred when a tumor was located adjacent to the central liver veins. MWA is not as susceptible to the “heat sink” effect” as RFA [17], thereby obtaining better tumor control in these situations. Additionally, MWA was preferred in patients with recurrence within or in close proximity to an already ablated area. In necrotic areas following ablation, the impedance of the tissue increases, and the effect of RFA will be limited. MWA is not as affected by the impedance, and therefore achieves a better treatment effect in necrotic areas [18, 19].

Ultrasound-guidance was the preferred procedure. However, if tumor margins could not be properly identified

2.2. Information on Patients and Procedures

We obtained information on time of diagnosis and location of the primary tumor from The Danish Cancer Registry [15]. Records of deaths were collected from The Danish Registry of Causes of Death [16], which allowed us to follow our cohort from the date of diagnosis until death or the end of the follow-up period (December 31, 2015). Patients were divided into three subgroups according to the time of first ablation procedure (2000-2004; 2005-2009 and 2010-2014) to assess changes in survival over time (Table 1).

by ultrasound, computed tomography (CT) guidance was used. Ablation was contraindicated in the case of extrahepatic disease unless this could be treated locally (resection, ablation, or radiotherapy).

2.5. Evaluation

CT scans were conducted at one, four, eight and 12 months following ablation treatment, and subsequently every six months for a minimum of five years, unless the follow-up was less than five years (End of follow-up, December 31st 2015). In case of reablation, this follow-up regime was reintroduced.

CT was performed using a Brilliance 64 or iCT (Philips, Best, The Netherlands) in connection with intravenous administration of the contrast medium iodixanol (Visipaque, GE Healthcare) 270mg iodine/mL adjusted to body weight using 2 mL/kg, and an injection rate of 4 mL/s. The CT scans were performed during the portal-dominant phase of enhancement using a bolus tracking technique to compensate for differences in cardiac output. CT acquisition parameters were 120 kV (or 140 kV if bodyweight >100 kg); 64 x 0.625 mm collimation; attenuation-based tube current-modulation; 0.5 s tube rotation time; and pitch 1.0. Two-millimeter axial slices were reconstructed with an increment of 1 mm.

All follow-up CT scans were evaluated by experienced interventional radiologists. A hypoattenuating ablation zone with a well-defined margin of homogeneous liver tissue indicated a sufficient ablation. Progressing size or budding of semi-hypoattenuating nodules in the ablation rim was highly suggestive of recurrence/residual tumor tissue. When residual tumor tissue or recurrence was suspected, examination by ultrasound, was performed to supplement the CT scan. In case of recurrence the patient was reevaluated at an MDT conference.

2.6. Statistics

Overall survival from the first ablation was calculated using date of death or the end of the follow-up period.

Median survival times were estimated using the Kaplan-Meier method. An unadjusted log rank test was used to assess overall differences in the survival. The Cox proportional hazards regression model was used in the multivariate analysis to identify risk factors for the overall survival rate. $P < 0.05$ was considered statistically significant. All statistical analyses and graphical presentations were performed using STATA, version 13.1 (STATA corp, College Station, TX, USA).

2.7. Study Ethics

This study was approved by the Danish Data Protection Agency (jr.no. 2013-41-2056) and the National Board of Health (jr.no. 3-3013-507/1+2) and therefore informed consent was necessary according to Danish law.

3. Results

3.1. Patient Characteristics

A total of 444 patients with CRLM underwent 741 ablations during the study period. Mean age at diagnosis was 64 years (Range: 28-92 years), and 288 patients (64.9%) were males. In 185 patients (41.7%), the primary tumor was

located in the rectum, while 259 patients (58.3%) had a colon cancer as their primary tumor. The mean number of procedures performed was 1.7 (Range: 1-8), but the majority (64.2%) only had one procedure performed. Median follow-up time from first ablative procedure was 2.5 years (Interquartile range (IQR): 1.5-4.1). More than half of the patients (257 = 57.9%) underwent their first ablative procedure within 1 year after their primary diagnosis. No patients were lost to follow up.

3.2. Survival

Survival rates increased over time, and the increase was statistically significant (Log rank test: $p < 0.001$, Figure 1). Cox proportional hazards regression model also showed an increase in survival over time (Hazard ratio (HR): 0.68; 95%CI: 0.58-0.81; $p < 0.001$). Overall, from 2000 to 2014, the hazard ratio was reduced by half (HR=0.46; 95%CI: 0.33-0.66; $p < 0.001$, Table 2), which is also indicated in the survival curves and rates (Figure 1 and Table 1). Survival significantly decreased in the group of patients with age ≥ 70 years (HR=1.36; 95%CI: 1.01-1.84; $p=0.04$, Table 2). There was no difference in the survival between genders or the location of the primary tumor.

Table 2. Estimated hazard ratios (HR) and corresponding 95% CIs, using Cox proportional hazards regression model.

Covariate	From first ablation treatment	
	HR (95%CI)	p-value
Age, years		
< 60		
≥ 60	0.82 (0.61-1.10)	0.19
≥ 70	1.36 (1.01-1.84)	0.04
Gender		
Male		
Female	0.99 (0.77—1.29)	0.99
Primary tumor		
Colon		
Rectum	1.02 (0.80-1.31)	0.85
Number of ablations		
1		
2	0.95 (0.70-1.30)	0.75
3	0.90 (0.60-1.34)	0.60
4	0.75 (0.42-1.33)	0.33
5	0.65 (0.29-1.47)	0.30
6	0.40 (0.10-1.65)	0.21
Subgroup		
2000-2004		
2005-2009	0.72 (0.52-0.98)	0.04
2010-2014	0.46 (0.33-0.66)	< 0.01

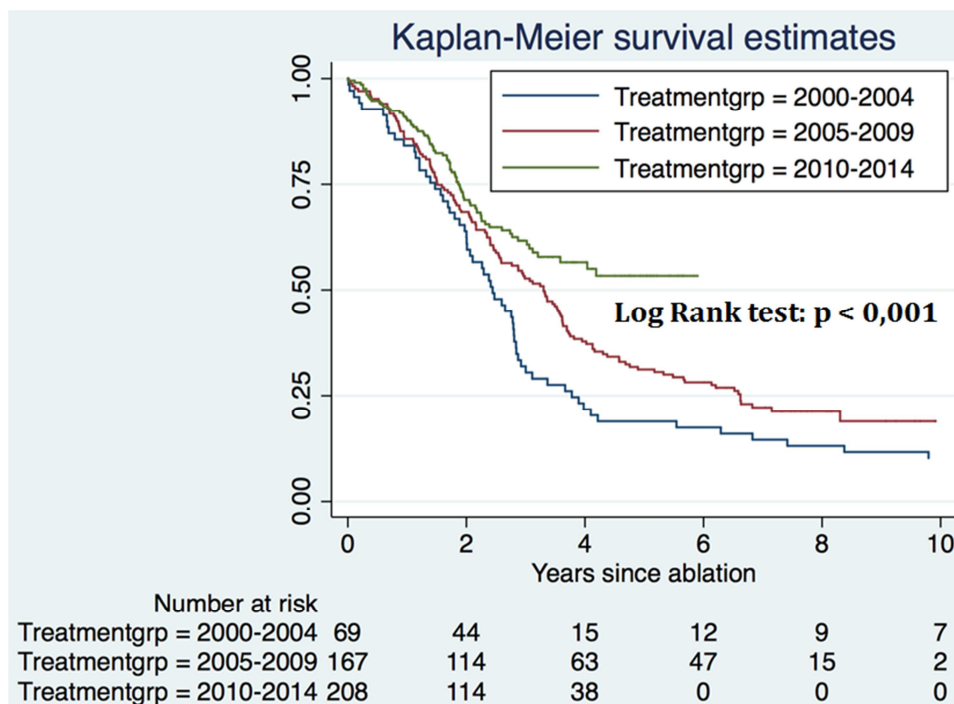


Figure 1. Cumulative survival curves in 444 patients from first ablation procedure for colorectal liver metastases.

4. Discussion

The present study demonstrates survival following ablation of CRLM at our institution has increased during the study period, and that current survival rates are comparable to those reported following surgical resection [20].

We demonstrated a 5-year survival rate of 53.3 % for those treated in the years 2010-2014, which is substantially higher than the 5-year survival rate of 18.4 % presented by Siperstein *et al* in 234 patients [21]. The discrepancy between the two studies might be explained by the fact that 23% of their patients had extrahepatic disease. Solbiati *et al* presented a 5-year survival rate of 47.8% in 99 patients, which is similar to the results in the present study [9].

Increase in the survival presented in this study is multifactorial. Firstly, improvements in ablation procedures (experience/techniques/equipment) may partly explain the increase in survival during the study period. At our institution, only a few dedicated and experienced interventional radiologists performed all ablations ensuring uniform procedures, as there is a significant learning curve in performing ablation of liver tumors [22].

Secondly, patients treated from 2009 and onwards were offered neoadjuvant oncological treatment, which undoubtedly is an important part of the improved survival in the final period. Furthermore, advances in oncological therapies in general, may also have contributed to the improved survival [23], including biological treatment introduced at our institution in 2011. Finally, advancements in the imaging modalities have improved the quality of the evaluating follow-up regime, allowing us to detect and treat local recurrence and new metastases earlier.

Surgical resection is still considered the reference standard

in the curative treatment of CRLM with reported 5-year survival rates ranging from 25-58% depending on selection criteria [2-6]. But only 8-27% of patients are candidates for surgery due to poor performance status, comorbidity, and degree of disease advancement [9]. Especially in the group of patients unfit for surgery, ablation treatment is an appealing alternative because of the low morbidity and mortality associated with this procedure [9, 24]. However, proper selection of patients for ablation is of paramount importance. This is emphasized by a study from Shady *et al* who investigated 162 patients treated for 233 CRLM [25]. They found that metastases with a diameter of more than 3 cm had an especially negative impact on survival. This supports our treatment selection criteria as the national guideline prescribe that only lesions less than 3 cm in diameter should be considered for ablation.

When comparing ablation of CRLM with surgical resection in retrospective studies, it is important to keep in mind the possibility that some patients selected for ablation had undetected carcinosis at the time of treatment, which will affect survival negatively. However, patients selected for surgery have been shown to have more extensive hepatic involvement, with larger metastases affecting larger parts of the liver, which has also been shown to have a negative impact on survival [5, 6, 26].

Due to the retrospective nature of the present study, it was possible to include a large cohort with a long follow-up time. The large cohort combined with the high quality of the Danish National Health Registers allowed for very robust survival estimates. However, a significant weakness is also related to the retrospective study design. Since all data origins from different national registries, it only facilitated the correlation of the survival with factors included in these

registries. Important clinical factors as e.g. total number and specific location of the metastases, tumor size, tumor response, and other preceding or simultaneous treatment strategies (oncological treatments, radiotherapy, resection etc.), could not be assessed.

5. Conclusion

The present study of 444 patients demonstrates ablation as an effective treatment of CRLM, with a recent 5-year survival rate of 53.3% in a selected group of patients not suitable for resection only. Survival rates have improved over time since 2000 probably due to better oncological treatment strategies, and advances in ablation procedures.

Main points

- (a) Radio-frequency ablation (RFA) or micro-wave ablation (MWA) in the treatment for colorectal liver metastases (CRLM) is effective.
- (b) Survival rates in the present study improved following introduction of new ablative techniques.
- (c) Survival rates following RFA and MWA for CRLM are comparable to those following surgical resection.

Conflicts of Interests

All the authors do not have any possible conflicts of interest.

Information Box

Danish National Guidelines (Ablation treatment of Colorectal Liver Metastases)

Based on a contrast-enhanced computed tomography in the portal-dominant phase of enhancement:

- (a) No more than 5 tumors at a maximum of 3 cm in diameter
- (b) No extrahepatic disease, unless this can be curatively treated as well.

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