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LOCAL CONTROL AND OVERALL SURVIVAL FOLLOWING RADIOFREQUENCY ABLATION OF COLORECTAL LIVER METASTASES AFTER CONVERSION CHEMOTHERAPY

Submitted for publication
Abstract

Introduction
Systemic chemotherapy is able to convert colorectal liver metastases (CRLM) that are initially unsuitable for local treatment into locally treatable disease. Surgical resection further improves survival in these patients. Our aim was to evaluate outcomes for patients with CRLM treated with RFA following effective downstaging by chemotherapy, and to identify factors associated with recurrence and survival.

Methods
Included patients had liver-dominant CRLM initially unsuitable for local treatment but eligible for RFA or RFA with resection after downstaging by systemic chemotherapy. Chemotherapeutic regimens consisted predominantly of CapOx, with or without bevacizumab. Follow-up was conducted with PET-CT or thoraco-pelvic CT.

Results
Fifty-one patients had a total of 325 CRLM (median = 7). Following chemotherapy, 183 lesions were still visible on CT (median = 3). Twenty-six patients were treated with RFA combined with resection. During surgery, 309 CRLM were retrieved on intra-operative ultrasound (median = 5). Median survival was 49 months and was associated with extrahepatic disease at time of presentation and recurrences after treatment. Estimated cumulative survival at 1- 3- and 4 years was 90%, 63% and 45%, respectively. Median disease-free survival was 6 months. Twelve patients remained free of recurrence after a mean follow-up of 32.6 months.

Conclusion
RFA of CRLM after conversion chemotherapy provides potential local control and a good overall survival. To prevent undertreatment, the involvement of a multidisciplinary team in follow-up imaging and assessment of local treatment possibilities after palliative chemotherapy for liver-dominant CRLM should always be considered.
Introduction

The prognosis of patients with colorectal liver metastases (CRLM) has improved significantly in recent years. As recently as 1976, 5-year survival for multiple metastases was zero (1), whereas studies now report survival rates of 30-50% (2;3). Although surgical resection is still considered the major contributor to overall survival, 70-80% of patients are excluded as candidates for surgical resection due to site, size or location of their metastases.

The local ablative therapies that have emerged over recent decades, the most important of which is currently radiofrequency ablation (RFA), have led to a considerable broadening of curative and palliative treatment options. RFA was introduced for CRLM unsuitable for hepatic resection in the mid-1990’s and was regarded as a treatment option with palliative intent for patients that failed to respond to systemic therapy. With greater experience and more refined techniques, results have improved significantly and RFA now offers improved survival with the possibility of cure in selected patients (4-6).

Patients who are not candidates for local CRLM therapy commonly rely on systemic chemotherapy to slow disease progression. Modern chemotherapeutics are effective and can prolong survival, achieving a median survival of 20 months without additional local treatment (7). Chemotherapy is still considered a palliative treatment since reports of complete tumour clearance are scarce (8). However, chemotherapy can downstage primarily irresectable CRLM in selected patients, allowing curative hepatic resection to be performed. This so-called ‘conversion chemotherapy’ enables hepatic resection in 10-20% of the patients with previously irresectable disease, and reported survival rates are similar to the patients with primarily resectable tumours (9-11).

Patients with CRLM who are initially unsuitable for any local treatment, and thus receive palliative chemotherapy, can also become candidates for RFA after downstaging of the tumour load. Although literature on this subject is surprisingly scarce (12;13), the rationale behind this use of RFA is complete tumour eradication and improved survival compared to chemotherapy alone. The aim of the present study was to evaluate disease-free survival, overall survival, and complications in patients treated with RFA after conversion chemotherapy, and to identify factors associated with improved survival.
Material and Methods

Patients

Patients treated between January 2006 and July 2013 at a university hospital and a large teaching hospital were candidates, and the data of all patients with CRLM treated with RFA, or RFA combined with resection, were recorded in a database. This retrospective study included all patients with liver-dominant CRLM that were initially ineligible for local treatment but became candidates for RFA alone or in combination with resection after their metastases were significantly downstaged by chemotherapy. The decision to initially treat was made by our multidisciplinary liver board based on imaging with fluorine-18 deoxyglucose positron emission tomography (FDG PET) and computed tomography (CT), and after 2007, with integrated FDG PET-CT and diagnostic contrast enhanced (ce)CT or magnetic resonance imaging (MRI). All images (pre- and post-chemotherapy) were revised to confirm that inclusion criteria were met.

Patients were deemed unfit for initial local treatment because number, size or site would not permit complete resection of their CRLM or a safe 1cm ablation margin. These patients were referred for systemic chemotherapy. Chemotherapy only ceased when local treatment could be performed, on disease progression or due to unacceptable toxicity. Treatment response was evaluated every 3-6 cycles using FDG PET-CT and a ceCT and/or MRI of the liver. As previously stated, effective downstaging was defined as the decrease of tumour load in the liver, in number and/or in size of the lesions that allowed complete tumour clearance by RFA, or RFA combined with resection (12;13). Patients with persistent liver-dominant disease were re-evaluated for local treatment by our multidisciplinary liver board. The decision to perform local treatment after downstaging of the metastases was only made when the overall strategy could potentially achieve complete treatment of the tumour load. Time between imaging and surgery was a maximum of 6-8 weeks. Patients were not included when chemotherapy was only indicated to treat additional extrahepatic disease. RFA rather than resection was performed if metastases were considered non-resectable or, rarely, if a patient’s condition did not permit major surgery. The definite decision to perform RFA rather than resection was made during surgery and was aided by intraoperative ultrasound (IOUS), palpation and inspection.

Chemotherapy

Patients followed a variety of chemotherapeutic regimes initiated at their local hospital. Capecitabine and oxaliplatin (CapOx) were given in 3-week cycles, usually 6-8 cycles in total; intravenous oxaliplatin 130 mg/m² (day 1) followed by oral capecitabine 1000mg/m² twice daily (day 1, evening, to day 15, morning), followed by a week’s rest before starting the next
cycle.
When bevacizumab was added to this regime, 7.5 mg/kg was administered on the first day of every cycle.

FOLFOX was administered as follows: oxaliplatin, administered as a 85 mg/m² intravenous infusion over 2 hours on day 1, concomitantly with leucovorin (LV) as a 400 mg/m² infusion over 2 hours, followed by 5-FU, given as a 400 mg/m² bolus injection, and then as a 2400 mg/m² continuous infusion over 46 hours. Cycle length was 2 weeks and consisted of approximately 49 hours of infusion and 12 days of rest.

RFA
An open approach was chosen as an initial treatment, due to the added benefit of uncovering unsuspected lesions or lesions that became invisible on CT after chemotherapy through the use of IOUS, and the potentially lower local recurrence rate than with percutaneous RFA (14-16). After inspection for peritoneal tumour depositions, an experienced interventional radiologist evaluated maximum diameter, number and location of all lesions using IOUS. Based upon size and site of the lesion, 2.0-5.0cm expandable-needle electrodes (LeVeen, Boston Scientific, USA) were placed using ultrasound. Ablation was performed using a commercially available generator (RF3000, Boston Scientific, USA) and tract ablation was performed routinely to prevent ‘tract seeding’. A successful ablation was defined as an ablation zone including a 1cm tumour-free margin as seen on IOUS. Tumours exceeding 5cm were treated with multiple repositions of the single RFA needle for one or more overlapping ablations, with the use of bipolar RFA (InCircle, RFA Medical Inc., Fremont, USA) or microwave ablation (Evident MWA Percutaneous Antenna 3.7cm and Evident MWA Generator and Pump, Covidien, Dublin, Ireland).

Follow-up
Perioperative morbidity and mortality were defined as complications and death occurring during hospitalization or within 30 days after discharge. Complications were graded according to NCI Common Terminology Criteria for Adverse Events (NCI CTCAE v4.0). Patients were subsequently followed-up after RFA at regular intervals of 3-6 months using full-body FDG PET-CT or thoraco-pelvine ceCT. A local site recurrence was defined as an area on PET-CT of focally increased FDG uptake in or within 1cm of the treated lesion, or growth of a lesion on two consecutive ceCT scans. A new lesion was defined as recurrence anywhere in the liver 1cm outside of the ablation zone. In case of intra- or extrahepatic recurrence, renewed (local) treatment options were always considered.

Statistical analyses
Quantitative and qualitative variables are described as the mean, median and frequencies.
Categorical variables were compared using the chi-square or Fisher’s exact test and continuous variables were compared using the Student’s t-test. Overall- and disease-free survival were estimated using the Kaplan-Meier method with the log-rank test and a Cox regression analysis to determine differences between groups. A confidence interval of 95% was used for each analysis, and all calculations were performed using SPSS ver. 20 (SPSS Inc., Chicago, IL, USA).

Results

A total of 56 patients received induction chemotherapy and subsequent laparotomy with the intention for local treatment using RFA. However, IOUS revealed additional lesions in 5 patients (8.9%) that were too extensive for local treatment. These patients were excluded from further analyses. The studied population therefore consisted of 51 patients, of whom 30 were male (59%). The mean age at RFA treatment of 60 years (range 35-75 years). The primary tumour was located in the rectum in 20 patients (39.2%) and 39 patients were diagnosed with synchronous metastases (76.5%). Twenty-five patients were treated with RFA only (49%), while the procedure was combined with surgical resection in 26 patients. Nine patients (17.6%) showed concomitant limited extrahepatic disease (lung n=5, local recurrence n=1, lymph node n=3) at the start of chemotherapy.

Chemotherapy

Pre-operative chemotherapeutic regimes varied between patients. More than half of patients (30 patients; 59%) received CapOx combined with bevacizumab. Twelve patients were treated with CapOx, but switched to capecitabine mono-therapy in two patients due to toxicity. The remaining patients received FOLFOX (n=6) or capecitabine mono-therapy (n=3). The number of therapeutic cycles ranged from 3 to 18. Nineteen patients received chemotherapy only before RFA, two patients continued chemotherapy after RFA and in 30 patients chemotherapy was resumed following diagnosis of recurrent disease. None of the patients that remained free of disease received chemotherapy following RFA.

Imaging before and after chemotherapy

All patients underwent ceCT and PET-CT analysis before starting chemotherapy. The total number of lesions on CT at time of diagnosis was 325, with a median of 7 (IQR 3-9) and a maximum of 25 per patient. All showed FDG uptake on PET-CT. After chemotherapy, the total number of lesions visible on ceCT was reduced to 183, with a median of 3 (IQR 2-5) and a maximum of 13 per patient.
Following chemotherapy, PET-CT was completely negative in 19 patients (43.2%) and only 68 of the initial 325 lesions still showed FDG uptake (in 25 patients; 56.8%). Six of the 19 (31.6%) FDG-negative lesions proved to be >3cm on IOUS, compared to 12 of the 25 FDG-positive lesions (42%) (p=0.22). Seven patients (13.7%) were only evaluated using ceCT without PET-CT after chemotherapy. Extrahepatic disease in 4 patients showed a complete response after chemotherapy. All other patients showed partial extra-hepatic disease responses after chemotherapy and were locally treated using stereotactic body radiotherapy or resection.

Intra-operative ultrasound
All procedures were performed under general anaesthesia during a laparotomy. An interventional radiologist was always present to assist with the procedure. The total number of lesions found during surgery was 309, compared to 183 on ceCT, with a median number of 5 per patient (IQR 2.5-8) and a maximum of 17 (see table 1). The mean size was 31mm (range 9-70mm), with 21 lesions >3cm. In 24 patients (46%) the number of lesions found during surgery was compatible to the number of lesions on pre-chemotherapy imaging. More lesions than expected on pre-chemotherapy CT were found in 10 patients, and in the remaining 17 patients not all lesions were retrieved on IOUS.

<table>
<thead>
<tr>
<th>Table 1 Lesions identified with specific imaging modalities</th>
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<td>Pre-chemotherapy Post-chemotherapy FDG uptake on PET-CT IOUS</td>
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<tr>
<td>ceCT ceCT ceCT ceCT</td>
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<td>Total 325 183 68 309</td>
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<td>Median (n) 7 3 2 5</td>
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Pathology
Postoperative examination of resected specimens (n=26) or biopsies (n=12) of the ablated lesions was possible in 38 patients (74.5%). Twenty-six specimens (68.4%), including 7 biopsies, showed vital adenocarcinoma, while the remaining 12 specimens lacked vital tumour (31.6%), with only necrosis present. Vital tumour tissue correlated positively with FDG enhancement on PET after chemotherapy in 15/26 patients (58%), while 6/26 patients showed no FDG enhancement on PET (23%). A PET scan was unavailable for 5 patients (19%). When PA showed only necrosis, 5/12 scans still showed FDG uptake (42%), 6/12 scans were negative (50%) and no PET scan was available for 1/12 patients (8%).
Follow-up
Nine grade III complications (17.6%) occurred in 9 patients after RFA (2 abscesses, 4 pneumonias, 2 pulmonary emboli, 1 biloma), and complications were more frequent in patients who underwent RFA in combination with resection (p=0.02). There were no grade IV complications or mortalities. Mean follow-up was 32.6 months (range 5-80, SD 19.3), including 12 patients who remained free of disease (23.5%). Median disease-free survival (DFS) was 6 months (95%CI 4-8 months). First recurrences had solely intrahepatic locations in 26 patients and were both intra- and extrahepatic in 13 patients. A better DFS was associated with a lower number of lesions found on IOUS compared to the number originally diagnosed on pre-chemotherapy ceCT (p=0.03) (table 2). A worse DFS was associated with patients with extrahepatic disease at time of presentation (p=0.01). The median overall survival was 49 months. Estimated cumulative survival at 1- 3- and 4 years was 90% (CI 82.8-97.2%), 63% (CI 47.7-78.3%) and 45% (95% CI 26-64), respectively. Impaired overall survival was associated with extrahepatic disease at time of presentation (p<0.01) and the presence of recurrence after initial treatment (p<0.01). A trend towards worse survival was noted in tumours that measured >5cm on IOUS (p=0.06). Both extrahepatic disease at time of presentation and the presence of recurrence after initial treatment remained independent predictors of overall survival in a multivariate analysis.

Discussion
This study presents the results of patients with CRLM treated with modern chemotherapeutics prior to RFA. Overall survival in this selected study population was comparable to the very best survival rates reported after RFA or resection, despite the relatively short disease-free survival. Factors that may have contributed to good overall survival include a good response to repeated chemotherapy and local treatment of recurrences. In uncovering additional lesions, IOUS proved to be superior to ceCT and PET-CT after chemotherapy. The number of complications was relatively high but only when RFA was combined with surgical resection, which accords with the relatively high complication rate suggested in literature reports on surgical resection after conversion chemotherapy (17). Although treated, extrahepatic disease was associated with decreased overall- and disease free survival.

Despite the impressive survival improvement in patients treated with modern systemic chemotherapy, cure solely attributed to chemotherapy is still extremely rare. As is seen in our study, even complete radiologic response to chemotherapy does not predict complete remission. Another study that investigated recurrence rates of lesions that had disappeared
after chemotherapy, and were therefore not resected during surgery, found that 83% of these lesions recurred in the first year after treatment (18). This was confirmed by a study that showed that complete radiologic response is not correlated to complete pathologic response (8). That a complete pathologic response is very rare and cannot be predicted by pre-operative imaging has been shown by studies in which only 4-8% of the CRLM resected after systemic treatment lack tumour cells in the surgical specimen (8;19). This inability to distinguish between complete and incomplete responses after conversion chemotherapy makes complete eradication of remnant lesions essential to achieving cure in patients. A complete pathologic response has been reported to be a strong predictor of overall survival. After resection of residual disease, patients with a complete response to chemotherapy showed a significant increase in disease-free and 5-year overall survival compared to patients with viable tumour cells in the resected specimen (8;20). Our data did not support this conclusion: necrosis or vital adenocarcinoma in the resected specimens or biopsies did not influence survival in our series. It should be noted that bevacizumab, now a common element of first or second line treatment, was not used in these earlier studies. Paradoxically, our study showed that failure to retrieve all lesions on IOUS, which were therefore left in situ, led to improvements in DFS. However, this did not translate to a better overall survival. This outcome supports the theory that not all tumour cells are eradicated by chemotherapy, but that some metastases show a better response and therefore take longer to recur.

Downsizing of initially irresectable CRLM using systemic chemotherapy was first described in 1999 and is now accepted practice (21), with some studies claiming that up to 20% of irresectable CRLM are eligible for potentially curative resection. When resection after downstaging is possible, 5-year survival rates are now approaching 40% and are therefore comparable to patients with initially resectable lesions (22-24). Patients that never become eligible for resection and are treated with chemotherapeutics alone have a median survival of ‘only’ 20 months (7). Although a valid comparison of these two groups is not possible, this difference supports the benefits of local treatment. Still a group of patients remain that never become candidates for resection after conversion chemotherapy.

RFA is now a valuable local treatment option for patients with tumours ineligible for surgical resection. Although unsupported by a RCT, numerous studies have shown that RFA can result in complete tumour clearance and an increased life-expectancy, with 5-year survival rates of 20%-43%. RFA also appears to be superior to chemotherapy alone (4;6;25), especially in cases of bilateral disease in which chemotherapy is needed to downstage the tumour load. RFA combined with resection in bilateral disease is associated with improved overall survival compared to resection alone (26).

However, as shown by the relatively limited median DFS, a risk of incomplete ablation
remains. In contrast, the median overall survival in this study is comparable to the top end of studies reporting on patients primarily candidates for RFA (27). This discrepancy can be explained by two mechanisms. Firstly, the opportunity to ablate local recurrences in the liver is known to be able to achieve complete tumour eradication and therefore prolonged survival (4). Secondly, modern chemotherapeutic regimens have changed considerably over recent years and the addition of bevacizumab in particular is believed to be responsible for an improved pathological response of CRLM compared to oxaliplatin-based chemotherapy (28). However, a recent multicentre retrospective cohort study was not able to show improved DFS or OS after resection of bevacizumab-treated CRLM (29).

The specific individual contribution of RFA and chemotherapy to survival remains hard to distinguish. Ruers et al. attempted to clarify this in an EORTC study that compared RFA combined with chemotherapy and chemotherapy alone. These authors found that the combination with RFA resulted in a significantly prolonged DFS (30). Although studies that describe the effect of RFA after conversion chemotherapy are scarce, similarly to resection after chemotherapy, they report improvements in overall survival (12;13). Tumour eradication, by either resection or RFA, seems to have a beneficial effect for the patient.

A good radiological response of the lesion to chemotherapy may be a preferred outcome for the oncologist and the patient, but it can present a problem during surgery (31). Complete radiological resolution of the target lesions makes it hard to plan liver surgery. As over 80% of these lesions will recur during follow-up, local treatment remains obligatory when pursuing cure (18). Imaging half-way through the chemotherapeutic regime may indicate response to systemic therapy and local treatment can be initiated in time before complete disappearance on imaging.IOUS is essential due to its ability to identify 20-40% of additional lesions after chemotherapy compared to any other pre-operative imaging modality (14;15).

Several limitations, inherent to local ablative treatment, also played a role in this study. All patients included in the study were eventually deemed eligible for local treatment using RFA. Patients that never became candidates were excluded. Since tumour shrinkage was a condition for later local treatment, the tumour biology in these patients is likely to differ and thus introduce a selection bias. An additional bias may have resulted from selection of patients for this study with intrinsically better median survival prospects compared to patients in other studies evaluating the effect of chemotherapy. To improve comparability, all images were re-evaluated after inclusion to confirm patient suitability for local treatment. The lack of a uniform definition of unsuitability for local ablative treatment is a limitation in the evaluation of our results. In the past, contra-indications for resection of CRLM were clear and included >3 metastases, presence of extrahepatic disease or when a tumour free margin of 1cm could not be achieved (32). However, it has become clear in recent years that patients who do not meet the original inclusion criteria derive benefit from surgical
resection (33). New inclusion criteria to define resectability were therefore proposed (34). In
general, the future remnant liver should exceed 25% of a healthy liver, and 30% after
systemic chemotherapy with adequate vascular in- and outflow and biliary drainage and two
contiguous liver segments. The influence of time to progression, age and localisation is still a
subject of considerable debate. To the best of our knowledge, no such proposal exists for
ablative therapies. As a consequence, inclusion and exclusion criteria for treatment rely on
personal experience and interpretation of the literature by a multidisciplinary liver team.
Without clear definitions, the exact role of chemotherapy in the treatment effect will remain
hard to determine.

This study reinforces the need to evaluate all patient responses to chemotherapy, even
when initiated with palliative intent. Suitability of patients with CRLM for local treatment is a
decision that requires the expertise of a specialized regional multidisciplinary liver team
consisting of liver surgeons, radiologists, a radiation oncologist and medical oncologists. The
field of local CRLM treatment is rapidly evolving and new surgical techniques such as two-
staged hepatectomy and portal vein embolization, and ablative techniques like RFA, MWA
and recently irreversible electroporation, have extended the therapeutic possibilities. The
need for specialization and centralization is therefore only increasing and non-specialist
decision making may lead to undertreatment. This is emphasized by a study that reported
that over 60% of the patients with CRLM that were deemed irresectable by non-specialized
surgeons were considered resectable by specialist liver surgeons (35).

RFA after conversion chemotherapy is safe and appears to contribute to overall survival.
These results, in a selected patient population, require further validation in prospective
trials. All patients with liver-dominant disease that are treated with palliative chemotherapy
should undergo regular evaluation of the treatment effect by a multidisciplinary team. Only
then can patients be identified as candidates for local treatment, even when the initial stage
of the disease precluded any prospect of cure.
Reference List


