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Effektivität der bildgesteuerten Radiofrequenzablation, Chemoembolisation und Selektiven Internen Strahlentherapie maligner Lebertumore am Beispiel vom Hepatozellulären Karzinom und neuroendokrinen Lebermetastasen

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1. Einleitung

1.1. Zusammenfassung

Auch wenn die Chirurgie, die Chemotherapie und die perkutane Strahlentherapie weiterhin die tragenden Säulen der onkologischen Medizin darstellen, erfahren die bildgesteuerten minimal-invasiven Therapieformen in der onkologischen Therapie einen immer höheren Stellenwert. Dieser Trend ist insbesondere dem enormen technologischen Fortschritt in der medizinischen Bildgebung zu verdanken. In den zwei von mir zur Dissertation bei der Hohen Medizinischen Fakultät der Ludwigs-Maximilians-Universität eingereichten Arbeiten werden jeweils retrospektiv die Effektivität der drei zurzeit gängigsten bildgesteuerten Therapieformen evaluiert. Dabei wird im ersten Fachartikel die Effektivität der Kombinationstherapie aus der transarteriellen Chemotherapie (TACE) und der Radiofrequenzablation (RFA) in der Behandlung von nicht-resezierbaren hepatozellulären Karzinomen (HCC) untersucht. Hierbei konnte anhand der retrospektiven Analyse gezeigt werden, dass diese Kombinationstherapie eine hohe lokale Tumorkontrolle und vielversprechende Überlebensdaten erzielen kann.

Im zweiten Artikel sind die klinischen und radiologischen Daten von 42 Patienten mit nicht-resektabelen Lebermetastasen von neuroendokrinen Tumoren, die mit der Selektiven Internen Radiotherapie (SIRT) behandelt wurden, erhoben worden. Die Autoren kommen hier zu dem Ergebnis, dass die SIRT eine effektive und sichere Therapieform für diese Metastasen darstellt. Da die Schlussfolgerungen aus retrospektiven Analysen gezogen wurden, sollten diese vielversprechende Ergebnisse in prospektiv-randomisierten Studien untersucht werden.

1.2. Summary

Although surgical resection, systemic chemotherapy and radiotherapy are representing the mainstay in oncological treatment, image-guided interventional therapies recently gained increasing awareness. This is mainly because of the tremendous progress in imaging techniques, which has been observed in the last decade.

In the two submitted manuscripts the efficacy of the three most applied image-guided therapies were evaluated retrospectively. In the first scientific article we demonstrated that a combined therapy consisting of RFA and TACE lead to high local tumor control and promising survival data for non-resectable HCC. In the second article clinical and radiological data of 42 patients with non-resectable liver metatstases from neuroendocrine tumors treated with SIRT were evaluated.

Authors concluded that radioembolization with 90Y-microspheres is a safe and effective treatment option in patients with treatment-refractory neuroendocrine liver metastases. The results and conclusions of both studies require further validation by prospective randomized trials.

1.3. Einführung

Während die Chirurgie, die Strahlentherapie sowie die systemische Chemotherapie zu den tragenden Säulen der Tumortherapie gehören, zeigt sich ein zunehmender Einzug der minimal-invasiven Techniken in der Behandlung von malignen Tumoren.

Dieser Trend ist durch die enormen Fortschritte der letzten Jahrzehnte in der medizinischen Bildgebung sowie in der lokalen Tumortherapie bedingt. Dabei spielen die bildgesteuerten Interventionen insbesondere in der Behandlung von Lebertumoren eine immer wichtigere Rolle.

In den vorliegenden Fachartikeln werden mit dem Hepatozellulären Karzinom (HCC) sowie mit Lebermetastasen von Neuroendokrinen Tumoren (NETLM) zwei der häufigsten malignen Lebertumore untersucht, nämlich das HCC als der häufigste lebereigener Tumor und die hepatische Metastasierung, als die häufigste maligne Lebererkrankung überhaupt.

In den vorliegenden Arbeiten werden drei der wichtigsten minimal-invasiven, bildgesteuerten Behandlungsmethoden vorgestellt.

Im ersten Artikel wird die Effektivität der Kombinationstherapie, bestehend aus konventioneller transarterieller Chemoembolisation (TACE) gefolgt von Radiofrequenzablation (RFA), in der Behandlung des HCC vorgestellt.

Die Evaluation erfolgte dabei durch eine retrospektive Auswertung von klinischen und radiologischen Parametern von 85 Patienten mit HCC und mit einer Kombinationsbehandlung mit TACE und RFA in der Vorgeschichte.

Im zweiten Artikel wird die Effektivität einer weiteren interventionellenTherapieoption zur Behandlung von Lebermetastasen untersucht, nämlich die Selektive Interne Radiotherapie (SIRT).

Es wurde dabei eine retrospektive Analyse von 42 Patienten mit nicht-resektabelen Lebermetastasen von neuroendokrinen Tumoren (NETLM,) die alle eine SIRT als Therapie bekommen hatten, durchgeführt.

Im Folgenden werden die zwei genannten Fachartikel detailliert dargestellt und diskutiert und dabei auch mein Beitrag zu den jeweiligen Publikationen näher erläutert.

Multimodality treatment with conventional TACE and RFA for unresectable HCC:

Das Hepatozelluläres Karzinom (HCC) gehört zu den häufigsten malignen Erkrankungen und ist zudem der zweithäufigste krebsbedingte Todesursache weltweit.
Die Inzidenz der HCC variiert weltweit abhängig von der Prävalenz der am häufigsten zu Grunde liegende Erkrankung, nämlich der Leberzirrhose.
Die Leberzirrhose ist fast immer mit einer chronischen Lebererkrankung, am häufigsten Hepatitis B und C vergesellschaftet.
Damit sind die chronischen Hepatitiden (Hepatitis B und C) letztendlich in 80 – 90 % ursächlich für die Entwicklung eines HCCs auf dem Boden einer Leberzirrhose.
Während die Prävalenz der Hepatitis in Asien hoch ist, zeichnet sich auch in Europa und in Nordamerika in den letzten Jahrzehnten eine deutliche Zunahme der Prävalenz ab.
Dadurch kommt es auch zu einem Anstieg der Inzidenz des HCCs.
Dabei können zum Zeitpunkt der Diagnosestellung nur wenige Patienten mit HCC kurativ mit chirurgischer Resektion oder Lebertransplantation behandelt werden.
Für einen Großteil der Patienten scheidet leider zum Zeitpunkt der Diagnose aufgrund der Tumorausdehnung oder der Leberfunktionseinschränkung eine chirurgische Behandlung als Behandlungsoption aus.
Zusätzliche Ausschlusskriterien für eine Resektion sind eine extrahepatische Tumormanifestation oder eine Invasion der Pfortader.
Vor diesem Hintergrund treten die minimal-invasiven loko-regionären Therapieoptionen vermehrt in das Interesse der behandelnden Ärzte. Entweder als „neoadjuvante“ Therapie vor chirurgischer Resektion zum potentiellen „Downstaging“ der HCC-Herde oder als „Bridging“-Therapie für Patienten, die für eine Lebertransplantation gelistet sind. Für diese Patientengruppe gilt es einen „Drop-out“ von der Transplantationsliste während der Wartezeit auf das Spenderorgan zu vermeiden, da die Transplantation sowohl das HCC als auch die zu Grunde liegende Leberzirrhose heilt.
Sowohl durch die Fortschritte in der medizinischen Bildgebungstechnik, wie auch die technischen Entwicklungen im Bereich der minimal-invasive Therapien stehen den Patienten mittlerweile multiple interventionelle Therapieoptionen für die Behandlung von Lebertumoren zur Verfügung.
In dieser retrospektiven Arbeit haben wir bei 85 Patienten die Überlebensraten sowie

das lokale Tumoransprechen gemäß den mRECIST-Kriterien (modifizierte RECIST-Kriterien) bei einer Kombinationstherapie aus TACE und RFA erhoben.
Wir konnten in dieser Studie zeigen, dass die angewandte multimodale Therapieform potentielle Vorteile insbesondere in der lokalen Tumorkontrolle bei nicht-resezierbaren HCCs mit einem Barcelona Clinic Liver Cancer (BCLC) Stadium A oder B mit sich bringen könnte.
Die effektive lokale Tumorkontrolle bzw. die hohe antitumorale Wirkung dieser Therapie konnte durch eine hohe Rate von Patienten mit komplettem Ansprechen („complete response", (CR) nach mRECIST) in über 82% der behandelten HCC-Knoten demonstriert werden.
Ein besonders hohes Therapieansprechen zeigten in dieser Studie Patienten mit einem singulären HCC, hierbei betrug der Anteil der Knoten mit einer kompletten Remission (CR) 91%.
Hinsichtlich des Überlebens zeigten unsere Ergebnisse weiterhin ein medianes Überleben von 25.5 Monaten des gesamten untersuchten Patientenkollektivs. Diese Ergebnisse verdeutlichen einen signifikanten Unterschied des medianen Überlebens zwischen den Patientengruppen mit BCLC A (74.3 Monaten) und BCLC B (50.3 Monaten) und demonstrierten somit den Nutzen dieser Kombinationstherapie insbesondere für Patienten mit BCLC-Stadium A.
Zusammenfassend legen diese Ergebnisse die hohe lokale Wirksamkeit dieser Therapieregime, insbesondere für HCCs im frühen Stadium nahe.

Bei dieser multimodalen Therapieform sind zwei Vorteile von großer Bedeutung und mutmaßlich auch beitragend zu der hohen antitumoralen Wirkung, die aus unserer Studie, aber auch aus weiteren Studien hervorgehen:

1. Durch die vorangegangene transarterielle Chemoembolisation der HCC-Herde sind diese durch die Lipiodol-Speicherung in der CT-gesteuerten RFA deutlich leichter erkennbar und dadurch auch besser zugänglich. Zudem werden durch die transarterielle Therapie auch potentielle, in der Bildgebung nicht sichtbare, kleine Satellitenherde mitbehandelt.

2. Durch die vorangegangene Chemoembolisation wird durch die vaskuläre Okklusion ein Abtransport der thermischen Energie aus dem Herd verringert und die Wirkung der RFA wird dadurch verstärkt.

Da diese Studie durch den retrospektiven Charakter hinsichtlich ihrer Aussagekraft limitiert ist, sollten unsere Feststellungen in einer prospektiv-randomisierten Studie überprüft werden.
So könnte überprüft werden, ob der multimodale Therapieansatz gegenüber der Einzeltherapie mit RFA bei HCC Knoten unter 3 cm und bei HCC Knoten zwischen 3- 5 cm einen signifikanten Vorteil erbringt.
Darüber hinaus kann auch überprüft werden in welcher Reihenfolge dieser multimodale Therapieansatz am besten angewendet werden könnte, wie in unserer Studie mit einer der RFA vorangegangene Chemoembolisation oder in einer umgekehrten Reihenfolge, TACE nach RFA. Letztere hätte den Vorteil, dass durch die Thermoablation unmittelbar um das Ablationsareal, also um das HCC, ein hyperämer Randsaum entsteht, welcher dann bei einer unmittelbar nachfolgend durchgeführten TACE das embolisierende Gemisch aus Lipiodol und dem Chemotherapeutikum vorzugsweise aufnehmen würde. So könnten evtl. durch die alleinige RFA insuffizient behandelten Randbereiche des HCCs aber auch Satellitenherde in der näheren Umgebung behandelt werden.
Im Rahmen der ersten Studie haben wir retrospektiv die Daten von 85 Patienten, die in den vorangegangen 10 Jahren am Institut für Klinische Radiologie des Klinikums Großhadern eine Kombinationstherapie erhalten hatten, erfasst. Dabei wurden auch die laborchemischen Leberparameter vor und nach der Therapie verglichen.

Zudem wurde die Überlebensdaten der Patienten anhand der Aktenlage sowie aus den Daten des Münchener Tumorregisters erhoben.
Durch die Auswertung der kontrastmittelverstärkten CT- oder MRT-Untersuchungen, die 6-8 Wochen nach der kombinierten loko-regionären Therapie durchgeführt wurden, konnte das radiologisch- bildmorphologische Ansprechen (nach mRECIST) der HCC-Herde auf diese Therapie ermittelt werden.
Diese Daten (klinische Parameter, Überlebensdaten, radiologische Befunde) wurden in einer Tabelle übersichtlich erfasst und analysiert.

Die Statistik insbesondere hinsichtlich des Überlebens wurde mit Hilfe einer der Mitautoren erstellt. Es erfolgte eine ausführliche Literaturrecherche der vergangenen 10 Jahre und eine anschließende Zusammenfassung der Ergebnisse dieser Studie.

Letztere wurden schließlich mit der aktuellen Datenlage im Vergleich gesetzt und diskutiert.

Radioembolization of Symptomatic, Unresectable Neuroendocrine Hepatic Metastases Using Yttrium-90 Microspheres:

Neuroendokrine Tumore (NET) sind definiert als Tumore mit der Fähigkeit der Synthese und Sekretion von Polypeptiden, welche eine hormonelle Aktivität besitzen.
Neuroendokrine Tumore sind selten und repräsentieren eine vielfältige Gruppe von malignen Tumoren in unterschiedlichen Organsystemen, einschließlich des Gastrointestinaltraktes, hier insbesondere Dünndarm und Appendix sowie im respiratorischen Trakt.
Unglücklicherweise haben die meisten Patienten zum Zeitpunkt der Diagnosestellung bereits Lebermetastasen.
Obwohl viele Patienten einen langen symptomarmen Krankheitsverlauf zeigen, weisen die meisten Patienten (80%) unbehandelt eine mediane Überlebenszeit von weniger als 5 Jahren auf.
Eine aggressive lokale Tumortherapie hat sich dabei sowohl hinsichtlich des Überlebens wie auch hinsichtlich der Verbesserung der tumorassoziierte Symptomatik als effektiv erwiesen.
Leider qualifiziert sich jedoch nur eine kleine Minderheit (< 10%) der Patienten mit hepatischen Metastasen aufgrund der Tumorausdehnung für eine chirurgische Resektion.
Die transarterielle Embolisation (TAE) und die transarterielle Chemoembolisation (TACE) haben in früheren Studien zwar eine Verbesserung des Überlebens und der tumorassoziierten Symptomatik gezeigt, diese Effekte sind jedoch von beschränkter Zeitdauer. Ferner wird kontrovers diskutiert wann, wie oft und in welcher Form (TAE oder TACE) dieser therapeutische Ansatz gewählt werden soll.
Aufgrund der scheinbar fehlenden Wirksamkeit der systemsichen Chemotherapie in der Behandlung von NET wird die Selektive Interne Radiotherapie (SIRT) zunehmend als palliative Behandlungsoption eingesetzt.
Die SIRT wurde erstmals 2003 in Europa eingeführt und steht seitdem Patienten mit nicht-resektabelen Lebermalignomen (Metastasen und HCC) als palliative Therapieoption zur Verfügung.
Eine Voraussetzung für diese transarterielle Therapie ist die duale Blutversorgung der Leber mit einer dominanten Versorgung der hepatischen Malignome über die Leberarterien, während das nicht tumortragende Lebergewebe vorrangig über die

Pfortader versorgt wird.

Harzmikrosphären, an die der Betastrahler ^{90}Yttrium gekoppelt ist, werden über einen transfemoralen Katheter selektiv in die Leberarterien appliziert. Auf diese Weise können hohe Konzentrationen im Gefäßbett des Tumors erreicht werden, wobei das restliche strahlensensible Leberparenchym weitestgehend ausgespart bleibt. Dieses Vorgehen kombiniert zwei therapeutische Effekte: zum einen die Embolisation der präkapillären Tumorgefäße durch die Mikropartikel und zum anderen eine interstitielle Hochdosis-Strahlentherapie durch das ^{90}Yttrium.

Vor der SIRT sind eine Reihe vorbereitender Untersuchungen des Patienten unerlässlich. Dazu gehören eine angiographische Darstellung der A. hepatica mit der Applikation von Technitium 99-MAA und anschließender szintigraphischen Untersuchung zum Nachweis / Ausschluss eines relevanten hepatopulmonalen Shuntvolumens oder eines ektopen Abstroms über aberrante Gefäße in den Gastrointestinaltrakt.

Im Rahmen der vorliegenden Arbeit sind die Daten zu 42 Patienten mit nicht-resektablen Lebermetatasen eines neuroendokrinen Tumors, die mittels SIRT behandelt wurden, retrospektiv erfasst und ausgewertet worden.

Dabei bestand die Zielsetzung dieser Studie in der Erhebung der Sicherheit, der Effektivität sowie der tumorassoziierten Symptomkontrolle der SIRT in der Behandlung von Lebermetastasen von neuroendokrinen Tumoren.

Die lokale Tumorkontrolle wurde nach RECIST-Kriterien anhand der radiologischen Untersuchungen, die 3 Monaten nach der Therapie durchgeführt wurden evaluiert.

Dabei zeigte sich bei lediglich 2.5% der Patienten eine Progression, während 97.5% der Patienten eine Partielle Remission (PR) oder eine Stabile Erkrankung (SD) zeigten.

Diese Ergebnisse spiegeln die hohe antitumorale Wirkung dieser Therapie wieder und sind konkordant mit der ebenfalls in dieser Studie festgestellten signifikanten Senkung der Tumormarkerspiegel (Serotonin, Chromogranin A) der Patienten nach der Therapie.

Ferner konnte bei den 38 symptomatischen Patienten in ca. 95% der Fälle eine Besserung der tumorassoziierten Symptomatik beobachtet werden.

In der Summe konnte bei dieser Studie gezeigt werden, dass die SIRT eine sichere und effektive Therapieoption in der Behandlung von NETLMs darstellt. Die Effektivität bezieht sich dabei einerseits auf die Verbesserung der Symptomatik der Patienten und anderseits auf den antitumoralen Effekt, welcher sich als ein radiologisches Ansprechen und in einer Verringerung der Tumormarker zeigen konnte.

Im Rahmen meiner Koautorenschaft bei dieser Studie habe ich bei der retrospektiven Erhebung der klinischen und laborchemischen Patientenparameter mitgewirkt und dabei insbesondere an der Erhebung der klinischen Symptomatik der Patienten vor und nach der Therapie durchgeführt.
Diese wurden aus Befragungen der Patienten bzw. deren behandelnden Ärzten erhoben. Ferner habe ich anteilig auch die radiologischen Untersuchungen der Patienten mitbeurteilt und dabei insbesondere das radiologische Tumoransprechen nach RECIST erhoben und gemeinsam mit weiteren Mitautoren eine detaillierte Literaturrecherche zu diesem Thematik durchgeführt.

1.4. Ausblick

Im Hinblick auf die sich abzeichnende stärkere Miteinbeziehung minimal-invasiver und lokal hochwirksamer Therapieansätze in der onkologischen Medizin, werden die bildgesteuerten loko-regionalen Therapien in diesem Rahmen künftig eine feste Größe darstellen.

Die hohe antitumorale Wirksamkeit der Therapieoptionen aber auch die vielversprechenden klinischen Parameter (Überleben, Klinische Symptomatik), die in den Ihnen vorliegenden Fachartikel, retrospektiv dargestellt wurden, rechtfertigen diese Tendenz. Als retrospektive Studien sind beide jedoch, wie bereits erwähnt, hinsichtlich Ihrer Aussagen und Ergebnisse limitiert. Diese können jedoch als Motivation für randomisierte und prospektive Studien angesehen werden, anhand derer die Effizienz dieser Therapieoptionen einerseits überprüft und andererseits deren Stellung in den Therapieparadigmen der onkologischen Medizin definiert werden sollte.

2.

Multimodality treatment with conventional TACE and RFA for unresectable HCC

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Multimodality treatment with conventional TACE and RFA for unresectable HCC

2.1. Abstract

Background/Aims:

To evaluate the efficacy of multimodality treatment consisting of conventional transcatheter arterial chemoembolization (TACE) and radiofrequency ablation (RFA) in patients with non-resectable and non-ablatable hepatocellular carcinoma (HCC).

Methods:

In this retrospective study eighty-five consecutive patients with HCC (59 solitary,29 multifocal HCC) received TACE followed by RFA between 2001 and 2010. The mean number of tumor per patient was 1.6 (+/- 0,7) with a mean size of 3.0 cm (+/- 0.9). Both, the local efficacy as well as the patients' survival was evaluated.

Results:

Of 120 treated HCCs 99 (82.5 %) showed complete response (CR), while in 21 HCCs (17.5%) a partial response (PR) was depicted. Patients with solitary HCC revealed CR in 91% (51/56); in patients with multifocal HCC (n = 29) CR was achieved in 75% (48 of 64 HCCs). The median survival for all patients was 25.5 months. The 1-, 2-, 3- and 5-year survival-rates were 84.6%, 58.7%, 37.6% and 14.6%, respectively. Statistical analysis revealed a significant difference in survival between BCLC A (73.4 months) and B (50.3 months) patients, while analyses failed to show a difference for Child-Pugh score, CLIP score and tumor distribution pattern.

Conclusion:

TACE combined with RFA provides an effective treatment approach with high local tumor control rates and promising survival data especially for BCLC A patients. Randomized trials are needed to compare this multimodality approach with single modality approach for early stage HCC.

Keywords: liver**,** hepatocellular carcinoma, radiofrequency ablation, transcatheter arterial chemoembolization.

2.2. Introduction

Hepatocellular carcinoma (HCC) is considered to be one of the major malignant diseases in the world today. It is the second leading cause of cancer mortality worldwide (Jemal, Bray et al. 2011) and the fifth most common cancer (Parkin, Bray et al. 2001; Albrecht 2008). The incidence of HCC varies in different geographic areas, depending on the prevalence of the major causes, namely chronic liver disease due to chronic viral hepatitis and alcohol induced liver cirrhosis. Together hepatitis C virus (HCV) and hepatitis B virus (HBV) account for 80–90% of all HCC worldwide (Bosch, Ribes et al. 2005).

The incidence of HCC in North America and in Europe has been increasing in the last decades due to the migration from areas with high prevalence of HCC and due to the epidemic of hepatitis C in North America and Europe between 1950 and 1970 (Sherman 2010).

Whereas the incidence of hepatocellular carcinoma has increased in the past decades (El-Serag, Davila et al. 2003), only a small portion of patients with early stage HCC can be treated curatively with resection or orthotopic liver transplantation.

However, most patients are no candidates for surgery at time of diagnosis due to either lesion size, number of lesions, liver function or comorbidity.

Due to the advances in medical imaging technology as well as minimal-invasive, locoregional treatment options various approaches to interventional oncology treatments have been developed.

Recently published studies have shown the efficacy and safety of a wide array of locoregional therapies.

These methods include Transcatheter Arterial Chemoembolisation (TACE) and Radio Frequency Ablation (RFA). They have gradually played more and more important roles in the treatment of HCC (Zhang, Fan et al. 2009). The superiority of RFA over percutaneous ethanol injection (PEI) has been shown in several studies (Lencioni, Allgaier et al. 2003; Kettenbach, Blum et al. 2004; Lin, Lin et al. 2004; Lencioni, Della Pina et al. 2005; Lin, Lin et al. 2005; Shiina, Teratani et al. 2005). Other studies reporting on RFA indicate that a complete short-term necrosis can be achieved in 80%-90% of tumors smaller than 3-5 cm in diameter (Buscarini, Buscarini et al. 2001; Poon, Fan et al. 2002; Kettenbach, Blum et al. 2004). In very early HCC (BCLC-classification) RFA can be considered as an valuable alternative treatment option to surgical resection, especially since RFA is easily repeatable, shows a lower morbidity profile, and therefore can be offered to patients who refuse surgery or have to be rejected for other medical conditions (Livraghi 2009; Kagawa, Koizumi et al. 2010). On the other hand TACE induces an ischemic necrosis by using antitumor drugs and embolizing agents and prolongs survival (Llovet, Real et al. 2002; Lo, Ngan et al. 2002).

Evidence suggests that TACE combined with RFA have a synergistic effect (Rossi, Garbagnati et al. 2000; Clasen and Pereira 2007) in treating HCC and is superior to TACE or RFA alone in terms on the effect of survival (Bloomston, Binitie et al. 2002; Kirikoshi, Saito et al. 2009). The decrease of blood flow in the HCC lesion by TACE appears to increase the efficacy of RFA in destroying tumors.

Especially in lesions larger than 5cm, a combined approach of RFA and TACE results in a higher percentage of complete necrosis (Dupuy and Goldberg 2001; Yamakado, Nakatsuka et al. 2002). The prognosis of patients with HCC depends on tumor status, liver function reserve, general health status and efficacy of treatment (Bruix, Sherman et al. 2001).

Various prognostic staging systems have been developed to provide treatment strategies and to determine the survival of the patients. The Barcelona Clinic Liver Cancer (BCLC) staging and treatment algorithm considers tumor burden, liver function status and patient's physical status providing a stratification of patients in different treatment groups (Llovet, Bru et al. 1999).

In Europe the BCLC classification is recommended by the European Association for the Study of the Liver (EASL) (Bruix, Sherman et al. 2001) and the American Association for the study of Liver Diseases (AASDL)(Bruix and Sherman 2005), because it is the only validated system that includes tumor burden, patient's performance status and liver function leading to a stage-related treatment strategy (Marrero, Fontana et al. 2005).

Therefore we applied the BCLC score for the stratification of the patients in our analysis.

The aim of this retrospective analysis was to determine the efficacy of the combined treatment approach by evaluating contrast enhanced CT/MR scans for the assessment of local tumor control and to evaluate survival rates of HCC patients stratified by BCLC, Child-Pugh, CLIP and tumor distribution.

2.3. Materials and Methods

Patients:

Between April 2001 and Mai 2010, 85 consecutive patients with HCC (68 men, 17 women; age 41-92 years (mean 65 years +/- 9.1) were treated with combined therapy (conventional TACE followed by RFA). Details are presented in table 1.

Out of the 85 patients 60 met the Milan criteria. From these 60 patients 44

patients were listed for liver transplantation. The remaining 16 patients had comorbidities like coronary heart disease (n = 6) a second malignant disease (n = 7) or COPD with pulmonary hypertension (n = 3). The intention to treat for the listed patients was to avoid a drop out from the waiting list. For the 25 patients not listed the combined therapy targeted at downstaging the patients. The remaining 16 patients with severe comorbidities were treated palliatively.

Due to their comorbidities they were both withdrawn from the transplantation list and also refused for surgical approach, so a palliative treatment approach was the only alternative although these 16 patients met the MILAN- criteria.

The hepatic function was determined for each patient utilizing the Child-Pugh scoring system. 80 patients presented with Child-Pugh A cirrhosis and 5 patients with Child-Pugh B cirrhosis. A prerequisite for locoregional treatment was a sufficient blood clotting status with a PTT < 40s; INR < 1.75 and a platelet count > 40.000/mm^3.

As part of the pretreatment work-up, CT examinations with a multiphasic protocol (contrast flow rate 5ml/s; (unenhanced, arterial, portal-venous and late phases)) were performed in each patient using multidetector scanners (Somatom Sensation 16 and 64, Somatom Definition, Somatom Definition Flash and Somatom Definition AS+, Siemens®, Forchheim, Germany).

Frequently also an MRI examination were performed as a pretreatment work-up and especially during the follow-up (figs.1a and1h). The contrast-enhanced MRI examinations (Gd-EOB-DTPA Dinatrium (Primovist ®) / Ferucarbotran (Resovist ® , until 2007)) were performed in high field scanners (Magnetom Sonata (1,5 T), Magnetom Avanto (1,5 T) and Magnetom Verio (3T), Siemens ®, Forchheim, Germany) and were among others composed of a dynamic phase and accumulation phase.

MRI was performed as a pretreatment work-up in 36 patients (42.4%) and especially during the follow-up after 6 – 8 weeks in 77 patients (90.6%).

The diagnosis of HCC was confirmed either by biopsy or by imaging techniques (Fig.1a) according to the European Association for Study of the Liver consensus conference criteria (Bruix, Sherman et al. 2001).

Prior to the combined treatment approach 56 patients presented with a single HCC manifestation while 29 had multinodular disease with a maximum of 5 lesions. Infiltrating HCC or portal vein thrombosis were exclusion criteria for this retrospective evaluation. Other exclusion criteria were an Eastern Cooperative Oncology Group performance status >2 (Oken, Creech et al. 1982) or advanced/ terminal tumor stage according to the BCLC-classification.

According the BCLC-classification 65 patients presented with early stage HCC (BCLC A) while 20 patients were stratified as BCLC B patients (intermediate stage HCC). BCLC B patients were considered eligible for combined locoregional treatment if HCC lesions deemed accessible for image guided placement of the RFA device.

The total number of HCCs in all patients was n =132. However, 12 lesions were not treated by the combined locoregional treatment approach due to their anatomical location (7), inadequate visualization in CT (2) or due to patients' comorbidities or other complications (3). However the mean number of HCC nodules per patient was 1,6 (+/- 0,7).

The maximum diameter of the 120 treated lesions varied from 0.7 cm to 6.0 cm (mean 2.5 cm +/- 0.9 cm, median 2.5 cm). The sum of the maximum diameter of all HCCs per patient ranged from 1.1 cm to 10.5 cm (mean 3.8 cm, median 3.4 cm).

39 of the treated HCCs were < 2 cm (32.5%), whereas 81 were > 2 cm (67.5 %).

Written informed consent was obtained from all patients before treatment.

Conventional Transcatheter Arterial Chemoembolization (TACE):

In each patient prior to RFA a conventional Lipiodol-based (max. 10cc) TACE with a chemotherapeutic drug (Epirubicinhydrochloride) was perfomed. Calibrated microspheres (diameter 250 µm) were added in those patients where the lipoidol did not devascularize the HCC nodule completely.

Under angiographic control (Polystar Angio Suite, Axiom Artis dTA, Axiom Artis Zeego, Siemens®, Forchheim, Germany) first a 4-F angiographic catheter (pigtail configuration) was inserted through the femoral artery in the aorta to perform a mapping angiography of the liver supplying arteries. After the intubation of the superior mesenteric artery and the common hepatic artery by switching to a cobra or sidewinder configuration (4F), a super-selective catheterization of the hepatic arteries and the superior mesenteric artery was performed. In all cases patency of the portal vein was verified by acquiring a portal venogram after injection of contrast in either the splenic or superior mesenteric artery. After superselective catheterization of the hepatic and tumor feeding arteries utilizing a coaxial technique and microcatheters (2.7F, Progreat, Terumo; Leuven®, Belgium; Fig. 1b) an emulsion consisting of 50mg Epirubicinhydrochloride (Farmorubicin®, Pfizer Pharma) and max. 5cc iodized oil (Lipiodol® Ultra-Fluid, Guerbet) were slowly infused under fluoroscopic guidance until stasis within the HCC lesion or the tumor feeding vessel was reached (Fig.1c). Calibrated polyvinyl alcohol (PVA) particles (BeadBlock®, Biocompatibles International; Farnham, UK) or other microspheres (Embozene®, Celonova Biosciences; Atlanta, Georgia, USA) were applied to achieve complete stasis in the tumor if necessary. Patients were carefully observed during the entire procedure, and analgesics and anti-emetics were administered on demand.

Radiofrequency Ablation (RFA):

After multiphase contrast-enhanced computed-tomography (CT) was performed, the optimal electrode pathway to the HCC lesion was determined. All RF-ablation procedures were performed using multi-tined expandable electrodes (Starburst® XL, Xli, Talon, AngioDynamics; Cambridge, UK / LeVeen® needle electrode, Boston Scientific, Ratingen, Germany). With this electrode design, an array of multiple, stiff, curved wires was deployed in the HCC and distended to its maximum diameter of 2-
5 cm. The electrodes were placed under CT- / CT-flouroscopy and occasionally Ultrasound (US) (Sonoline Elegra, Sonoline prima Acuson S 2000, Siemens®, Forchheim, Germany) - guidance.

In cases of HCC nodules with critical anatomical locations or lesions that are not amenable to US a CT-fluoroscopy guidance (Somatom Sensation 4, 16, 64, Somatom Definition AS+; Siemens®, Forchheim, Germany) was performed.

The exact positioning of the electrode and the complete coverage of the lesion with the hooks fully distended was warranted by CT- / CT-fluoroscopy guidance (Fig. 2c), or when there was doubt, with additional contrast-enhanced CT scans. After attaching to the high power RF-generator the RF-current was emitted from the active, non-insulated curved electrodes. The delivered power was increased until the target temperature of 95 - 100°C was reached. Subsequently, the energy was maintained as long as 20 to 45 minutes. When the LeVeen® system was used energy was applied until an increase of impedance was noted twice indicating complete coagulation necrosis. To control the achieved coagulation zone instantaneously after completing the procedure, a post-procedural contrast-enhanced CT scan with the electrode still in place was performed to depict incomplete ablation with the option of an immediate additional ablation as well as to detect potential peri-procedural complications. For HCCs less than three cm in size, a single session of ablation with a maximum electrode diameter of 5 cm was used to provide a sufficient safety margin. In larger lesions, the electrode was repositioned several times in a single session in order to achieve a volume large enough to cover the entire HCC including a safety margin. To reduce the risk of puncture related bleeding, electrode-track ablation was performed after completion of the procedure at a reduced power level. Our standard approach for RF-ablation was to perform the procedure under moderate sedation and local anesthesia. The majority of ablations were performed with administration of a combination of midazolam maleate, parecoxib-sodium and piritramid. Blood pressure, heart rate and oxygen saturation were monitored continuously. In patients who presented with low tolerance to pain, or lesions that were difficult to target, the procedure was performed under general anaesthesia. Pre-interventional antibiotics were used for all patients.

Local efficacy:

During the follow up Imaging- examinations mostly by contrast-enhanced MRI, the treated HCC nodules were stratified according to the modified-RECIST criteria (Lencioni and Llovet 2010) into complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD).

Statistical Analysis:

Continuous survival data are displayed as mean ±standard deviation and as proportions for binary data. Survival curves and median survival as well as pertaining 95%-confidence intervals were estimated by the Kaplan-Meier method and group comparisons were made by log-rank test statistics. Patients on the waiting list for the liver transplantation were censored at the time of transplantation. All analysis was performed by SAS (Version 9.2, SAS Institute Inc., Cary, NC, USA) and a two-sided p-value <0.05 was considered to indicate statistical significance.

2.4. Results

The median duration of follow-up after combined treatment was 16 months (range 2 to 74 months). The mean patient age was 66 years (range 42 to 93 years). The mean number of HCC lesions per patient was 1.6 with a range from 1-5 lesions. The mean diameter (sum of maximum diameter of HCCs per patient) of the treated lesions was 3.8 cm (range 1.1 to 10.5 cm). RFA were performed after a median time of 1 day after TACE (range 1 to 20 days; mean 3,8 days).

According to the SIR (Society of interventional Radiology)-guidelines no major complications were observed. The most common post procedure morbidity was post embolization syndrome, consisting of fatigue, mild nausea, low-grade fever, and abdominal pain that were easily managed with oral narcotics and antiemetics. In 8 % of the cases there were a slight subcapsular bleeding after RFA with neither clinical symptoms nor progression in a additional CT-Scan performed the day after RFA.
Until the end of the study 13 patients of the listed patients were transplanted whereas 4 patients were removed from the waiting list due to tumor progression or death.
From these 4 patients one patient died due to liver failure; the 3 remaining patients were removed from the waiting list owing to tumor progression with intrahepatic distant new HCC nodules.

Efficacy of combined treatment (TACE + RFA):

The efficacy was determined using contrast-enhanced CT or MR scans obtained 6-8 weeks and then every 3 months after combined locoregional therapy (Fig.1h).
In 99 of 120 lesions (82.5 %) and in 70 of 85 patients (82.3%) the first follow up using CT/MRI 6-8 weeks after combined treatment revealed complete response (CR). Lesion diameter at the time of treatment ranged from 0.7 to 6.0 cm (mean 2.5 cm (+/- 0.9 cm); median 2.5 cm). In 21 of 120 lesions (17.5%; patients n = 15) the follow up displayed a partial response (PR). In this subgroup the lesion diameter ranged from 0.7 to 5.0 cm (mean 2.8 cm (+/- 0.9 cm); median 2.5 cm). There was no statistical significant difference regarding the maximum diameter between groups.
When response was analyzed for patients who had a solitary HCC, CR was achieved in 51 of 56 (91%) lesions with a PR in the remaining 5 (9%) lesions. For the 64 lesions treated in our 29 patients with multifocal tumor, MRI indicated CR in 48/64 (75%) while

there was PR in 16/64 (25%). When analyzed, the difference in CR observed between the two groups (single lesion vs. multiple lesions) was significant ($p < 0.05$).

During follow-up (mean = 16 months, range 2 – 74 months) CR was maintained in 93/120 (77.5%) of the HCCs.

In lesions with a diameter <5 cm CR was maintained over time in 88/111 (79%) while 23/111(21%) showed PR. Among the 9 HCCs with a diameter ≥5cm only 5/9 (55%) revealed CR while 4/9 (45%) did show residual tumor. CR was maintained during follow-up in 44 out 56 HCCs in the 56 patients who initially presented with solitary HCC while in the 29 patients with multifocal disease CR was maintained only in 48 out of 64 HCCs.

Survival:

Overall survival

Survival curves were evaluated using the Kaplan-Meier method. The median survival rate for all patients, with calculation started on the date of RF-ablation, was 25.5 months (95%-CI: 23 to 35%) (fig. 2). The 1-, 2-, 3- and 5-year survival-rates were 84.6% (95%-CI: 77 to 92%), 58.7% (95%-CI: 48 to 69%), 37.6% (95%-CI: 27 to 48%) and 14.6% (95%-CI: 6 to 23%), respectively.

Prognostic value of BCLC stage

There was a statistically significant difference in the survival probability of patients with BCLC A (n = 52) and BCLC B (n = 20) patients (log-rank test, p = 0.0334) *(fig. 3)*. The median survival durations were 73.4 and 50.3 months for BCLC A and BCLC B patients, respectively.

Prognostic value of Child-Pugh score

There was no statistically significant difference in survival between patients with Child-Pugh A (n = 67) and Child-Pugh B (n = 5) liver cirrhosis (log-rank test, p = 0.92) *(fig. 4)*. The median survival duration was 73 months in Child-Pugh A patients. For the subgroup of Child-Pugh B, median survival was not calculated as the number of patients with Child-Pugh B (5) was limited.

Prognostic value of CLIP score

A separate Kaplan-Meier evaluation of patients with a CLIP score of 0 (n = 42) or 1 (n = 30) *(fig. 5)* revealed substantially different survival rates but failed to demonstrate statistical significance (log-rank test, p = 0.64). The median survival durations for patients with CLIP 0 and CLIP 1 were 73 and 49 months, respectively.

Prognostic value of tumor distribution

There was no statistically significant difference in the survival probability of patients with solitary (n = 48) and multifocal HCC (n = 24 patients) (log-rank test, p = 0.6318). *(fig. 6)*. The median survival durations were 73.4 and 59.3 months for patients with solitary and multifocal HCC, respectively.

2.5. Discussion

Since the rate of complete necrosis in RFA decreases as tumor size increases, combining RFA with therapies that occlude arterial supply or other local ablative therapy has been proposed and studied to increase the area of coagulative necrosis. Researchers hypothesized that blood flow occlusion in the tumor can decrease heat dispersion by the bloodstream, and increase the size of the necrotic area produced with ablation (Buscarini, Savoia et al. 2005; Clasen and Pereira 2007).

In this connection the question raises how TACE and RFA should be sequenced. The advantage of TACE prior to RFA is as previously mentioned the reduced heat sink effect with the ability to create larger ablation zones more easily. The advantage of using TACE after RFA is that RFA generates a hyperaemic rim surrounding the ablation areas, which then can consequently, be targeted by transarterial means more effectively. Further studies need to clarify how loco-regional treatment options should be implemented in the treatment paradigm of non-resectable HCC.

However the efficacy of the combined therapy with TACE-precede RFA has been shown in several previous studies.

In a study by Buscarini et al. involving 14 patients affected by HCC (mean diameter 5,2 cm) the efficacy of combined therapy consisting of RFA and TACE in treatment of HCCs larger than tumors suitable for segmental TACE or RF application alone was demonstrated (Buscarini, Buscarini et al. 1999).

In another study Lencioni et al. could show in a pilot multicentre clinical trial performed in 62 HCC patients treated by TACE and RFA a successful ablation of HCC lesions (ranging 3.5-8.5 cm) in 82 % of the cases (Lencioni, Cioni et al. 2001), which exactly matches the numbers we are reporting in this study.

Veltri et al. (Veltri, Moretto et al. 2006) demonstrated in a study in 46 unresectable, non-early HCC patients with a total of 51 lesions (30-80 mm, mean 48.9), complete responses in 66.7% of the lesions. In accordance with these previous studies we are reporting on a CR rate of 82.5 % of the treated HCCs. The difference to the CR rate reported by Veltri et al. may be contributed to the fact, that we also included patients with early HCC (BCLC), where effective tumor treatment might be easier to accomplish. Among other prognostic factors (pre-treatment of the lesions, lesion diameter) we investigated the influence of multifocality on the local result following combination therapy.

In our study the percentage of CR in solitary HCC (91%) is significantly higher than in multifocal tumors (75%).
Statistical analysis shows that HCC-lesions larger than 50 mm are more difficult to treat, as reported in literature (Livraghi, Goldberg et al. 2000; Dupuy and Goldberg 2001; Yamakado, Nakatsuka et al. 2002). However, due to the small number of HCCs larger then 5cm included in this analysis, final conclusions are difficult to derive. Anyhow, consistent with published results our statistical analysis further showed that during the follow-up CR was maintained in 79 % of lesions with diameter <5 cm whereas CR was maintained in the follow up in only 55% of lesions with diameter ≥5cm.
These results are well in line with previously published studies. With respect to lesion size, Rossi et al. reported a 90% positive outcome in 62 cirrhotic patients with HCC with a mean diameter of 47 mm (interval 35–85 mm) (Rossi, Garbagnati et al. 2000) treated with combined therapy. In another study Veltri et al. showed a CR in 85 % of patients with lesions < 5 cm (Veltri, Moretto et al. 2006).
Similar results to our study depicted a retrospective study by Kim, W.H .(Kim, Kim et al. 2011) with tumor progression rates of 16 % with TACE + RFA during a follow up time of 37 months in single small (< 3cm) HCC nodules.
Kim J.H. et al (Kim, Won et al. 2011) depicted in single intermediate-sized (3.1-5.0 cm) HCCs with a tumor progression rate of 40 % for TACE + RFA and 70 % of RFA alone also superiority in favour of the combined treatment approach.

Regarding clinical results, TACE is considered a mid-term effective therapy for non-operable HCC. The impact of this procedure on survival of patients with intermediate advanced HCC treated with combined therapy was evaluated in numerous retrospective and prospective studies as well as in meta-analyses which have shown promising results (Vetter, Wenger et al. 1991; Camma, Schepis et al. 2002).
However, a recent meta-analysis has suggested that there is no statistically significant difference in survival at 3 and 6 months between patients treated with this procedure and patients treated with other palliative procedures (Geschwind, Ramsey et al. 2003).
In our study the 1-, 2-, 3-, and 5-, year survival-rates were 84.6 %, 58.7%, 37.6% and 14.6 % respectively. Similarly, Veltri et al. demonstrated 1- and 2-year survival rates of 89.7% and 67.1 %, respectively (Veltri, Moretto et al. 2006).

In a study with 62 patients Kagawa et al. demonstrated that RFA combined with TACE is an efficient and safe treatment that provides overall survival rates similar to those achieved with surgical resection (Kagawa, Koizumi et al. 2010). These survival rates are higher than the survival rates presented in our study or in the study published by Veltri et al. This might be most likely contributed to a selection bias towards patients with smaller, fewer or anatomically favorable tumors. Furthermore differences in the cause of the underlying cirrhosis and tumor biology might impact on the patient's survival.

This is partly supported by the statistically significant difference between the median survival of patients with BCLC A (73.4 months) and patients with BCLC B (50.3 months) in our study, which amplifies the idea the early detection and treatment of the tumors will result in increased patient survival.

The comparably low overall survival reported in our study might be explained by the following issues: 16 patients with servere comorbidities were included in the study. Furthermore there is a selection bias against IR (Interventional Radiology) since only patients who have been rejected from surgery (coronary heart disease, COPD, second tumor) have been recruited for this multi-modality treatment approach.

In a recent retrospective study Kim, J.W. et al (Kim, Kim et al. 2011) compared the local efficacy and the overall survival of combined TACE and RFA vs. RFA alone in single small-sized (2-3 cm) HCC nodules. They depicted a favourable local tumor control with combined TACE and RFA with similar survival rates for either treatment approach.

The 1-, 3-, and 5-year overall survival rates in the TACE+RFA group were 93%, 72%, and 63%, respectively. The superiority of these reported data compared with our results may be contributed to the lower tumor burden (single HCC with diameter < 3cm) in that cohort.

Marelli L et al. (Marelli, Stigliano et al. 2006) showed in a meta-analysis involving 4 RCTs (randomized controlled trials) a significant decrease in mortality in patients with either small (< 3 cm) or large HCCs (>3 cm) treated with TACE plus percutaneous therapies (PEI (Percutaneous Ethanol Injection) or RFA) in comparison with a single modality approach consisting of TACE only.

Overall it remains unclear whether TACE plus RFA provides a survival benefit for patients with early-stage HCC especially in comparison with RFA as a single modality treatment.

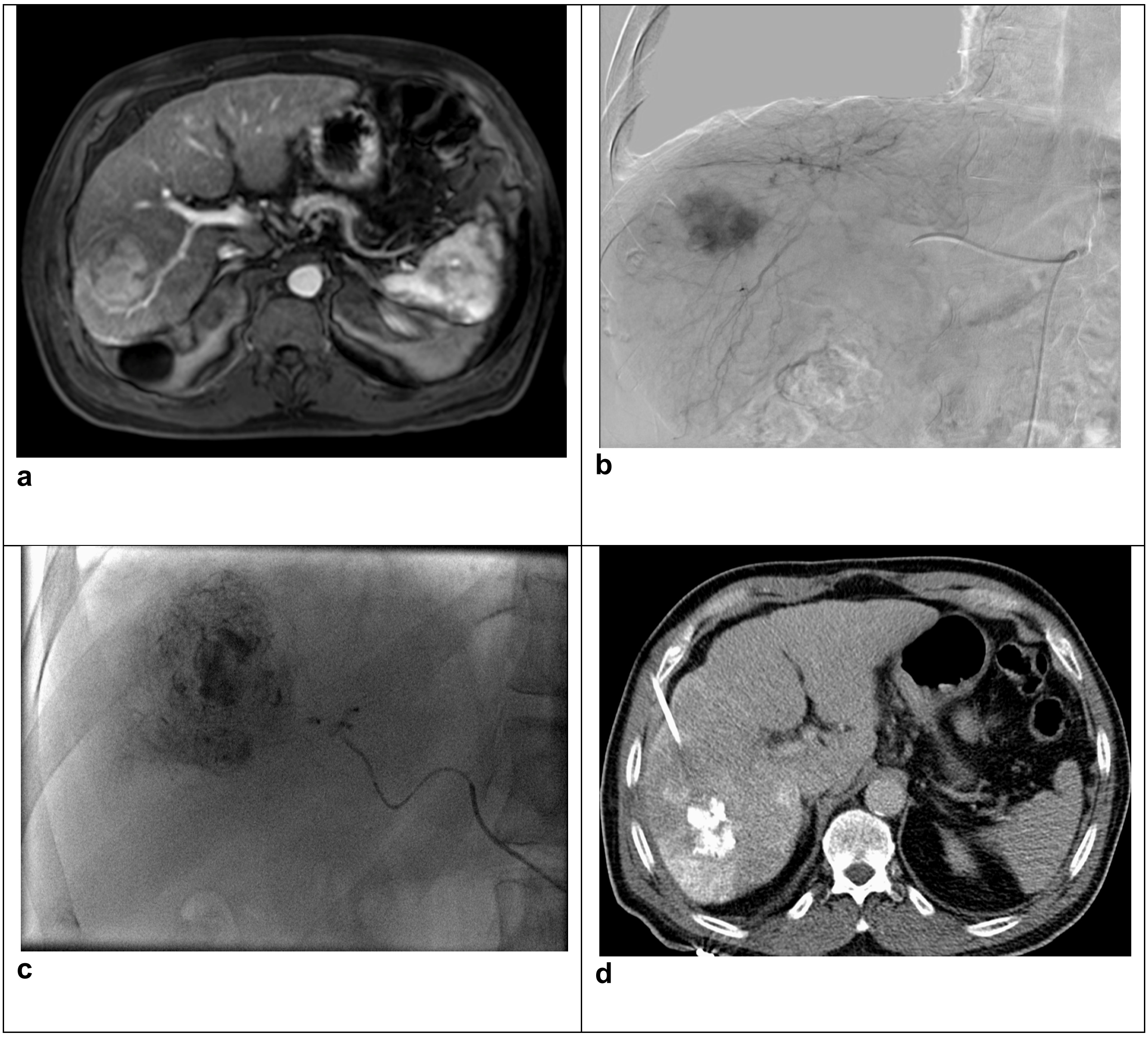
This view is encouraged by another recent study by Wang J H et al. (Wang, Wang et al. 2011) in which RFA and surgical resection were compared with regard to survival in BCLC 0 and BCLC A. The 3- and 5- year survival rates for early stage HCCs in this study were 73.5 and 57.4 months, respectively. These results are superior to our survival rates and comparable to the survival rates evaluated by Kim, J.W. et al(Kim, Won et al. 2011)

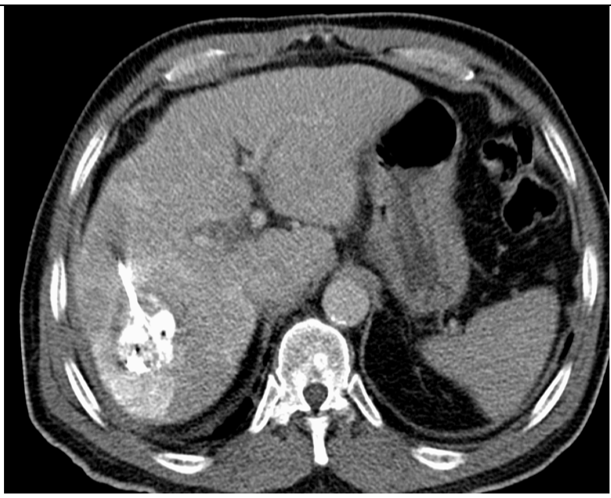
Conclusion

In this study we could demonstrate that the combined use of TACE and RFA in HCC patients provides an effective treatment approach with high local tumor control rates and promising survival data especially for BCLC A patients. Large-scale randomized trials are needed to compare this minimal invasive approach with surgical resection and to evaluate the local efficacy, the survival rate and the cost/benefit ratio. Regarding a potential survival benefit of TACE plus RFA in comparison with RFA alone larger multicenter trials are needed. Besides, the therapy sequence (TACE after RFA or RFA after TACE) and its benefit over other single modality treatment options should be verified in randomized controlled trials.

2.6. Figures and Tables

Figures 1 a-h





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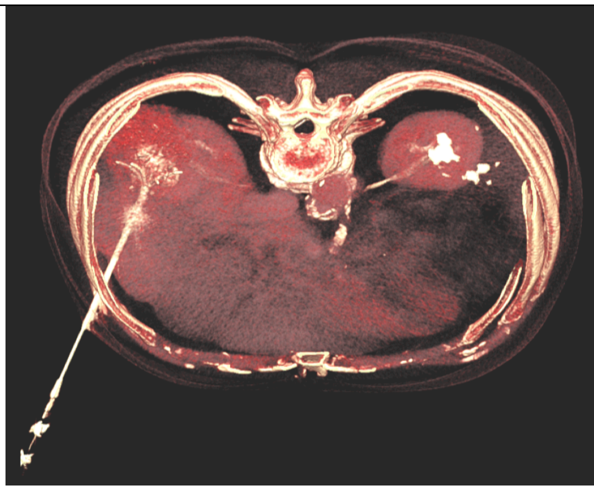

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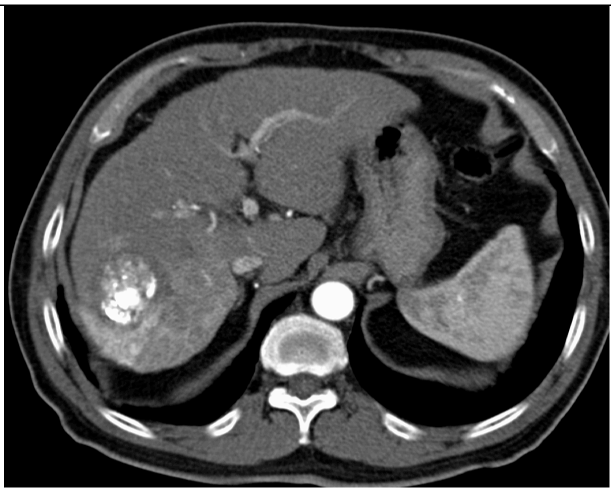

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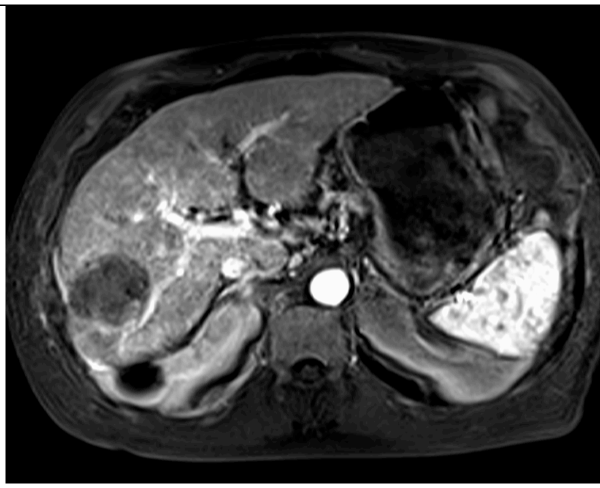

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Figure 2

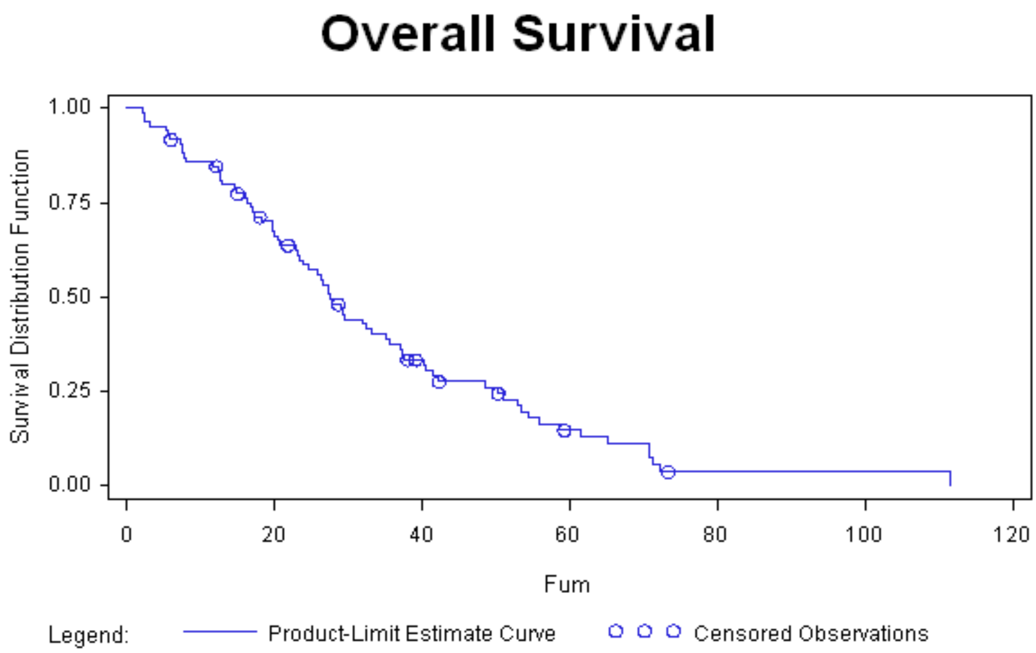
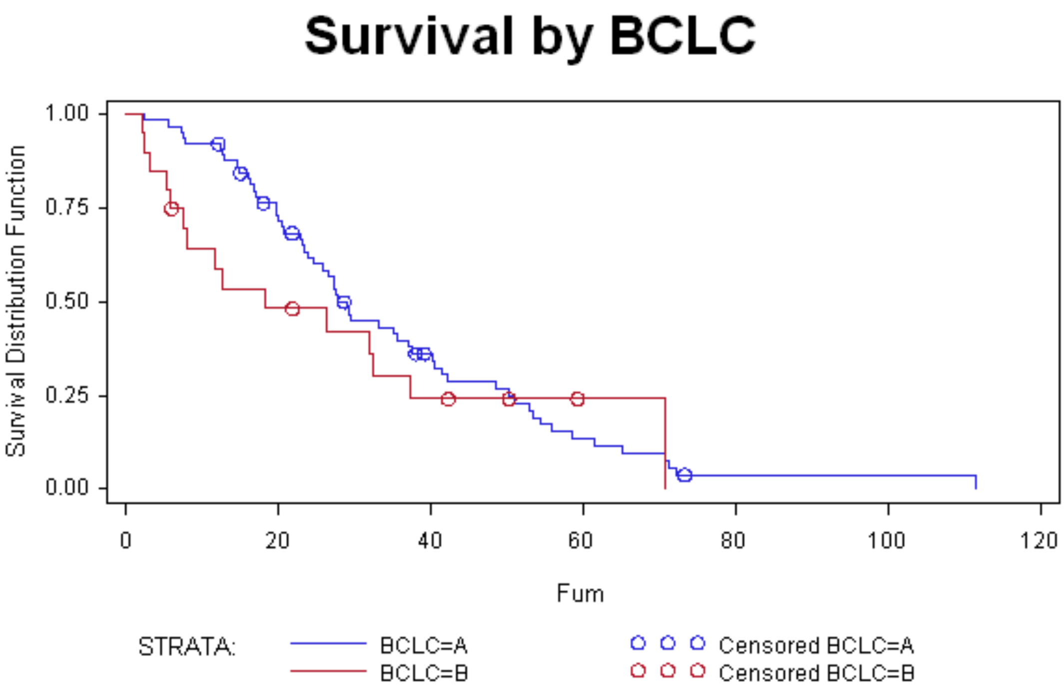

Overall Survival
1.00
0.75
0.50
0.25
0.00
Survival Distribution Function
0
20
40
60
80
100
120
Fum
Legend:
Product-Limit Estimate Curve
Censored Observations

Figure 3


Survival by BCLC
Survival Distribution Function
1.00
0.75
0.50
0.25
0.00
0
20
40
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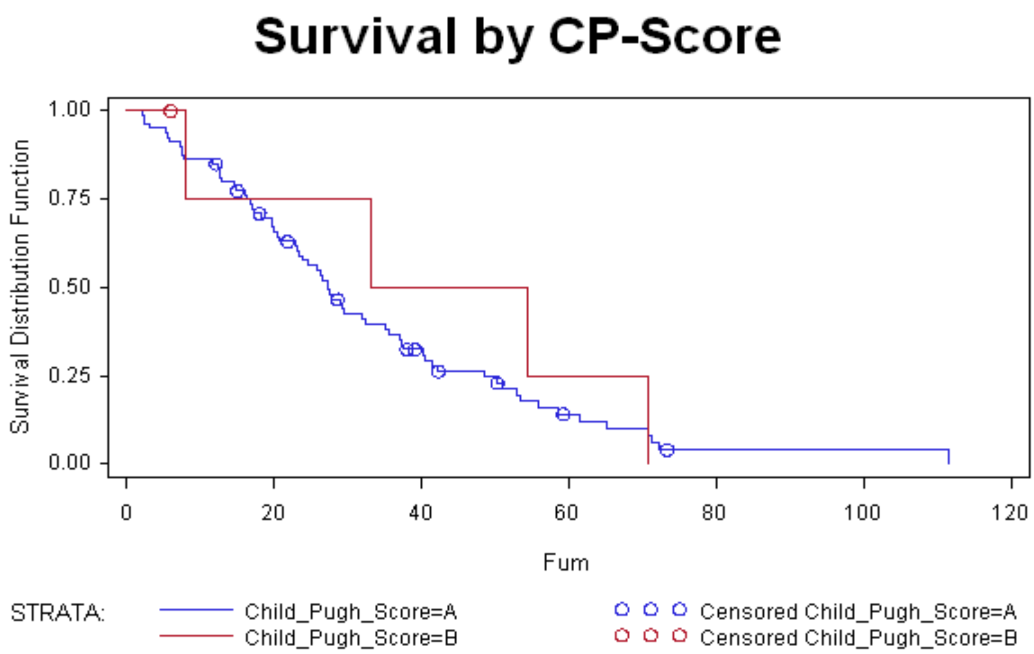
STRATA:
BCLC=A
BCLC=B
Censored BCLC=A
Censored BCLC=B

Figure 4


Survival by CP-Score
Survival Distribution Function
1.00
0.75
0.50
0.25
0.00
0
20
40
60
80
100
120
Fum
STRATA:
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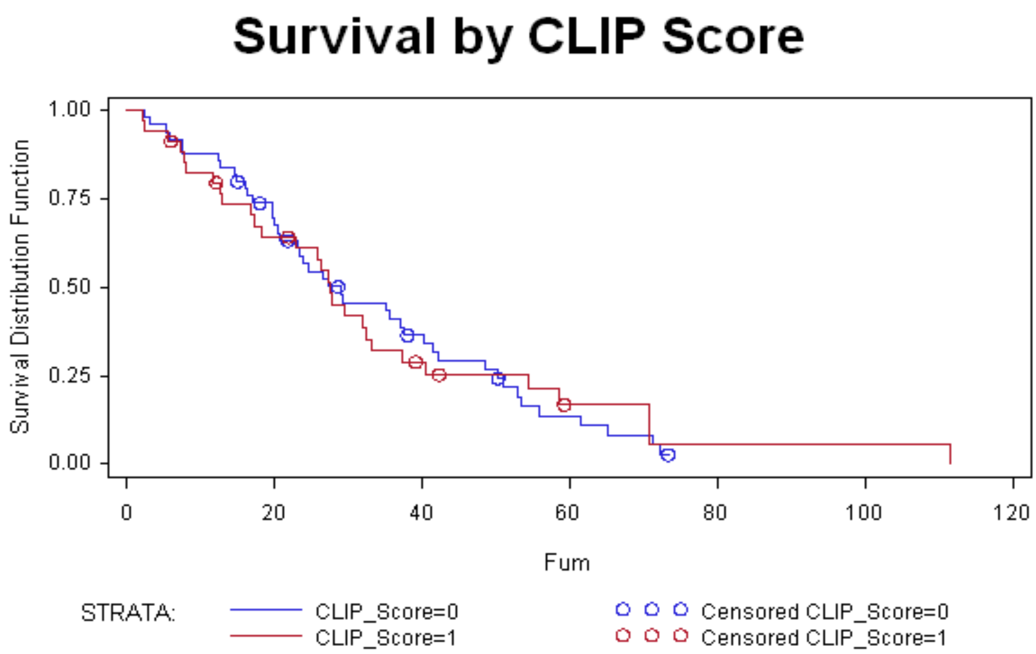
Censored Child_Pugh_Score=B

Figure 5


Survival by CLIP Score
Survival Distribution Function
1.00
0.75
0.50
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0.00
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20
40
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CLIP_Score=0
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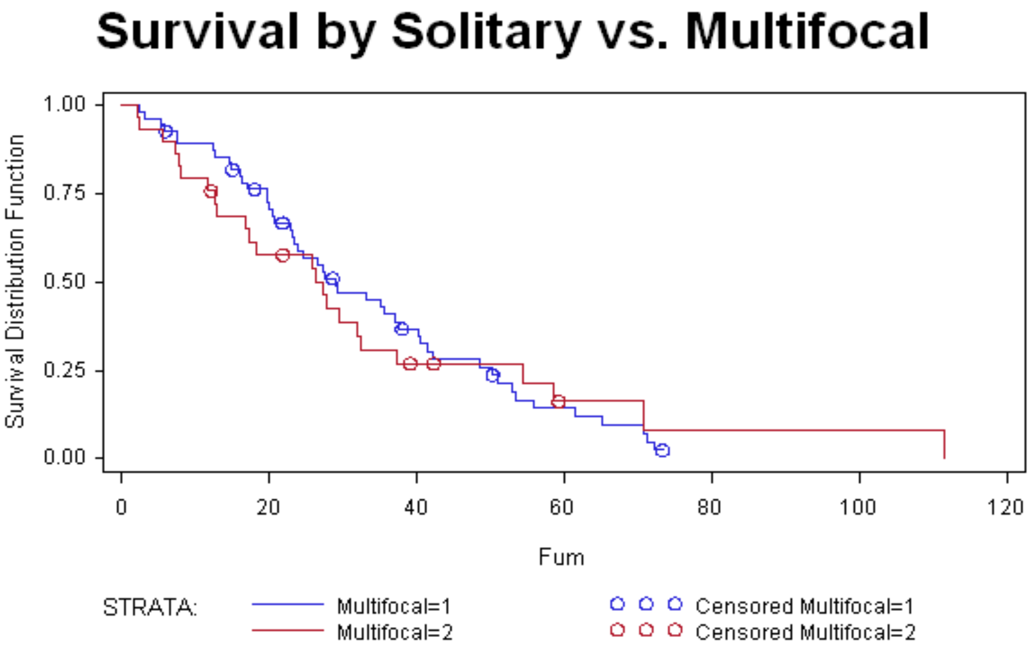
Figure 6



1 = solitary; 2 = multifocal

Table 1.

Patients' characteristics

patients	n = 85	
gender (male / female))	68/17	
age (year) [mean±SD]	65.9 +/- 9,1	
Child-Pugh score:		
class A	80	
class B	5	
BCLC		
stage A	65	
stage B	20	
CLIP		
score 0	50	
score 1	35	
tumor distribution (number of pts.)		
solitary	56	
multifocal	29	
number of tumors		
1	n = 56	(65.9%)
2	n = 17	(20%)
3	n = 9	(10.5%)
4	n = 2	(2.4%)
5	n = 1	(1.2%)
follow-up (months) [mean ± SD]	2 – 74	(22.5 +/- 14)
treated HCCs	120	
N/patient ± SD	1,4 ± 0,57	
lesions diameter mm (mean ± SD)	7 – 60 (25 ± 9)	
etiology of cirrhosis		
HCV	n = 34	
HBV	n = 8	
alcohol	n = 25	
others	n = 18	

BCLC indicates Barcelona Clinic Liver Cancer; CLIP, Cancer of Liver Italian Program; SD, standard deviation; HCV, hepatitis C virus; HBV, hepatitis B virus

2.7. Legends

Figs. 1a-f:

73-year-old patient with Hepatitis C induced liver cirrhosis and with a solitary HCC in liver segment 8. The contrast enhanced T1w GRE sequence reveals arterial enhancement of the HCC-lesion (a). Angiography before (b) and after (c) TACE. RFA after 2 days (d-f). First follow up 24 hours after RFA with heterogeneous uptake of iodized oil in the central aspect of the lesion surrounded by an ablation rim (g). Follow-up MRI after 6 weeks reveals CR without arterial contrast uptake within the lesion (h).

Fig. 2:

Kaplan-Meier survival curve after the combined therapy for all patients

Fig. 3:

Kaplan-Meier survival curve of patients with BCLC A and BCLC B HCC with a significant difference in the survival probability (p = 0.0334)

Fig. 4:

Kaplan-Meier survival curve depicts no statistically significant difference in survival between patients with Child-Pugh A and Child-Pugh B (liver cirrhosis (p = 0.92)

Fig. 5:

Kaplan-Meier survival curve of patients with a CLIP score of 0 and 1 without a statistically significance difference (p = 0.64)

Fig. 6:

Kaplan-Meier survival curve of patients with solitary and multifocal HCC failed to show a significant difference between the two groups (p = 0.6318)

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3.

Radioembolization of Symptomatic, Unresectable Neuroendocrine Hepatic Metastases using Yttrium-90 microspheres (Radioembolization of NETLMs)

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Radioembolization of Symptomatic, Unresectable Neuroendocrine Hepatic Metastases using Yttrium-90 microspheres (Radioembolization of NETLMs)

3.1. ABSTRACT

PURPOSE:

To evaluate safety, efficacy and symptom-control of radioembolization in patients with unresectable liver metastases from neuroendocrine tumors (NETLMs).

MATERIALS AND METHODS:

Forty-two patients with a mean age of 62 years and treatment-refractory NETLMs underwent radioembolization utilizing Yttrium-90 resin-microspheres. Post-treatment tumor response was assessed by cross-sectional imaging using the Response Evaluation Criteria in Solid Tumors (RECIST) and tumor marker levels. Laboratory/clinical toxicities and clinical symptoms were monitored.

RESULTS:

The median activity delivered was 1.63 GBq (range 0.63 – 2.36). Imaging follow-up using RECIST at 3 months follow-up demonstrated partial response, stable disease and progressive disease in 22.5%, 75.0% and 2.5%, respectively. In 97.5%, the liver lesions appeared hypovascular or partially necrotic. The mean follow-up was 16.2 months with 40 patients (95.2%) remaining alive. The median decrease in tumor marker levels at 3 months was 54.8% (Chromogranin A) and 37.3% (Serotonin), respectively. There were no acute or delayed toxicities according to the Common Terminology Criteria for Adverse Events (CTCAE v3.0) higher than grade 2. No radiation-induced liver disease was noted. Improvement of clinical symptoms 3 months post-treatment was observed in 36 of 38 symptomatic patients.

CONCLUSION:

Radioembolization with ^{90}Y-microspheres is a safe and effective treatment option in patients with otherwise treatment-refractory NETLMs. Anti-tumoral effect is supported

by good local tumor control, decrease in tumor marker levels and improvement of clinical symptoms. Further investigation is warranted to define the role of radioembolization in the treatment paradigm for NETLMs.

Key Words: radioembolization, neuroendocrine tumors, liver metastases, clinical symptoms, SIRT

3.2. Introduction

Neuroendocrine tumors (NETs) are an uncommon, heterogeneous group of different slow-growing, hormone-secreting malignancies. Carcinoid tumors constitute the major proportion of NETs.

The overall age-adjusted incidence rate for carcinoids is about 2 to 3 cases per 100,000 population per year, depending on age, gender, and race (Modlin and Sandor 1997; Oberg 2002). Patients appear to be younger than other patients with solid tumors; the average age of patients with NETs is 60 years.

Primary NETs can originate from any anatomic site, but most commonly develop in the midgut (small intestine and appendiceal carcinoids) which comprises 40% to 70% of all carcinoids (Oberg 2002; Akerstrom, Hellman et al. 2005). Although the diagnosis and treatment of primary gastroentero- pancreatic NETs has improved over the last decades, liver metastases (LMs) from NET (NETLMs) are common (Delcore and Friesen 1994). NETLMs are frequently responsible for symptoms due to hormone secretion resulting in carcinoid syndrome (diarrhea, flush, bronchoconstriction) pressure on structures or liver-replacement (Oberg 2002; Akerstrom, Hellman et al. 2005; Modlin, Kidd et al. 2005).

Survival of patients with NET is very heterogenous and although a mean 20% 5-year survival rate for patients with liver metastases has been described (Oberg 1999), prolonged survival (over 5 years) is reported in many series (Capurso, Bettini et al.). Aggressive local treatments in the liver have demonstrated improvements in both symptomatic control and survival but less than 10% of these patients have limited disease and are candidates for surgical treatment (Madoff, Gupta et al. 2006). Transarterial procedures such as embolization (TAE) and chemoembolization (TACE) have demonstrated improvements in symptomatic control and survival (Madoff, Gupta et al. 2006). However, effects are usually of short duration and optimal timing and sequence of these interventional procedures remains controversial due to high variability in the progression of these tumors (Ruszniewski and Malka 2000; Gupta, Johnson et al. 2005).

With the lack of effective chemotherapy for NETs, radioembolization is used to control, eradicate, or simply debulk hepatic metastases, often to palliate carcinoid syndrome or local pain from liver capsular stretching. However, further investigations are needed to determine the exact role of radioembolization with Yttrium-90 microspheres regarding the local anti-tumoral effect, tumor marker levels, clinical symptoms and survival. Intra-arterial non-radioactive liver treatments with and without concurrent chemotherapy have shown efficacy and safety in multiple small studies (Moertel, Johnson et al. 1994; Eriksson, Larsson et al. 1998; Ruszniewski and Malka 2000; Gupta, Johnson et al. 2005; Osborne, Zervos et al. 2006). Moreover, acute and subacute toxicities associated with radioembolization appear to be more tolerable than those associated with other hepatic embolization procedures (Gray, Van Hazel et al. 2001; Carr 2004; Murthy, Nunez et al. 2005).

The aim of this study was to evaluate the safety, efficacy and symptom-control of radioembolization in patients with unresectable liver metastases from neuroendocrine tumors (NETLMs).

3.3. Material and Methods

Patient selection:

Forty-two patients with liver metastasis from neuroendocrine tumors who were treated consecutively with yttrium-90 resin-microspheres were retrospectively analyzed.

Inclusion criteria were:

- non-resectable liver metastases
- absence of significant extrahepatic disease (patients with extrahepatic disease were only included in the presence of severe symptoms due to the tumor mass in the liver such as carcinoid syndrome or abdominal pain: in these patients the aim was to palliate symptoms by reducing the tumor mass in the liver)
- failure to respond to other types of medical, surgical or local ablative treatment modalities; Radioembolization is only used as last line therapy in our institute.
- a patent portal vein, adequate biochemical and hematological function, an arteriovenous shunting <20% to the lung vascular bed
- somatostatin receptor negative; Patients who have been on octreotride treatment in an earlier course of their disease did not show any more positivity in DOTA-TATE PET and also a progress of their NETLMs during their follow up. So at this point octreotride therapy was not regarded as a treatment option any more.
- written informed consent; Since this was not a prospective trial ethic committee was not involved. The institutional review board approved this retrospective analysis.

Radiation source:

Yttrium-90 (^{90}Y) is a pure-beta emitter that decays to stable zirconium-90 with an average energy of 0.94 MeV (half-life 2.67 days), with a mean tissue penetration of 2.5 mm and a maximum range of 11 mm. The principle is the preferential tumor-related vascular distribution of the radioactive microspheres, which allows delivery of high doses with relative sparing of normal liver tissue.

In this study, only ^{90}Y resin-microspheres (SIR-Spheres®, Sirtex Medical Limited, Lane Cove, Australia) were used. A standard dose of ^{90}Y resin-microspheres is 1.5 – 2 GBq, which contain approximately 35 million microspheres (range, 20–50 million), each microsphere containing 50 Bq activity.

Dosimetry:

The patients in this report were treated employing the body surface area method (BSA method) of activity calculation. The consensus report (Kennedy, Nag et al. 2007) recommended BSA as the most appropriate method to avoid the rare occurrence of radiation-induced liver disease, a late effect of excessive hepatic radiotherapy. To avoid overestimating the required activity by using the BSA method in patients after surgical resection we evaluated the tumor volume by using special software (OncoTreat®, Mevis®). Additionally prior radionuclide therapy is a very difficult issue because there are no common rules which ca be applied in this issues, usually this was a very individual decision depending on liver function and time from prior to next radioembolization. Naturally the dose was reduced between 20% and 30% in order to avoid radiation induced liver disease.

Radioembolization procedure

Arteriography for ^{90}Y-microsphere therapy planning is described elsewhere in detail (Salem and Thurston 2006; Jakobs, Hoffmann et al. 2007; Jakobs, Hoffmann et al. 2008). Therapy planning arteriography was performed via a transfemoral approach. The magnitude of hepato-pulmonary shunting and the presence of angiographically occult afferent extrahepatic arteries were evaluated by hepatic arterial injection of approximately 100 MBq technetium-99m macroaggregated albumin (^{99m}TC-MAA) in the left and right hepatic artery seperately. Vascular occlusion using microcoil embolization of the origins of extrahepatic arteries arising from the hepatic arteries was performed when deemed a potential avenue for extrahepatic deposition of microspheres. We recommend an aggressive occlusion of the vessels prior to radioembolization! We coil always the gastroduodenal artery (exception: Dunbar syndrome). Additionally we coil all arteries (if visible) originating from the hepatic arterial branches such as the falciform artery, cystic artery, arteries from the pancreaticoduodenal arcade or the right gastric artery (Paprottka, Jakobs et al.).

At a second hepatic arterial catheterization conducted separately after the therapy-planning arteriography, ^{90}Y resin-microspheres suspended in sterile water were injected under intermittent fluoroscopic visualization, alternating with contrast medium to assess for preserved antegrade hepatic arterial flow. ^{90}Y-microspheres activity was prescribed per the package, calculated according to the body surface area formula and administered as described elsewhere via either single-session, whole-liver or lobar treatment, according to the tumor burden (Jakobs, Hoffmann et al. 2007). If the patients received a lobar therapy they had only metastases within the treatment area. Patients with tumor burden of the whole liver achieved a single session (not sequential) whole liver treatment, from our point of view it is important to probe the left, right and sometimes segment IV hepatic artery and to perform the treatment separately. We do not perform radioembolization from the common hepatic artery. After delivery, single photon emission computed tomography (SPECT) scans were performed within 24h of therapy delivery to confirm target deposition of the therapeutic material.

Follow-up: Response, toxicity, clinical symptoms, survival

After treatment, tumor response was assessed by contrast enhanced computed tomography (CT) and magnetic resonance imaging (MRI) using the Response Evaluation Criteria in Solid Tumors (RECIST) (Duffaud and Therasse 2000).

Pre- and post-treatment laboratory tests included liver function tests, complete blood counts and tumor markers (Chromoganin A and Serotonin). Patients resumed a routine schedule of laboratory tests and imaging at 3-month intervals. Most recent history was taken for side effects; these data were converted to a toxicity score according to the Common Terminology Criteria for Adverse Events version 3.0.

Eventual improvement of clinical symptoms was analyzed during first follow-up by interviewing the patients regarding typical symptoms of neuroendocrine disease (flush, diarrhea, bronchoconstriction) and those quantitative data were compared to the baseline results; calling the referring physicians or the patients directly captured the survival, which was calculated using the Kaplan-Meier method.

Statistics

Comparison of medians was performed with the Mann-Whitney-Wilcoxon-U test and Friedmann test with significance accepted at $p<0.05$. SPSS 15.5 for Windows software (SPSS Inc.®) was used for data management and statistical analysis.

3.4. Results

Forty-two patients (12 female, 30 male) with a mean age of 62 years (range, 43 – 84 years) and treatment-refractory liver metastases from neuroendocrine tumors underwent radioembolization utilizing ^{90}Y resin-microspheres (Table 1). Only 4 of our 42 patients had a reduced performance status according to the ECOG Criteria. The most common primary tumor sites were small intestine (n = 23) and pancreas (n = 9). Histological evidence of NET was available for all patients.

Prior treatments included surgery in 38 patients, surgical resection of the primary tumor and liver metastasis, chemoembolization in 18 patients, systemic chemotherapy in 18 patients, interferon-therapy in 8 patients and octreotide therapy in 23 patients (Table 1).

Synchronous occurrence of liver metastases was detected in 34 patients while 8 patients presented with liver metastases later during their course of the disease. The median period from the date of disease-specific diagnosis and radioembolization was 27.4 months and the median time between first diagnosis of liver metastases and radioembolization was 23.6 months (Table 1).

The estimated percentage of hepato-pulmonary shunting on ^{99m}Tc-MAA scans was 5.6% (range, 1.9 – 11.2%). No patient had to abandon treatment because of extensive shunting of the microspheres into the lung.

The mean total activity of ^{90}Y resin-microspheres delivered was 1.63 GBq (range 0.63 – 2.36 GBq). The median dose of 1.63 GBq is so low because many of our patients achieved an atypical liver resection in the past, therefore we had to adjust the dose to the reduced liver volume. The percentage of the prescribed activity that was administered to patients was high with a median of 99.2% (mean 96.8%). A total of 50 treatment sessions were performed (Table 2), comprising 24 single-session, whole-liver administrations, 17 right lobar and 8 left lobar treatments. Six patients received 2 treatments and 1 patient received 3 treatments.

Contrast-enhanced axial CT and/or MRI images were available in 40 patients, 2 patients were lost to imaging follow-up. Imaging follow-up using RECIST-criteria at 3 months follow-up demonstrated partial response, stable disease and progressive disease in 22.5%, 75% and 2.5%, respectively. In 97.5% the liver lesions appeared centrally necrotic or hypovascular (Table 3/Figure 2).

The mean follow-up time was 16.2 months (median 12.9 months; range 2.8 – 50.1 months) with 40/42 patients still alive at the time of analysis. During follow-up, 8 patients showed progressive liver disease at 2.2, 2.3, 3.3, 9.2, 13.1, 20.7, 23.9 and 27.7 months. One patient with progressive liver metastases showed again a stable disease after re-treatment of the same liver volume for 17.7 months (until end of this study).

There were no acute or delayed toxicities according to the Common Terminology Criteria for Adverse Events higher than grade 2 (Table 4). No radiation-induced liver disease was noted.

The median decrease of tumor marker levels was 54.8% (Chromoganin A) and 37.3% (Serotonin), respectively (Figure 1). 38 of 42 patients showed tumor-related clinical symptoms before treatment. In 36 of 38 patients a significant improvement or disappearance of clinical symptoms was observed three months after treatment (Table 5).

3.5. Discussion

Liver metastases of NET are a negative prognostic factor indicating only 40% 5-year survival compared to 75% – 99% 5-year survival in non-hepatic colleagues reported that patients undergoing debulking of liver metastases had a mean survival of 216 months compared to a mean of only 48 months for those without surgery (Soreide, Berstad et al. 1992). Surgical intervention results in 5-year symptom-free survival rates of approximately 70% in selected patients, but is feasible in only a small minority of patients with hepatic metastases (Chen, Hardacre et al. 1998; Musunuru, Chen et al. 2006).

Therefore, aggressive local therapies have been extensively used to treat hepatic metastases from neuroendocrine tumors; embolization with/without chemotherapy (Therasse, Breittmayer et al. 1993; Moertel, Johnson et al. 1994; Brown, Koh et al. 1999; Kress, Wagner et al. 2003; Osborne, Zervos et al. 2006) and external beam radiotherapy (Gaitan-Gaitan, Rider et al. 1975; Keane, Rider et al. 1981; Samlowski, Eyre et al. 1986; Abrams, King et al. 1987; Schupak and Wallner 1991; Chakravarthy and Abrams 1995).

Hepatic transarterial embolization (TAE and HAE) has consistently provided symptomatic relief and increased survival in selected cases of NET liver metastases. The addition of single or multi-agent chemotherapy (hepatic transarterial chemoembolization - TACE and HACE) to embolization has also been shown to improve the quality of life and occasionally produce significant tumor-size reduction although there is no consensus as to whether the addition of chemotherapy is of benefit or not (Therasse, Breittmayer et al. 1993; Moertel, Johnson et al. 1994; Brown, Koh et al. 1999; Kress, Wagner et al. 2003; Osborne, Zervos et al. 2006).

In comparison to non-radioactive embolic therapy (TACE and TAE), radioembolization appear to provide a similar level of tumor response by imaging studies and symptomatic improvement (Safford, Coleman et al. 2004; McStay, Maudgil et al. 2005; Kennedy, Dezarn et al. 2008).

The results of our study demonstrate that radioembolization with ^{90}Y resin-microspheres is a safe and effective treatment option in patients with otherwise treatment-refractory liver metastases from neuroendocrine tumors. Anti-tumoral effect is supported by good local tumor control and significant decrease in tumor marker levels. There were no acute or delayed toxicities according to the Common Terminology Criteria for Adverse Events higher than grade 2 and no radiation-induced liver disease was noted. Moreover, acute and delayed toxicities associated with radioembolization appear to be better tolerated than those associated with other hepatic embolization procedures (Gray, Van Hazel et al. 2001; Carr 2004; Murthy, Nunez et al. 2005).

The response rates reported in this study are comparable to other previous studies using ^{90}Y-microspheres for the treatment of NET liver metastases (Coldwell and Sewell 2005; Kennedy, Dezarn et al. 2008; King, Quinn et al. 2008). Cao et al. (Cao, Yan et al.) could additionally achieve a durable complete response in six patients with NETLMs. Taking everything into account, this appears to be a reflection of lesser disease burden and earlier disease stages. However, most researchers are aware of the drawbacks of the RECIST and therefore we additional observed that most lesions (39/40 patients) appeared hypovascular and partially necrotic, which can also be regarded as a treatment success. A promising tool for the evaluation of LMs after radioembolizatin in the future could be the diffusion weighted imaging by MRI.

One patient with progressive liver metastases responded after re-treatment of the same liver volume and regained a stable disease response which lasted until the end of this study (17.7 months). In future, we are therefore going to evaluate closely the potential benefits and risks of re-treating patients who have progressed following an initial response to radioembolization.

At completion of this study, 40 of 42 patients remained alive after a mean follow-up of 16.2 months. Further investigation is warranted to determine the long-term survival benefits but it is known that patients with neuroendocrine tumors have a prolonged survival, which is connected with their tumor biology. Therefore an improvement of the health related quality of life is an important factor for these patients. 38 of our 42 patients were symptomatic, athough it is unusual that such a high proportion of patients is presenting with tumor symptoms this may represent a selection bias in our patient cohort. Since our earlier experience we know that especially symptomatic patients with NETLMs improve a lot from this treatment. In almost every case (94.7%), we observed a clinical improvement or disappearance of clinical symptoms 3 months after treatment. Using a not standardized evaluation form we asked for their symptoms before and after treatment and although it is not like an official quality of life document we consider this being a very important issue in this patients and valuable for mentioning in this manuscript.

To this day, surgical management of liver metastases has shown the greatest improvement in terms of survival and freedom from symptoms, which may be a reflection of reduced disease burden and earlier disease compared with non-surgical treatments (Que, Nagorney et al. 1995; Chen, Hardacre et al. 1998; Chamberlain, Canes et al. 2000; Nave, Mossinger et al. 2001; Yao, Talamonti et al. 2001; Norton and Kerlan 2003; Sarmiento and Que 2003; Norton 2005; Musunuru, Chen et al. 2006; Osborne, Zervos et al. 2006; Hibi, Sano et al. 2007; Reddy, Burroughs et al. 2007). Therefore an aggressive approach for treating liver metastases from NETs appears to be beneficial for patients and supports the use of local ablative therapies such as radioembolisation even at a later point in their disease. It needs to be taken into account that due to the small patient cohort and our study design the prognostic factors are limited. However, further studies need to define the role and time point of radioembolization in the treatment paradigm of NETLMs.

Conclusion

Radioembolization with ^{90}Y resin-microspheres is a safe and effective treatment option in patients with otherwise treatment-refractory liver metastases from neuroendocrine tumors. Anti-tumoral effect is supported by good local tumor control, decrease in tumor marker levels and improvement of clinical symptoms. Further investigation is warranted to define the role of radioembolization in the treatment paradigm of NETLMs.

3.6. Figures and Tables

Table 1: Patient baseline characteristics

All patients: n (%)	42	(100%)
Male	30	(71.4%)
Female	12	(28.6%)
Age, years: median (range)	62	(44 – 82)
ECOG performance status: median (range)	0	(0–2)
0	31	(73.8%)
1	7	(16.7%)
2	4	(9.5%)
Site of primary tumor: n (%)	42	(100%)
small intestine	23	(54.8%)
pancreas	9	(21.4%)
lung	1	(2.4%)
colon	5	(11.9%)
unknown	4	(9.5%)
Histology: n (%)	42	(100%)
Carcinoid	33	(78.6%)
Islet cell	6	(14.3%)
Insulinoma	2	(4.8%)
atypical	1	(2.4%)
Prior treatment: n (%)		
Surgery	38	(90.5%)
TACE	18	(42.9%)
Chemotherapy	18	(42.9%)
Interferon alpha	8	(19.0%)
Octreotide	23	(54.8%)
Radionuclide therapy (DOTA-TATE)	4	(9.5%)
RFA	3	(7.1%)
Radiation	2	(4.8%)
Percutaneous Ethanol Injection	2	(4.8%)
Surgery and sytemic therapy	36	(85.7%)
Surgery and TACE	12	(28.5 %)
Surgery, TACE and systemic therapy	12	(28.5 %)
Time from primary NET diagnosis to radioembolization, months		
Median (range)	27.4	(3.4 – 250.6)
Mean (Standard deviation)	51.1	(59.5)
Time from NETLM diagnosis to radioembolization, months		
Median (range)	23.6	(3 – 209.9)
Mean (Standard deviation)	40.9	(50)
Diagnosis of primary NET and NETLM: n (%)		
Metachronous	8	
Synchronous	34	
Tumor volume	n = 42	
< 25	8	19%
26 - 50%	28	67%
>50 %	6	14%

Table 2: Treatment characteristics

Hepato-pulmonary shunting, %	
Median (range)	5.58% (1.9 – 11.2%)
Target treatment volume; n (%)	
Right lobe	17 (40.5%)
Left lobe	8 (19.0%)
Whole liver	24 (57.1%)
Retreatment of target volume: n (%)	7 (16.7%)
2 treatments (median: 23.7 months/Min. 18.3 months/Max. 28.9 months)	6 (14.3%)
3 treatments (1. retreatment after 21.3 months, 2. retreatment after 14.8 months)	1 (2.4%)
Activity (^{90}Y) delivered: GBq	
Median (range)	1.57 (0.63 – 2.36)
Mean (Standard Deviation)	1.63 (0.49)
Percent of planned ^{90}Y delivered: %	
Median (range)	99.2% (76.9 – 108.3)
Mean (Standard Deviation)	96.8% (8.4%)

Table 3: Imaging follow-up using RECIST-criteria at 3 months follow-up

RECIST (3 months)	n=40
progressive disease	2,5 %
stable disease	75 %
partial response	22,5 %
complete remission	0 %

Table 4. Acute and delayed toxicities by Common Terminology Criteria for Adverse Events version 3.0..

	CTCAE Grade: n (%)			
	Grade 0	Grade 1	Grade 2	Grade >3
Fatique	26	12	4	0
Nausea	28	7	7	0
Abdominal pain	13	6	23	0
Vomiting	37	3	2	0
Diarrhea	41	1	0	0
Fever	18	18	6	0
Gastric ulcer	38	3	1	0

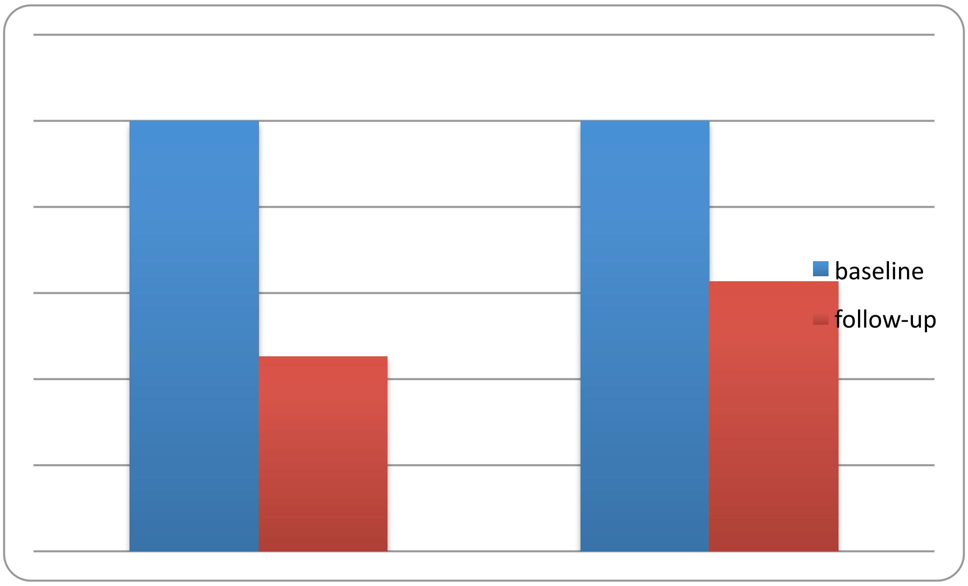
Table 5. Clinical symptoms

Clinical symptoms before radioembolization: n (%)	42	
Symptomatic	38	(90.5%)
Asymptomatic	4	(9.5%)
Clinical symptoms after radioembolization: n (%)	38	
Improved	36	(94.7%)
Unchanged	2	(5.3%)

Table 6: No significant (p > 0.5) changes of all listed laboratory data 3 months after radioembolization could be observed.

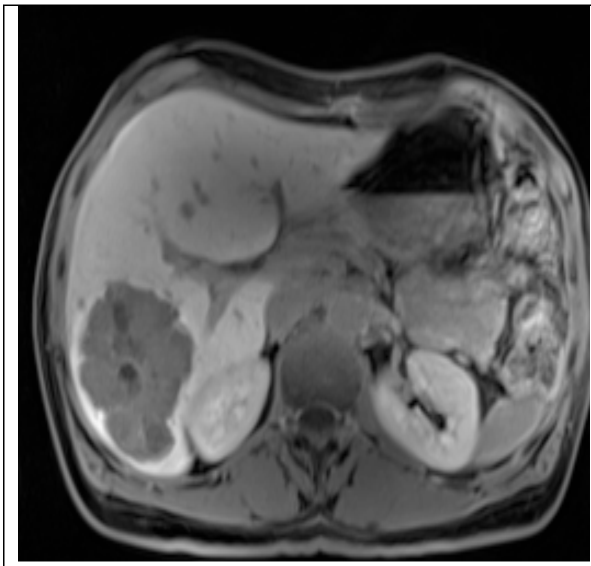
	Bilirubin mg/dl		**GOT U/l**	
	baseline	**follow-up**	**baseline**	**follow-up**
Median	0.6	0.7	34	52
SD	0.2	0.3	28	26
Min.	0.2	0.4	16	30
Max.	1.2	1.5	68	122
	GPT U/l		**alkaline phosphatase U/l**	
	baseline	**follow-up**	**baseline**	**follow-up**
Median	33	55	152	245
SD	23	26	96	85
Min.	12	9	58	128
Max.	140	114	441	449
	LDH U/l		**Gamma-glutamyl transpeptidase**	
	baseline	**follow-up**	**baseline**	**follow-up**
Median	216	209	158	354
SD	68	45	308	309
Min.	126	142	14	75
Max.	441	291	1292	1350
	Cholinesterase		**Whole Protein**	
	baseline	**follow-up**	**baseline**	**follow-up**
Median	7	6.8	7.2	7.2
SD	1.3	1	0.7	0.5
Min.	3.7	5.5	5.5	6.5
Max.	10	9.2	8	8.4

Figure 1:

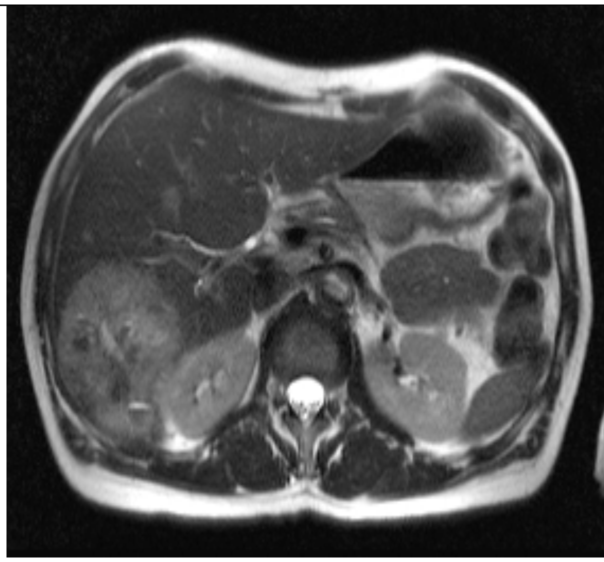


The median decrease of tumor marker levels was 54.8% (Chromoganin A) and 37.3% (Serotonin).

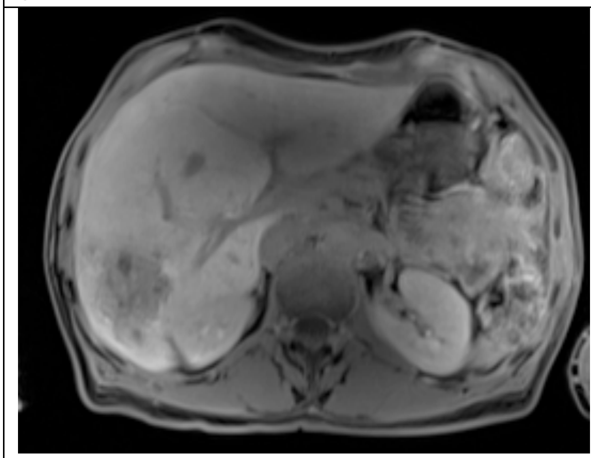
Figure 2:



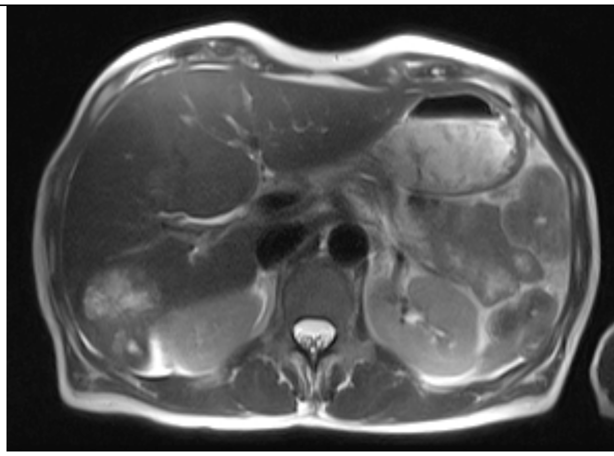
a



b



c



d

a + b) T1w 3D-GRE imaging with arterial contrast enhancement and HASTE-sequence of the liver, baseline scan. A hypervascular, centrally necrotic neuroendocrine tumor is depicted in the right liver lobe.

c+d) Follow-up scan after 3 months shows a significant decrease in size and vascularization after radioembolization.

Conflicts of Interest Notification:

Actual or potential conflicts of interest *do not exist*.

3.7. References

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Wissenschaftlicher Werdegang (Publikationen):

1. Severity Assessment of Pulmonary Embolism using Dual Energy CT – Correlation of a Pulmonary Perfusion Defect Score with Clinical and Morphological Parameters of Blood Oxygenation and Right Ventricular Failure (European Radiology)
   Thieme SF; Ashoori N; Sommer W; Reiser MF; Nikolaou K

2. 90Yttrium-Radioembolization of Chemotherapy-refractory Colorectal Cancer Liver Metastases (CVIR)
   Paprottka PM, Hoffmann RT, Ashoori N, Reiser MF, Jakobs TF

3. Multimodality HCC treatment with TACE and RFA for unresectable HCC (Digestion)
   Ashoori N, Paprottka PM, Reiser MF, Jakobs TF