Histopathologic Outcome of Neoadjuvant Image-Guided Therapy of Hepatocellular Carcinoma

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Abstract

Background and aims: The best curative treatment for hepatocellular carcinoma (HCC) is liver transplant (LT), with the limitation to either a solitary lesion < 5 cm or up to three lesions < 3 cm each. Arresting tumor growth or downstaging to make patients eligible for LT can be obtained by neoadjuvant treatments suchas transarterial chemoembolization (TACE), selective internal radiation therapy (SIRT), chemical or radiofrequency ablation (RFA). We evaluated the histopathologic response in explant specimens to neoadjuvant image-guided therapy of HCC prior to LT. **Methods:** Twenty-eight patients with 39 HCC nodules eligible for LT underwent neoadjuvant image-guided therapy 1-393 days prior to transplant. Treatment included TACE (5 nodules), SIRT (7 nodules), RFA (12 nodules), chemical ablation (3 nodules) combined TACE and acetic acid injection (1 nodule) and combined TACE and RFA (11 nodules). 19/28 patients not transplanted within 30 days had interval MRI and 3 patients with progressive disease were retreated. **Results:** Residual viable tumor was seen in 42% of patients with post-treatment imaging. Explant pathology revealed viable tumor in 35 of 39 (90%) treated nodules and somewhere in the explanted liver in all patients. Viability and/or progression of the treated tumor was noted in 5/5 nodules treated with TACE, 6/7 with SIRT, 11/12 with RFA, 2/3 with chemical ablation and 11/12 with combined treatment. **Conclusion:** Viable local or remote tumor was identified on explanted liver in the majority of patients with HCC after neoadjuvant therapy, despite apparent successful treatment on MRI.

Key words

Hepatocellular carcinoma – liver transplant – neoadjuvant treatment.

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Introduction

It is estimated that 1 million people die annually of hepatocellular carcinoma (HCC) worldwide [1]. The rising incidence of HCC in the United States is mostly attributed to the increasing hepatitis C (HCV) infection prevalence. Orthotopic liver transplantation (LT) has emerged as the best long-term treatment for patients with HCC, but eligibility is limited to patients meeting the Milan criteria (one nodule < 5 cm or no more than three nodules < 3 cm each) which limit the risk of tumor recurrence after LT [2]. The reported 5-year survival rates after LT for HCC have been consistently above 70% [3]. Tumor progression while waiting for a matching donor is the most common cause of drop-out of the transplant list [4, 5]. Neoadjuvant treatments intended to control the progression of HCC prior to LT include transarterial chemoembolization (TACE), selective internal radiation therapy (SIRT), radiofrequency ablation (RFA) and percutaneous injection therapy using either ethanol or acetic acid (PEI, PAI) [6, 7]. Although not curative, neoadjuvant therapy reduces the viable tumor volume and slows tumor progression [8, 9]. The purpose of our study was to evaluate the efficacy of NT of HCC on the pathologic examination of the explanted liver. Secondarily we assessed the accuracy of follow-up imaging on treatment response.

Subjects and methods

Twenty eight patients with HCC were treated with neoadjuvant therapy before LT at our institution between February 1996 and January 2004, for a total of 39 nodules. The mean age was 55.3 years (40 – 74) and male to female ratio was 6:1. Nineteen patients had solitary HCC, 5 patients had 2 nodules and 4 patients had 3 nodules. The Milan criteria were not respected for 4 patients: 1 patient with bifocal HCC with largest lesion measuring 4.8 cm and 3 patients with 3 nodules measuring 4.5, 4.9 and 6 cm, respectively.

The diagnosis of HCC was based on the presence of risk factors, suggestive imaging findings (arterial phase enhancing nodule(s) on CT or MRI), and elevated AFP > 400 ng/dl. The cause of HCC was: HCV infection in 19 patients, HBV infection in 3 patients, alcohol-induced cirrhosis in

2 patients, HBV/HCV cirrhosis in 1 patient, nonalcoholic steato-hepatitis in 1 patient and cryptogenic in 2 patients.

The decision to implement neoadjuvant therapy was made in a multidisciplinary liver tumor management conference. Patients listed for LT with at least one HCC nodule >2cm and an anticipated wait time of greater than 3 months were considered for neoadjuvant therapy. There was no formal protocol in place for pretransplant therapy strategy. The following algorithm for the treatment selection was usually respected: if there was a single lesion under 3 cm RFA was the only treatment given; if the lesion was between 3 and 5 cm, the patient had TACE followed by RFA. TACE was used alone in multifocal tumor and when tumor location was unsuited to percutaneous ablation. SIRT was used when TACE was contraindicated or per patient's choice. Chemical ablation was used if the lesion was seen on MRI only or if the lesion location was a high risk for thermal ablation (e.g. too close to the diaphragm). Repeat treatment was the interventional radiologist's discretion if either gross residual disease or new lesions were detected on follow-up imaging. Three patients had repeated treatment (TACE, PEI/PAI, SIRT). Minimal residual viable tumor on follow-up imaging was not an indication for re-treatment, since the goal of neoadjuvant therapy was to stabilize tumor size as a bridge to curative transplantation.

Transarterial chemoembolization was either lobar (for multiple lesions) or supraselective for solitary tumors. Eight patients had TACE followed the next day by RFA of the dominant lesion and one patient had TACE followed by PEI. The chemoembolization emulsion consisted of 100 mg of cisplatin (Bristol Myers Squibb, Princeton, NJ), 50 mg of doxorubicin (Adriamycin; Pharmacia-Upjohn, Kalamazoo, MI), and 10 mg of mitomycin C (Bedford Laboratories, Bedford, Ohio) dissolved in 10 mL of water-soluble contrast material emulsified with ethiodized oil (Ethiodol, Savage laboratories, Melville, NY). This was followed by 0.1–0.2 mL of 150–250-µm polyvinyl alcohol particles (Target Therapeutics, Fremont, CA), which were administered to reduce the arterial inflow to the tumor (pruned appearance on postembolization angiogram).

Selective internal radiation therapy was performed using selective lobar injection of Yttrium-90 glass microspheres (90Y-µS; TheraSphere, MDS Nordion, Ottawa, Canada) after test administration of 3.0 mCi of Tc-99m MAA with over 95% of the injected activity located to the liver. The administrated dose was calculated based upon the lobar volume to be treated, with a mean dose of 66.80 mCi/lobe.

Radiofrequency ablation was performed percutaneously under CT or ultrasound guidance or operatively using the Leveen probe (Radiotherapeutics, Boston Scientific, MA, USA) with overlapping ablations until impedance roll-off was achieved twice. The RITA (RITA Medical, Inc., Mountain View, CA) RF-probe was used in one patient with overlapping ablations for 15 minutes. Tract ablation was performed during needle removal in each patient.Chemical ablation was carried out under ultrasound, CT and MRI guidance using dehydrated ethanol (98%) or acetic acid (50%) with the amount based on the volume of tumor.

Follow-up was by clinical examination and contrast enhanced MRI at 1 and then every 3 months after the initial treatment. Contrast-enhanced, triple phase abdominal CT was performed in 1 patient. Follow-up imaging was reviewed for size and enhancement of the treated lesions and appearance of new lesions.

Transplantation and pathological examination of the explanted liver

The explanted livers were examined in a fresh state. The entire organ was sliced into parallel 1-cm thick sections. All nodules > 1 cm were sectioned in their entirety and examined microscopically by two hepatopathologists using H&E stains on paraffin-embedded tissue. The pathologic examination focused on the viability of the treated nodules, the existence of satellite nodules, lympho-vascular invasion and new lesions.

Follow-up was obtained from the transplant clinical notes. The mean follow-up after LT was 15 months (1 - 61 months).

Results

The pretreatment nodule characteristics by treatment allocation are shown in Table I.

The interval between the first treatment and transplant was 1-393 days (mean 99 days).

Tabel I. HCC size and number at initial imaging by treatment allocation

Treatment	Patients	Total Nodules	Solitary	Multifocal	Nodule size (cm)	Mean time to LT (days)
RFA	10	12	8	2	3.21 (2.2-4.8)	70 (6-193)
PEI/PAI	2	3	1	1	1.63 (1-2.4)	61.5 (25-98)
TACE+RFA	8	11	6	2	3.67 (1-5)	120 (3-393)
TACE+ PEI	1	1	1	0	4.8	58
TACE	3	5	1	2	3.04 (0.9-6)	98 (21-237)
SIRT	4	7	2	2	3.41 (1.1-4.9)	145 (1-334)
Total	28	39	19	9	3.14 (0.9-6)	99 (1-393)

RFA: radiofrequency ablation; PEI/PAI: percutaneous injection therapy using ethanol or acetic acid; TACE: transarterial chemoembolization; SIRT: selective internal radiation therapy

The mean size of the HCC nodules was 3.14 cm (0.9-6 cm).

Follow-up imaging

Nine of the 28 patients received LT within 30 days after treatment and had no follow-up imaging. Nineteen patients had follow-up imaging between 25 and 385 days after initial treatment. Persistent enhancement or increase in size of the tumor were seen in 13 of the 25 treated nodules (52%) in 8 patients (Table II). Six new nodules were identified. Eleven patients had no viable tumor detected on their final pre-transplant imaging.

Pathology results

In 35 of the 39 treated nodules (90%), viable residual tumor was seen (Table III). No patient was completely free of tumor. Viability and/or progression of the treated tumor was noted in 5/5 nodules treated with TACE, 6/7 with SIRT, 11/12 with RFA, 2/3 with chemical ablation and 11/12 with combined treatment.

Correlation between follow-up imaging and pathology

The mean time interval between the last follow-up imaging and LT was 28 days (1-149). Imaging for 25 treated HCC nodules demonstrated 12 (48%) nodules with complete necrosis. Pathology identified 2 of these lesions as totally necrotic. The positive predictive value of imaging for complete necrosis was 18%. If we include the nodules with >90% necrosis (n=6), the positive predictive value becomes 54%. Imaging missed 10 new lesions with a mean size of 1.1 cm.

Specific outcomes by treatment modality

TACE: 3 patients with a total of 5 nodules were treated with TACE. Pathologic examination revealed 90-95% central necrosis of the initially treated nodules in all three patients. One patient had lympho-vascular invasion and 4 satellite nodules despite 95% necrotic tumor nodule. One patient had 90% necrosis of the main nodule but 8 satellite nodules and tumor thrombus extending in the left portal vein. This was not recognized on imaging performed 2 weeks before LT. This patient did not meet the Milan criteria. Posttransplant, he had HCC recurrence and expired 35 months after the LT.

TACE and RFA: 8 patients (11 nodules) were treated with chemoembolization followed the next day by RFA. Only 1/8 patients had 100 % necrosis of the treated tumor (consistent with the MRI finding) but had 4 new lesions. 5 patients treated for solitary HCC had 90-98% necrosis, no lymphovascular invasion or satellite nodules (Fig. 1). Two of them appeared 100% necrotic on MRI. Two of the three patients with multifocal disease had 20% and 100% viable tumor and 60%, 100% and 100% viable HCC respectively with lymphovascular invasion and multiple satellite nodules. The findings were consistent with the imaging results.

RFA: 10 patients (12 HCC nodules) were treated with RFA, 7 percutaneous and 3 operative ablations. Pathologic examination of the liver revealed viable tumor in all but one treated nodules with 50-100% necrosis (mean of 72%). The percentage of necrosis in the 4 patients with apparently complete necrosis on follow-up MRI ranged between 75 - 95%. Five new lesions in 3 patients were identified at pathological examination, none of which was seen on follow-up imaging.

Chemical ablation: One patient was treated with selective right hepatic artery TACE followed by acetic acid ablation, 35 days later. Chemical ablation was favored over RFA because of the subdiaphragmatic location, in proximity of the heart. The patient was transplanted 21 days after ablation. Pathologic examination of the liver revealed 95% necrosis but with microscopic invasion of the diaphragm.

Two patients with small (<2.5 cm) solitary HCCs were

Table II. Follow-up imaging by treatment allocation

Treatment	Patients	Nodules treated	Residual viable tumor nodules	No viable tumor nodules	New nodules
RFA	6	7	2	5	0
PEI/PAI	2	2	1	1	1
TACE	2	4	3	1	3
TACE+RFA	7	10	7	3	1
SIRT*	2	2	0	2	1
Total	19	25	13	12	6

* One new nodule was diagnosed in 1 patient and retreated with SIRT
For abbreviations see Table I.

Table III. Pathologic examination findings.

Treatment	Patients	Nodules	Nodule size (cm)	Necrosis			HCC with satellites	Lympho-vascular invasion	New nodules
				100%	90-99%	<90%			
RFA	10	12	3.41 (2.1-6)	1	5	6	2	1	5
PEI/PAI	2	3	2.33 (2-2.5)	1	1	1	0	0	1
TACE+RFA	8	11	4.15 (1-6)*	1	6	4	1	1	7
TACE+PEI*	1	1	4.5	0	1	0	0	1	0
TACE**	3	5	3.6 (1-6.5)	0	5	0	2	2	2
SIRT	4	7	3.25 (1-4.9)	1	0	6	1	0	1
Total	28	39	3.56 (1-6)	4	18	17	6	5	16

* One patient had invasion of the diaphragm and pleural metastasis;** One patient had portal vein invasion, not diagnosed on imaging. For abbrevations see Table I.

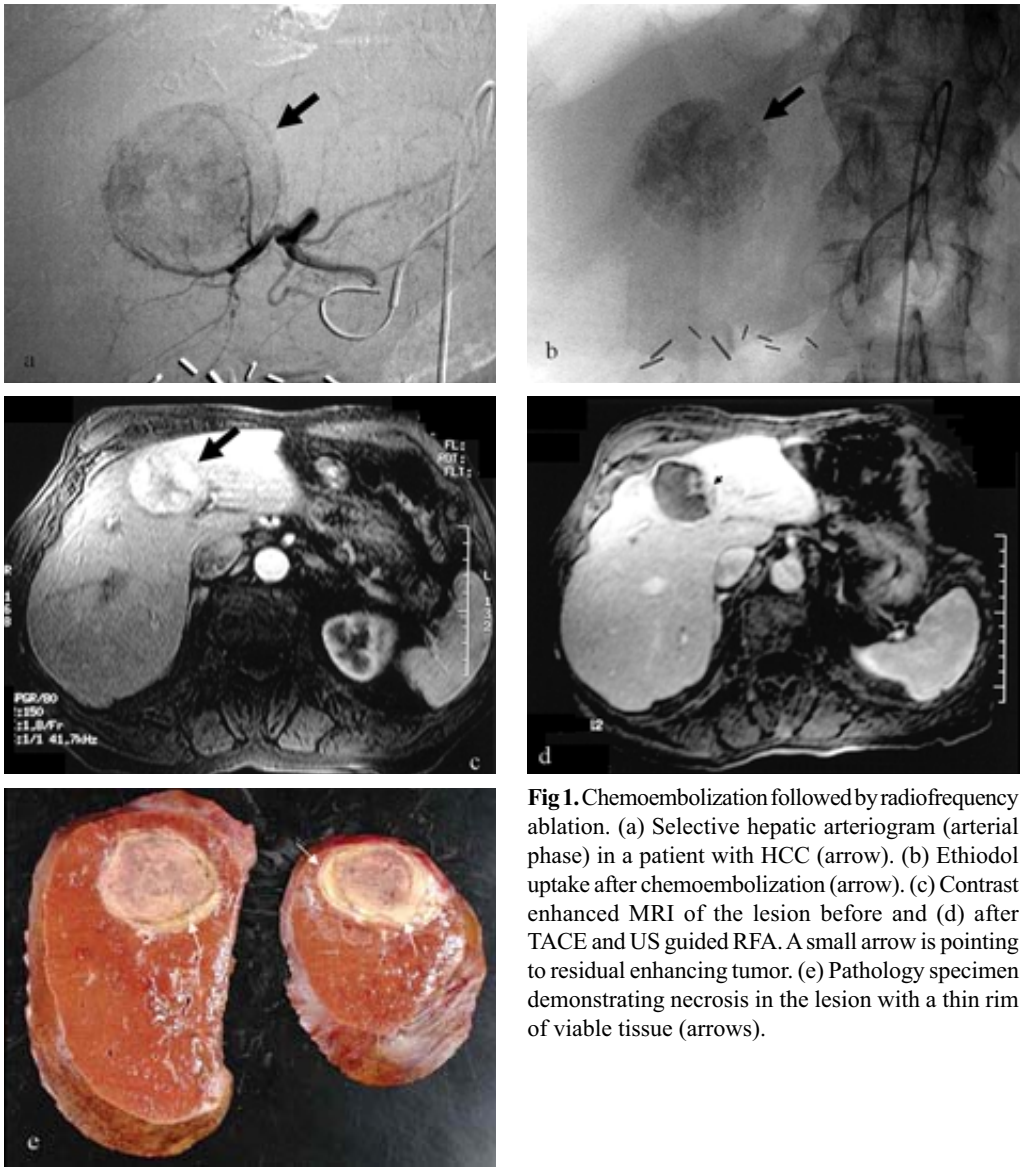

Fig 1. Chemoembolization followed by radiofrequency ablation. (a) Selective hepatic arteriogram (arterial phase) in a patient with HCC (arrow). (b) Ethiodol uptake after chemoembolization (arrow). (c) Contrast enhanced MRI of the lesion before and (d) after TACE and US guided RFA. A small arrow is pointing to residual enhancing tumor. (e) Pathology specimen demonstrating necrosis in the lesion with a thin rim of viable tissue (arrows).

treated with PEI/PAI respectively. RFA was not available for the first patient (treated in 1996) and chemical ablation was used in the second patient because the lesion was only seen on MRI. At follow-up imaging, one patient had no enhancement, while the second patient had residual peripheral enhancement and appearance of a second lesion. The initial lesion was retreated with PAI and the new lesion was treated with PEI. For the first patient, pathologic examination of the liver revealed intra-tumoral hemorrhagic necrosis, no lymphovascular invasion or satellite tumor, and a 1 cm new HCC was found. For the second patient, the explant pathology showed peripheral viable tissue (90% necrosis) (Fig. 2), complete ablation of the second lesion and appearance of a third, undiagnosed 3.5 cm lesion.

Selective intra-arterial radiation therapy (SIRT): 4 patients (6 HCC nodules) were treated with Y90 TheraSpheres. Pathologic examination revealed viable tumor (100%) in 6 treated nodules (Fig. 3) and complete fibrosis of one nodule.

Survival

Recurrence-free post transplant survival was 24/28 patients (85%) with a mean follow-up of 15 months. All 4 patients with recurrent disease posttransplantation did not meet Milan criteria at baseline.

Discussion

Liver transplantation is the best curative treatment for HCC, because in addition to tumor removal, it removes the liver tissue with multifocal HCC potential. The efficacy of a timely transplantation in cases of tumors respecting the Milan criteria has been proven by several authors [2, 10-13]. Survival data from United Network for Organ Sharing (UNOS) for patients transplanted for malignant liver pathology showed a three year survival rate of 70%, compared to a survival of 78.3% for other indications [3]. The timeframe to transplantation is a major prognostic factor for HCC patients. The waiting time to transplantation has

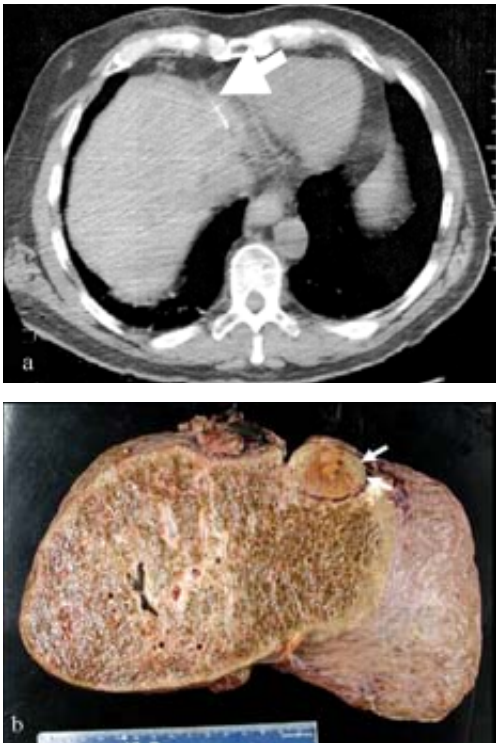

Fig 2. (a) Percutaneous ethanol injection of a 2.5 cm subcapsular HCC (large arrow) under CT guidance. (b) Pathologic specimen showing a crescent of viable tumor (small arrows).

progressively increased because of a relative donor shortage. Drop-out rates because of tumor progression >20% have recently been reported [14, 15]. The Model for End-stage Liver Disease (MELD) system for allocation of organs by UNOS is assigning a priority score for patients with small HCC so that timely liver transplantation can be performed for these patients. In the recent years, waiting time for patients with HCC has lengthened because of a change in the level of priority [4, 16].

Drop-out from the transplant list correlates with the length of waiting time and initial tumor characteristics [17]. It also decreases overall survival of LT for HCC on an intention to treat analysis [18].

Neoadjuvant treatment has a bridging effect by delaying tumor progression, with the intent of decreasing drop out from the LT list. This benefit is most evident at intermediate wait times, between 4 and 12 months, and is the practice at our institution for patients listed with HCC >2cm whose waiting time is expected to exceed 3 months.

Analysis of the explants permits a detailed histopathologic analysis of tumor response to the various image-guided therapies, radiologic-pathologic correlation among patients with interval imaging, and assessment of the prevalence of viable occult HCC nodules among pre-treated patients.

Transarterial chemoembolization is the most common modality used in patients awaiting LT, with low complication rate [19, 20] and without increasing risk of hepatic artery thrombosis after transplantation [21]. Although necrosis rate in the literature is 56-100% [22-24], there is a chance of heterotopic recurrence even in cases with complete necrosis. TACE downstages the main tumor and treats the satellite micro-metastases reducing the risk of post-transplant tumor recurrence. Neoadjuvant TACE was proven to prolong recurrence free survival in patients with large tumors (>5 cm), if significant tumor volume reduction was achieved, compared to patients who did not respond to TACE [25, 26]. There are also negative reports regarding the impact of TACE on the course of HCC. Partial tumor necrosis was found to

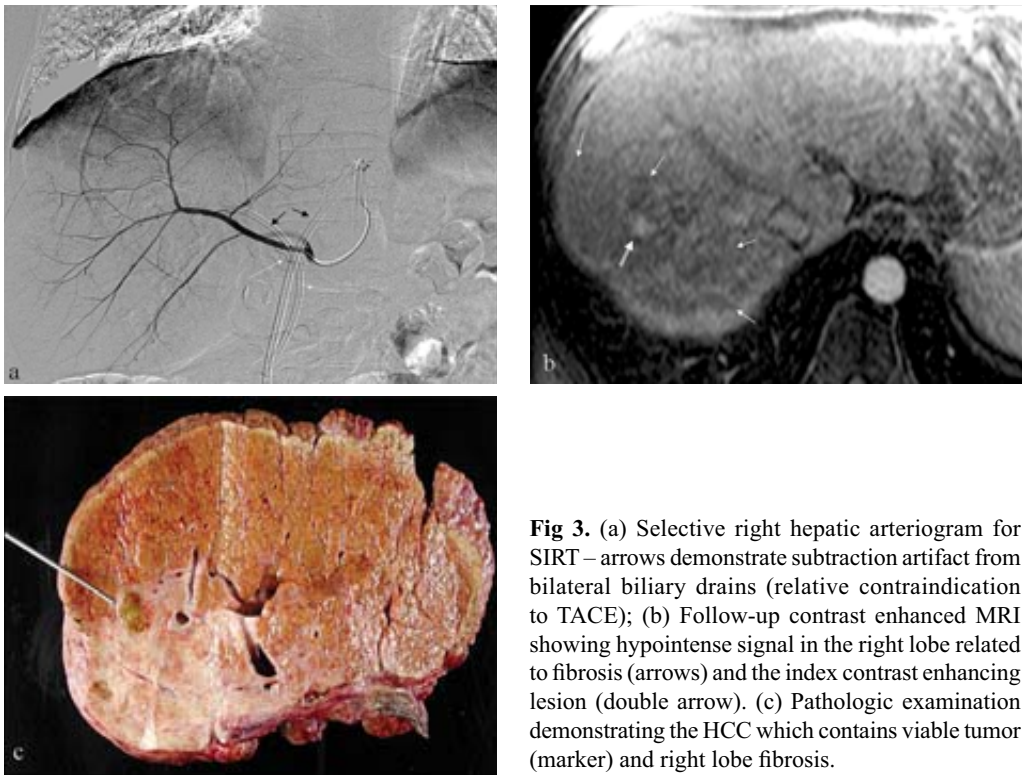

Fig 3. (a) Selective right hepatic arteriogram for SIRT – arrows demonstrate subtraction artifact from bilateral biliary drains (relative contraindication to TACE); (b) Follow-up contrast enhanced MRI showing hypointense signal in the right lobe related to fibrosis (arrows) and the index contrast enhancing lesion (double arrow). (c) Pathologic examination demonstrating the HCC which contains viable tumor (marker) and right lobe fibrosis.

predict HCC recurrence after LT [27] and also to increase the incidence of pulmonary metastasis [28]. In our study, 3 patients were treated with TACE, resulting in > 90% tumor necrosis on pathology. One patient developed lung metastasis posttransplant and one patient had tumor recurrence in the transplanted liver.

Selective internal radiation therapy involves selective arterial lobar administration of radioisotopes such as Y90 microspheres (TheraSphere) to the tumor. SIRT is better tolerated than TACE in cases of severe liver failure [29]. Follow-up imaging in SIRT was reported to have a higher accuracy in identifying viable HCC compared to TACE because of the absence of the confounding effect of Ethiodol or particle embolization [30]. Total treatment response was incorrectly identified by MRI in 1 out of 2 patients similar with a previous report suggesting radiologic-pathologic discordance [31]. SIRT was reported to have a 47% objective tumor response [29]. Although, to date several thousands of HCC patients have been treated with SIRT, there is little data on SIRT used as neoadjuvant pre LT treatment. A report by Kulik et al. [31] included 8 patients who underwent LT after TheraSphere treatment, with complete necrosis in 62.5%. In our study, four patients treated with SIRT had very good tumor control (decrease in size, no lymphovascular invasion or satellite nodules) despite viable tumor in 6 of 7 nodules.

Chemical ablation is the oldest and least expensive ablation method [32]. Results are best for lesions < 3 cm in size and above 5 cm, the local failure rate is high [33, 34]. Successful chemical ablation creates an area of necrosis larger than the index lesion, therefore arterial phase imaging is essential for follow-up. In our patients treated with ethanol/acid acetic injection, for lesions < 3cm, 95% necrosis was obtained which is similar to the literature data. One patient with a subcapsular 4.5 cm lesion, subdiaphragmatic, treated with combined TACE and PEI demonstrated invasion of the diaphragm at the time of LT, despite 90% tumor necrosis.

RFA is a more recent technique which uses focal heat deposition to cause coagulative necrosis. It can be used percutaneously or intraoperatively. Results are directly related to tumor size. The rate of complete necrosis for HCCs < 5 cm treated by RFA before LT has been reported to range between 13% and 43% [7, 12, 33-36]. Better results are reported in the same series for lesions less than 3 cm (complete necrosis found in 50%-78% of the treated nodules).

Follow-up imaging can be challenging because of the presence of perilesional inflammatory reaction mimicking a tumor [37]. In our 10 patients who underwent RFA, mean tumor necrosis was 72%.

Tumor seeding along the needle trajectory [38, 39] is a potential complication of percutaneous ablative techniques in the pretransplant setting. None of our 21 percutaneously RFA patients demonstrated new HCC lesions along the needle tract. This can be related to a thorough tract ablation.

A combination of transarterial and percutaneous ablation treatments acts synergistically on the index tumor, with a theoretical advantage of double targeting. The hypothesis is that by combining TACE with ablation, local ischemia created by TACE increases the vulnerability of the tumor cells to direct chemical or thermal effect of the ablation. Also, arterial embolization reduces the heat sink effect and increases the efficacy of RFA. The combination of TACE + RFA was our treatment of choice for tumors >3 cm.

The effectiveness of imaging techniques to identify residual or recurrent tumor is limited. Follow-up arterial phased MRI overestimated total necrosis in 82% of treated nodules. Also follow-up imaging had a sensitivity of 44% for detecting new nodules.

Our study evaluated treatment efficacy of various interventional neoadjuvant treatment methods in obtaining tumor control by using a gold standard endpoint of pathologic analysis of the explanted liver. Overall, regardless of the treatment method, residual viable HCC in the index nodule was identified in 90% of the treated lesions. Also, none of the 28 treated patients was free of tumor in the explanted liver because of microvascular invasion, satellite nodules or new nodules. Complete necrosis was defined as total absence of viable neoplastic cells on the explant specimen. Our results are similar to other histopathological correlation studies [24, 40]. The frequency of residual viable tumor was surprising, particularly among nodules treated with thermal ablation which is generally thought to be effective as a single modality in up to 80% of HCC nodules under 2.5 cm. One contributing factor in our analysis is that all treated nodules were sectioned in their entirety for histologic analysis; thus any microscopic nest of viable cells would be detected. Prior reports of explant analysis did not section nodules in their entirety, but sampled "suspicious" areas [40], and thus may have underestimated the prevalence of incomplete tumor necrosis. Another clinical factor in our series is that the intent of image-guided therapy was neoadjuvant to curative surgery, and not as primary therapy. Thus the goal was stabilization of tumor growth to maintain Milan criteria until the time of liver transplantation, and hence could be less aggressive than when the intention of treatment is 100% tumor kill. Minimal residual viable tumor on post-treatment imaging was an acceptable endpoint among listed patients; the risk of a secondary procedure was not justified when a curative transplant was anticipated. Nonetheless, the universal presence of viable tumor nodules somewhere in every explant is an instructive lesson regarding the limitation of image-guided therapies in the treatment of HCC, and of the inability of conventional imaging to accurately assess tumor response or to detect small HCC nodules.

The efficacy of neoadjuvant treatments remains to be proven. One study [15] has shown an increase of survival of patients with up to 6.5 cm lesions 85.9% compared with the literature control group (51%). We had 4 patients who did not meet the Milan criteria on initial evaluation. All 4 patients had multifocal HCC on explant pathology and developed recurrent HCC, which supports the finding by Millong et al. [26] that LT in patients with tumor burden beyond the Milan criteria have higher rates of recurrent HCC regardless of the

response to neoadjuvant therapy.

There is controversy regarding the utility of the neoadjuvant therapy in patients for whom the waiting period is less than 6 months [41]. At our institution, patients were referred for treatment after multidisciplinary review at time of transplant listing, with a mean waiting time of 80 days and only 5/28 patients stayed over 6 months on the transplant list. If gross residual or recurrent tumor was identified on follow-up imaging, the patient was retreated at the discretion of the primary interventional radiologist.

There are limitations of our study which is retrospective, single center, with a small sample size and no control group. Follow-up imaging was not available in all patients to identify residual lesions. The small number of patients in each group and the absence of a control group did not allow statistical analysis of individual neoadjuvant treatments.

Conclusions

Although locoregional therapy has proved to be effective in HCC progression control while waiting transplantation, viable residual tumor or remote tumors were identified in all patients. This does not preclude successful liver transplantation. Contrast imaging examinations have a tendency of underestimating the viable tumor component of the treated lesions and can omit new tumor sites.

Conflicts of interest

The authors have no conflicts to disclose.

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