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# **Surgical resection versus transarterial chemoembolization followed by moderately hypofractionated radiotherapy in hepatocellular carcinoma**

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# Surgical resection versus transarterial chemoembolization followed by moderately hypofractionated radiotherapy in hepatocellular carcinoma

## Abstract

**Aims:** Transarterial chemoembolization (TACE) is the gold-standard treatment in intermediate hepatocellular carcinoma (HCC), but long-term disease control remains low. Herein, we compared results of TACE followed by hypofractionated radiotherapy (TACE-hRT) to surgical resection (SR) in early single or paucinodular intra-hepatic HCC.

**Methods:** Between June 2004 and November 2016, data on 160 consecutive patients with **Barcelona Clinic Liver Cancer (BCLC) stage A** Child-Pugh A HCC treated with SR or TACE-hRT in our expert center were retrospectively reviewed. Time-to-progression (TTP), progression-free survival (PFS) and overall survival (OS) were evaluated. Clinical outcomes were compared using stabilized weights inverse probability of treatment weighting propensity score.

**Results:** Ninety-eight patients underwent SR and 62 were treated by TACE-hRT. Median total dose of RT was 54 Gy (IQR 54-54), 3 Gy fractions. **Median OS follow-up was 93 months.** TTP did not significantly differ with 1-year rates of 68.2% and 82.6% (**p=0.17**) **between patients following SR and TACE-hRT, respectively.** In contrast, PFS and OS were lower in TACE-hRT group (p=0.015 and p=0.006) **with a median OS time being 37 vs 63 months for patients having surgery vs TACE-hRT, respectively. In multivariate analysis, a significant negative impact on PFS and OS was seen for age at diagnosis, on TTP for alcohol-related liver disease, and on OS for total number of HCC nodules.** Symptomatic grade  $\geq 3$  adverse events were presented by 42 (42.9%) **SR** and 19 (30.6%) **TACE-hRT** patients (p=0.17).

**Conclusion:** In patients presenting Child-Pugh A BCLC-A HCC who are merely fit for surgery, TACE-hRT can be an effective and safe treatment. However, surgical management remains the standard of care whenever possible.

Keywords: hepatocellular carcinoma; transarterial chemoembolization; hypofractionated  
radiotherapy; SBRT; surgical resection; propensity score

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## Introduction

Hepatocellular carcinoma (HCC) is the sixth most common neoplasia and the third cause of cancer-related death worldwide [1]. Orthotopic liver transplantation (OLT), surgical resection (SR) and thermoablations are the standard of care as potential curative options according to **European Association for the Study of the Liver (EASL)** [2] and **American Association for the Study of Liver Diseases (AASLD)** guidelines [3]. Unfortunately, a substantial proportion of patients with **Barcelona Clinic Liver Cancer (BCLC) stage A** early HCC (20-40%) are ineligible to these curative options at diagnosis (tumor localization/size, comorbidities, or both) [4]. Thus, transarterial chemoembolization (TACE) becomes gold-standard therapeutic option. Since this treatment modality has low long-term disease control [5], various therapeutic combinations were evaluated [6].

Recent meta-analyses reported improved OS when combining TACE with conventional radiotherapy (RT) [6,7]. Furthermore, others reported that TACE combined with moderately hypofractionated radiotherapy (TACE-hRT) improved time-to-progression (TTP), progression-free survival (PFS) and OS compared to palliative sorafenib with macroscopic vascular invasion [8]. This combination of local treatments is a valuable option, achieving median OS of 55 weeks [8], but has never been compared to surgery. **We aimed to deliver an accelerated hRT to prevent tumor repopulation and limit overall treatment time in these comorbid patients, with an intermediate equivalent dose in 2-Gy fraction (EQD2, alpha/beta=10) near 60 Gy. Nevertheless, since first line systemic treatment included anti-angiogenic targeted therapies, we avoided highly hypofractionation and decided to deliver 54 Gy in 3Gy-fraction.** In the present study, we assessed efficacy and safety of TACE-hRT in single or paucinodular HCC, comparing its clinical outcome to SR and taking into account the expected prognostic discrepancies between these populations.

## Materials and Methods

### *Study population*

We retrospectively analyzed data of patients treated for HCC with TACE followed by RT or elective SR in our expert center between June 2004 and November 2016. Inclusion criteria were: 18 years or older; BCLC stage A HCC with a single nodule or 2- 3 adjacent lesions; Child-Pugh class A if cirrhosis; histologic or cytologic proven diagnosis of HCC and/or

1 noninvasive CT- or MRI-based diagnosed HCC using AASLD criteria; absence of truncular or  
2 lobar portal vein invasion, or suprahepatic vein invasion. Exclusion criteria were: transplanted  
3 liver; previous liver irradiation; BCLC stage B, C or D; Child-Pugh class B or C cirrhosis;  
4 patients previously treated for HCC with systemic therapy, or with a history of surgical  
5 resection in the previous 2 years.  
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Therapeutic decision was always taken during a weekly HCC multidisciplinary tumor board including onco-hepatologists, hepatobiliary and transplant surgeons, radiation oncologists and interventional radiologists. Standard treatment of localized HCC was surgical resection, thermoablations or OLT. However, patients with predictable high risk for surgical complication presenting BCLC-A HCC and good liver functions (Child-Pugh A), and ineligible for thermoablation due to tumor size/localization, were devoted to being treated by TACE-hRT.

Processing of personal data was performed according to French reference methodology n°004 (MR-004) of the Informatic and Liberties National Commission (CNIL). The requirement for written informed consent was waived. The study protocol was reviewed and approved by the institutional local ethics committee, and performed in accordance with the 1975 Helsinki declaration.

### *Transarterial chemoembolization*

Femoral arterial catheterization was performed using the Seldinger technique under local anesthesia. A baseline angiography of superior mesenteric artery, coeliac trunk and hepatic artery was performed to map out tumor arterial supply. A microcatheter of 2.4- to 2.8-Fr was then selectively or hyperselectively inserted to inject doxorubicin-loaded beads (DC Beads®; BTG, Farnham, United Kingdom) or an emulsion of 50 mg of doxorubicin and 10 mL Lipiodol, under fluoroscopic monitoring, and subsequent embolization performed with mixed absorbable gelatin sponge (Curaspon®; Cura Medical, Amsterdam, The Netherlands). Only one single TACE course was performed.

### *Irradiation technique*

Radiation therapy was delivered by a linear accelerator (Clinac®, Novalis Tx® or Truebeam®; Varian, Palo Alto, CA) 1 to 3 weeks after the TACE. Planning computed tomography (CT) was performed with 2-5mm slice thickness with patient immobilized in head-

1 first supine position, **using BlueBAG vacuum cushion® (ELEKTA, Stockholm, Sweden).**  
2 To consider tumor motion, acquisition was made in both expiratory and inspiratory breath hold  
3 until 2008, and a 4D-CT in free breathing with 10 respiratory phases reconstruction was  
4 performed since 2009. Images were transferred to a computerized treatment planning system  
5 (Eclipse®; Varian, Palo Alto, CA).  
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9 The gross tumor volume (GTV) was outlined on each respiratory phase on the  
10 simulation CT, based on the lipiodol tumor uptake and pretreatment MRI **after manual rigid**  
11 **registration. No IV contrast agent was used during simulation CT.** The internal target  
12 volume (ITV) was generated by combining the individual GTVs. Target volumes were outlined  
13 by an experienced radiation oncologist and reviewed by an experienced radiologist before  
14 validation. ITV-to-planning target volume (PTV) margin range was 5 to 15mm. **These**  
15 **variations accounted** for setup **uncertainties (3D vs 4D CBCT)**, delineation uncertainties  
16 **(available pre-treatment MRI or not)**, and tumor motion **(10-phase ITV vs few patients**  
17 **treated without motion management). Fiducial placement was avoided as TACE included**  
18 **a radio-opaque agent.** Total dose and fractionation were 54-60 Gy and 3Gy/fraction,  
19 respectively, **prescribed on 95% isodose.** Patients were treated 5 fractions a week, with a daily  
20 pretreatment cone-beam computed tomography (CBCT) to correct translational setup errors.  
21 Radiation schedule was independent of cirrhotic status or severity, but lower total dose of 45-  
22 51 Gy was considered if **normal liver parenchyma V27Gy was >33% or if its Dmean was**  
23 **>25Gy.**  
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### 37 *Surgical resection*

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39 The surgical resection technique has been described elsewhere [9]. In brief, all SR  
40 procedures were performed by a highly experienced hepatobiliary surgeon under low central  
41 venous pressure by open or laparoscopic approach. Depending on size and location of the  
42 lesion, and on the severity of underlying liver disease, an anatomical- or wedge-resection was  
43 performed. A safety margin of 2 cm was expected except for lesions locating near sus-hepatic  
44 veins or Glisson's pedicles.  
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### 51 *Follow-up*

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53 Follow-up was performed 1 month after completion of radiotherapy or surgery, then  
54 every 3 months (first two years), then every 4 months (3 years), and every 6 months thereafter.  
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1 It included clinical evaluation, liver function testing, serum alpha-foetoprotein (AFP) level,  
2 and liver CT or MRI.

### 3 4 *Outcomes*

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7 Survival outcomes were evaluated from the day of the first TACE or the SR, and  
8 included TTP, PFS and OS. TTP was calculated up to local or distant progression **according**  
9 **to modified Response Evaluation Criteria in Solid Tumors (mRECIST)**. PFS was  
10 calculated up to local or distant progression, or death from any cause.  
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### 14 15 *Statistical analyses*

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18 Categorical variables were expressed as counts and percentages, and continuous  
19 variables were expressed as median and interquartile range (IQR). Comparisons between the  
20 two groups were performed using Chi2 test or Fisher's exact test for categorical variables and  
21 using Student *t* test or Mann-Whitney test for continuous variables.  
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26 We performed an inverse probability of treatment weighting (IPTW) propensity score  
27 to reduce selection and confusion biases, and used stabilized weights to maintain an appropriate  
28 type I error rate [10]. The propensity score was calculated using a multivariable logistic  
29 regression model with allocation of SR as the endpoint. We included in the model in a non-  
30 parsimonious manner all variables that could possibly influence treatment assignment or  
31 outcome: age, sex, pretreatment AFP, platelet count, serum albumin, prothrombin time, tumor  
32 size, number of nodules, number of previous treatments, presence of cirrhosis, portal  
33 hypertension, history of myocardial infarction, of cerebrovascular accident or transient  
34 ischemic attack, chronic obstructive pulmonary disease, peptic ulcer disease, and end-organ  
35 damage diabetes mellitus.  
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45 Median follow-up was determined using the reverse Kaplan Meier method. Survival  
46 rates were estimated using the Kaplan Meier method for both unadjusted and stabilized IPTW-  
47 adjusted cohorts. Survival curves were compared using the log-rank test. Variables with a *p*  
48 value <0.30 in univariable analysis were entered in a multivariable Cox model to identify  
49 independent variables associated with TTP, PFS and OS. All tests were two-sided and a *p*-  
50 value < 0.05 was considered significant.  
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56 Adverse events were graded according to National Cancer Institute Common  
57 Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0 for acute toxicity  
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1 occurring before or during month-4, and late toxicity (after month-5). Statistical analysis was  
2 performed using R version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria).  
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## 4 **Results**

### 5 *Patient characteristics*

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10 Between 2004 and 2016, 160 consecutive patients treated for a BLCLC-A HCC by  
11 TACE-hRT (n=62) or SR (n=98) were **prospectively identified, and data were**  
12 **retrospectively collected. In TACE-hRT group, one patient withdrew his consent and was**  
13 **excluded, and two included patients received normofractionated RT because of**  
14 **duodenum proximity.** Patient characteristics are shown in Table 1. A surgical resection was  
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16 performed on younger patients (p=0.002), with a lower age-adjusted Charlson Comorbidity  
17 Index (p<0.001), who presented larger size lesions (p<0.001). Patients receiving TACE and  
18 RT had lower platelet count (p<0.001) with 27.9% (n=17) under 100G/L, lower prothrombin  
19 time (p<0.001), and a more severe cirrhosis with portal hypertension (p<0.001) and Child-Pugh  
20 score A6 (p=0.003). The IPTW propensity score was accurate with an area under the curve of  
21 0.911 (95%CI 0.87-0.95).  
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### 31 *Treatment characteristics – TACE and hypofractionated radiotherapy*

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34 In the unadjusted TACE-hRT cohort, anticancer agent in TACE was doxorubicin or  
35 drug-eluting beads in 48 (77.4%) and 14 (22.5%) patients, respectively. The median time  
36 between TACE and RT was 17 days (IQR 14-21). Median RT dose was 54 Gy (IQR 54-54), 3  
37 Gy fractions (IQR 3-3) in 27 days (IQR 25-28). Patients were treated using 3D conformational  
38 RT (3DCRT), intensity-modulated radiotherapy (IMRT) or volumetric modulated arc-therapy  
39 (VMAT) in 41 (67.2%), 14 (23%) and 6 (9.8%) cases, respectively (**typical dose distribution**  
40 **in Fig. 1**). Median uninvolved liver, defined as total liver minus PTV, was 1514 cc (IQR 1248-  
41 1805).  
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### 49 *Treatment characteristics – Surgical resection*

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52 In the unadjusted surgical resection cohort, major ( $\geq 3$  segments) and minor anatomical  
53 resection were performed in 47 (47.4%) and 44 (44.4%) patients. Among the 12 non-  
54 anatomical resections, 4 were associated with an anatomical one. Surgery was performed by  
55 open approach, laparoscopic approach and laparoscopy converted to open approach in 87  
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1 (87.9%), 9 (9.1%) and 3 (3.0%) patients. Six (6.1%) patients had microscopic incomplete  
2 resection (R1), and none had macroscopic incomplete (R2) resection.  
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#### 4 *Time-to-progression*

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7 **The median follow-up of TTP was 63 months (IQR 36-87).** In adjusted cohort, there  
8 was no significant difference in TTP between TACE-hRT and SR groups in univariable  
9 (p=0.17) nor multivariable analysis (p=0.28). One- and 5-year TTP were 82.6% and 5.2% in  
10 TACE-hRT group, and 68.2% and 30.7% in SR group (see Fig.2). Median TTP were 23 and  
11 22 months, respectively. In univariable analysis, TTP was significantly lowered by presence of  
12 alcohol-related liver disease (ALD) and thrombocytopenia, as shown in Table 2. In  
13 multivariable analysis, only ALD remains significantly correlated to TTP, as shown in Table  
14 3. In an *a posteriori* comparison, tumor size was not different between ALD and non-ALD  
15 groups (p=0.33).  
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#### 24 *Progression-free survival*

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27 **The median follow-up of PFS was 81 months (IQR 55-121).** In adjusted cohorts, PFS  
28 was significantly higher in SR group than in TACE-hRT group with 2-year PFS of 43.9% and  
29 32.2% (HR=1.65; 95%CI 1.1-2.5; p=0.015) (see Fig.3). This difference remains significant in  
30 multivariable analysis with hazard ratio of 1.55 (95%CI 1.02-2.35; p=0.04). In univariable  
31 analysis, PFS was significantly related to age, pretreatment serum albumin, ALD and  
32 thrombocytopenia, as shown in Table 2. Age and ALD remained significantly correlated to  
33 PFS in multivariable analysis, as shown in Table 3.  
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#### 41 *Overall survival*

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44 **The median follow-up of OS was 93 months (IQR 66-132).** In adjusted cohorts, 1-  
45 and 5-year OS were 88.2% and 17% in TACE-hRT group, and 91.9% and 50.7% in SR group,  
46 respectively (HR=2.65; 95%CI 1.7-4.2; p<0.0001) (see Fig.4). Median OS were 37 and 63  
47 months, respectively. In multivariable analysis, difference remains significant with hazard ratio  
48 of HR=2.33 (95%CI 1.45-3.74; p<0.001). In univariable analysis, OS was significantly related  
49 to age, pretreatment serum albumin, ALD, thrombocytopenia and number of nodules, as shown  
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2 in Table 2. ALD and number of nodules remained significantly correlated to OS in  
3 multivariable analysis, as shown in Table 3.

#### 4 *Transplantation*

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7 After relapse, OLT could still be performed in 8 (12.9%) and 8 (8.2%) patients in  
8 TACE-hRT and SR groups (p=0.48), respectively.

#### 9 *Adverse events*

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12 Median length of hospital stay was 11 days (IQR 9-16) and 6 days (IQR 4-7) in SR and  
13 TACE-hRT groups (p<0.001), respectively. In SR group, 85 (84.8%) patients presented grade  
14 3+ adverse events, including 82 (81.8%) biological and 42 (42.9%) symptomatic adverse  
15 events. In TACE-hRT group, 44 (71%) patients presented grade 3+ adverse events, including  
16 37 (59.7%) biological and 19 (30.6%) symptomatic adverse events. The most frequent clinical  
17 grade 3+ adverse event was post-procedure ascitis, presented by 15 (15.3%) and 8 (12.9%)  
18 patients in SR and TACE-hRT groups, respectively.  
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### 28 **Discussion**

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31 Here we present, to our knowledge, the first study comparing clinical outcomes of SR  
32 to TACE-hRT. Despite higher PFS and OS after surgery, TACE-hRT achieved similar TTP  
33 and shorter hospital stay.  
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38 Liver transplantation, thermoablation and SR remain the standard of care of localized  
39 early BCLC-A HCC if feasible [2,3]. Surgery achieves a median OS of 36 month [11].  
40 Resection can highlight and treat satellite nodules.  
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44 In addition to tumor resectability or accessibility to thermoablations, HCC patients can  
45 often be unfit for surgery due to frequent comorbidities [12]. Furthermore, some patients can  
46 be ineligible to OLT. In these situations of local tumor in patients merely fit for surgery, TACE-  
47 hRT represents an encouraging less invasive therapeutic option. We showed that this  
48 combination induced shorter length of hospital stay and maintained similar TTP with a  
49 promising median of 23 months. Moreover, while recurrences are higher than 50% after  
50 resection [13], this multimodal therapy can still be performed after other local treatments.  
51 However in this population with predictable high risk for postoperative liver failure, PFS and  
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OS were significantly decreased, even after adjustment with IPTW propensity score. Therefore, SR remains the standard of care if it can be performed safely.

Recent radiotherapeutic innovations offer new treatment options in HCC. Two recent meta-analyses reported that combining TACE with RT significantly improved complete response and OS compared to TACE alone [6,7]. However, TACE combined with conventional RT achieves good short-term but poor long-term OS [14]. In addition to requiring fewer sessions, hypofractionated RT improved median OS in locally advanced HCC (28 versus 16 months;  $p=0.002$ ) compared to normofractionated RT [15]. High hypofractionation using liver stereotactic body radiotherapy (SBRT) is a promising treatment, that can even be performed in Child B patients [16]. In retrospective studies, SBRT achieved similar results compared to hepatic resection [17,18]. However, its combination with systemic treatments [19] or TACE [20,21] is still under evaluation and this recent technique should only be performed in highly experienced centers. Indeed previous publications reported decline in liver function in 10-30% patients and 5-10% grade 5 toxicity [22–25].

An important issue in liver hRT is daily target visualization on pretreatment imaging. Indeed, low contrast on CBCT associated with tumor motion can lead to treatment geographic miss inducing lower local control. Moreover, a recent study reported that interfraction abdominal organ motion led to constraint violation in 61/97 (62.9%) sessions [26]. This can explain the 12-67% grade 2 and 0-14% grade 3-5 gastro-intestinal side effects [24,27,28]. MR-Linac could allow PTV dose escalation or better OAR preservation due to daily adaptive planning [26], but the cost, maintenance, and important logistic burden of these machines will restrict access to limited centers in developed countries.

Best curative treatment of early stage HCC remains OLT [2]. Liver RT induces vascular damages and local fibrosis [29,30], suggesting a theoretical increase of postoperative morbidity. However, we previously reported satisfactory results of RT as bridge to OLT [31,32]. Results of the present work are also reassuring since transplantation could still be performed after TACE-hRT in 8% patients.

At the time of this study, sorafenib was the standard of care of locally advanced HCC [33]. However in case of macrovascular invasion, TACE combined with moderately hRT improved TTP ( $p<0.001$ ), PFS ( $p<0.001$ ) and OS ( $p=0.04$ ) compared to sorafenib in a

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2 randomized controlled trial [8]. Combining RT and sorafenib could be a valuable option, with  
3 improved OS compared to sorafenib alone in a recent publication [34].

4 Since 2020, new standard of care of advanced HCC is Atezolizumab associated with  
5 Bevacizumab [35]. This treatment achieves 1-year OS of 67.2% but induces 56.5% grade 3-4  
6 side effects [35]. Moreover, it results in an incremental cost-utility ratio of \$169,223 per QALY  
7 gained compared with Sorafenib [36]. A recent network meta-analysis [37] confirmed the  
8 superiority of Atezolizumab-Bevacizumab over other systemic therapies in unresectable HCC,  
9 but were not able to compare it with TACE or external beam radiotherapy. A direct comparison  
10 of those two combinations should be performed. Two safety trials are ongoing evaluating a  
11 combination of SBRT, Atezolizumab and Bevacizumab in resectable (NCT04857684; source  
12 [www.clinicaltrials.gov](http://www.clinicaltrials.gov)) and unresectable (NCT05096715; source [www.clinicaltrials.gov](http://www.clinicaltrials.gov))  
13 HCC.  
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23 Transarterial radioembolization should further be evaluated in this indication. The aim  
24 of the recently published LEGACY study was quite comparable to ours [38]. Salem et al.  
25 treated Child-Pugh A patients presenting solitary HCC less than 8 cm delivering high Yttrium-  
26 90 doses to the tumor. After achieving median dose in the treated volume of 410 Gy, they  
27 reported similar OS with 24- and 36-months rates of 94.8% and 86.6%, respectively. However,  
28 grade 3 side effects were much lower at 19.1% [38]. In addition, such “radiation  
29 segmentectomy” required only two transarterial procedures, making it a very competitive  
30 treatment compared to TACE combined with radiotherapy. Further studies defining the place  
31 of radioembolization will help physicians refine therapeutic indications.  
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40 Age and treatment modality were significantly associated with PFS and OS. We also  
41 reported that thrombocytopenia in univariable, and ALD in both univariable and multivariable  
42 analysis were correlated with poorer TTP, PFS and OS. Thrombocytopenia is a well-known  
43 prognostic factor [39] due to portal hypertension. Splenic blood pressure is often higher among  
44 patients with larger tumors, which can lead to a partially surrogate value of thrombocytopenia.  
45 Previous studies highlighted negative prognostic value of alcohol-related HCC [40,41] but  
46 similar OS within each BCLC stage. This poorer survival was explained by higher tumor stage  
47 at diagnosis and worse liver function [40,41]. We included only BCLC-A patients and found  
48 no significant difference in tumor size between ALD and non-ALD groups. Despite this,  
49 alcohol-related HCC patients presented worse prognosis. This result contrasts with Schütte et  
50 al. [42] who reported better survival in patients with alcohol-related than viral-related BCLC-  
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1 A HCC ( $p=0.046$ ). However, this result is based on a limited sample of 35 patients [42]. In our  
2 work, worse prognosis of ALD patients was probably due to worse initial liver function and a  
3 possible suboptimal follow-up in this population with socioeconomic issues.  
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6 Our study has several limitations, including retrospective data recording. We aimed to  
7 limit confusion factors by performing IPTW with a model including patient comorbidities and  
8 known prognostic factors, although confounding parameters could remain. Second and most  
9 significantly, treatment was not randomly chosen but depended on clear factors: patients who  
10 presented larger tumors were more prompt to undergo surgery whereas co-morbidities and  
11 advanced underlying hepatopathy inducing thrombocytopenia were more likely to be treated  
12 with TACE-hRT. Nevertheless, our study is the first to evaluate TACE-hRT in this frequent  
13 situation and report promising TTP.  
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## 21 **Conclusion**

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24 Patients with predictable high risk for surgical complication and postoperative liver  
25 failure who present Child-Pugh A, single or paucinodular HCC can effectively and safely be  
26 treated by TACE-hRT. Achieving a promising median TTP of 23 months, this multimodal  
27 therapy should be prospectively compared with current combinations of systemic treatments  
28 or with TACE-SBRT and its association with immunotherapy should be evaluated.  
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## 39 **Statements**

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## References

- 1  
2 [1] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global  
3 Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide  
4 for 36 Cancers in 185 Countries. *CA: A Cancer Journal for Clinicians* 2021;71:209–  
5 49. <https://doi.org/10.3322/caac.21660>.  
6  
7
- 8  
9 [2] Galle PR, Forner A, Llovet JM, Mazzaferro V, Piscaglia F, Raoul JL, et al. EASL  
10 Clinical Practice Guidelines: Management of hepatocellular carcinoma. *Journal of*  
11 *Hepatology* 2018;69:182–236. <https://doi.org/10.1016/j.jhep.2018.03.019>.  
12  
13
- 14 [3] Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM, et al. Diagnosis,  
15 Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by  
16 the American Association for the Study of Liver Diseases. *Hepatology* 2018;68:723–  
17 50. <https://doi.org/10.1002/hep.29913>.  
18  
19
- 20 [4] Bolondi L. Screening for hepatocellular carcinoma in cirrhosis. *Journal of Hepatology*  
21 2003;39:1076–84. [https://doi.org/10.1016/S0168-8278\(03\)00349-0](https://doi.org/10.1016/S0168-8278(03)00349-0).  
22  
23
- 24 [5] Sapir E, Tao Y, Schipper MJ, Bazzi L, Novelli PM, Devlin P, et al. Stereotactic Body  
25 Radiation Therapy as an Alternative to Transarterial Chemoembolization for  
26 Hepatocellular Carcinoma. *International Journal of Radiation Oncology Biology*  
27 *Physics* 2018;100:122–30. <https://doi.org/10.1016/j.ijrobp.2017.09.001>.  
28  
29
- 30 [6] Xie H, Yu H, Tian S, Yang X, Wang X, Yang Z, et al. What is the best combination  
31 treatment with transarterial chemoembolization of unresectable hepatocellular  
32 carcinoma? A systematic review and network meta-analysis. *Oncotarget*  
33 2017;8:100508–23. <https://doi.org/10.18632/oncotarget.20119>.  
34  
35  
36
- 37 [7] Huo YR, Eslick GD. Transcatheter arterial chemoembolization plus radiotherapy  
38 compared with chemoembolization alone for hepatocellular carcinoma a systematic  
39 review and meta-analysis. *JAMA Oncology* 2015;1:756–65.  
40 <https://doi.org/10.1001/jamaoncol.2015.2189>.  
41  
42
- 43 [8] Yoon SM, Ryoo BY, Lee SJ, Kim JH, Shin JH, An JH, et al. Efficacy and safety of  
44 transarterial chemoembolization plus external beam radiotherapy vs sorafenib in  
45 hepatocellular carcinoma with macroscopic vascular invasion : A randomized clinical  
46 trial. *JAMA Oncology* 2018;4:661–9. <https://doi.org/10.1001/jamaoncol.2017.5847>.  
47  
48  
49
- 50 [9] Mohkam K, Dumont PN, Manichon AF, Jouvet JC, Bousset L, Merle P, et al. No-  
51 touch multibipolar radiofrequency ablation vs. surgical resection for solitary  
52 hepatocellular carcinoma ranging from 2 to 5 cm. *Journal of Hepatology*  
53 2018;68:1172–80. <https://doi.org/10.1016/j.jhep.2018.01.014>.  
54  
55
- 56 [10] Xu S, Ross C, Raebel MA, Shetterly S, Blanchette C, Smith D. Use of stabilized  
57 inverse propensity scores as weights to directly estimate relative risk and its  
58  
59  
60  
61  
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63  
64  
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confidence intervals. *Value in Health* 2010;13:273–7. <https://doi.org/10.1111/j.1524-4733.2009.00671.x>.

- [11] Forner A, Reig ME, Rodriguez de Lope C, Bruix J. Current Strategy for Staging and Treatment: The BCLC Update and Future Prospects. *Seminars in Liver Disease* 2010;30:061–74. <https://doi.org/10.1055/s-0030-1247133>.
- [12] Mu X-M, Wang W, Jiang Y-Y, Feng J. Patterns of Comorbidity in Hepatocellular Carcinoma: A Network Perspective. *International Journal of Environmental Research and Public Health* 2020;17:3108. <https://doi.org/10.3390/ijerph17093108>.
- [13] Tabrizian P, Jibara G, Shragar B, Schwartz M, Roayaie S. Recurrence of Hepatocellular Cancer After Resection. *Annals of Surgery* 2015;261:947–55. <https://doi.org/10.1097/SLA.0000000000000710>.
- [14] Zhou ZH, Liu LM, Chen WW, Men ZQ, Lin JH, Chen Z, et al. Combined therapy of transcatheter arterial chemoembolisation and three-dimensional conformal radiotherapy for hepatocellular carcinoma. *British Journal of Radiology* 2007;80:194–201. <https://doi.org/10.1259/bjr/33521596>.
- [15] Wang C, Li S, Sun A, Chen L, Liang R, Li G, et al. The comparison of outcomes between hypofractionated and conventional 3D-CRT regimens used in combination with TACE as first-line treatment of advanced hepatocellular carcinoma. *Tumor Biology* 2015;36:4967–72. <https://doi.org/10.1007/s13277-015-3144-5>.
- [16] Culleton S, Jiang H, Haddad CR, Kim J, Brierley J, Brade A, et al. Outcomes following definitive stereotactic body radiotherapy for patients with Child-Pugh B or C hepatocellular carcinoma. *Radiotherapy and Oncology* 2014;111:412–7. <https://doi.org/10.1016/j.radonc.2014.05.002>.
- [17] Sun J, Wang Q, Hong ZX, Li WG, He WP, Zhang T, et al. Stereotactic body radiotherapy versus hepatic resection for hepatocellular carcinoma ( $\leq 5$  cm): a propensity score analysis. *Hepatology International* 2020;14:788–97. <https://doi.org/10.1007/s12072-020-10088-0>.
- [18] Yuan Z, Tian L, Pang Q, Song Y, Dong Y, Zhuang H. Comparative research on the efficacy of CyberKnife® and surgical excision for Stage I hepatocellular carcinoma. *OncoTargets and Therapy* 2013;1527. <https://doi.org/10.2147/OTT.S51452>.
- [19] Chiang CL, Chan ACY, Chiu KWH, Kong FM. Combined Stereotactic Body Radiotherapy and Checkpoint Inhibition in Unresectable Hepatocellular Carcinoma: A Potential Synergistic Treatment Strategy. *Frontiers in Oncology* 2019;9:1–9. <https://doi.org/10.3389/fonc.2019.01157>.
- [20] Chiang CL, Chan MKH, Yeung CSY, Ho CHM, Lee FAS, Lee VWY, et al. Combined stereotactic body radiotherapy and trans-arterial chemoembolization as initial

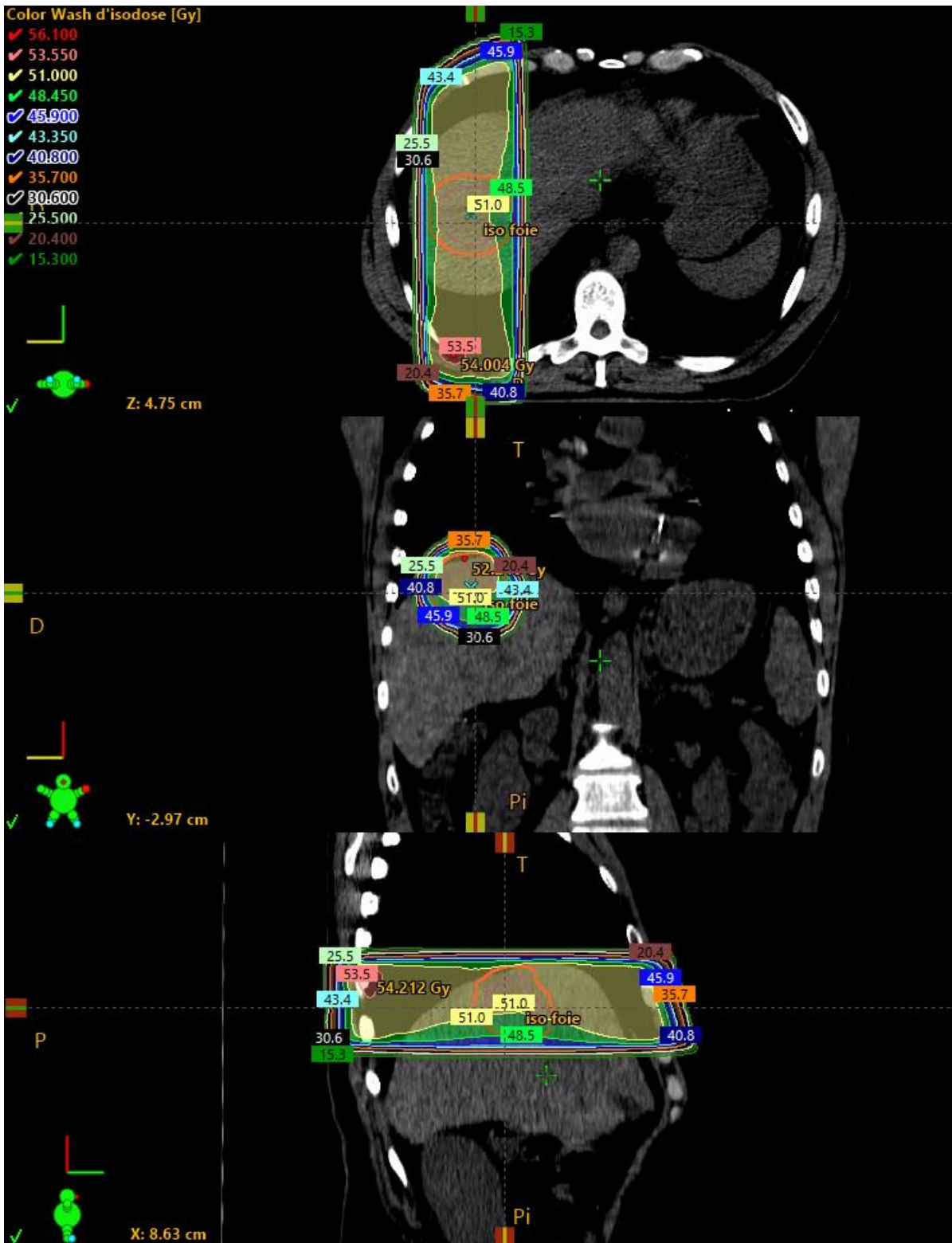


1 treatment in BCLC stage B–C hepatocellular carcinoma. *Strahlentherapie Und*  
2 *Onkologie* 2019;195:254–64. <https://doi.org/10.1007/s00066-018-1391-2>.

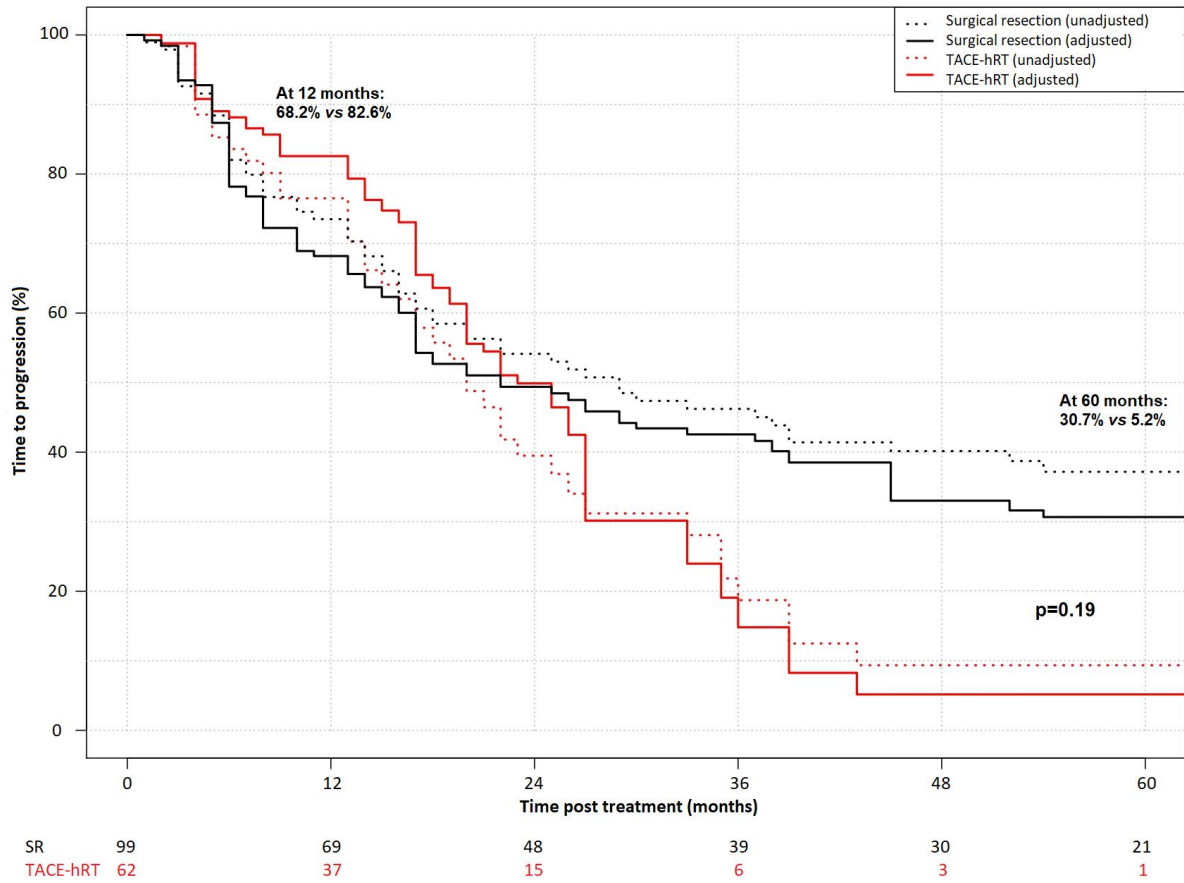
- 3  
4 [21] Hardy-Abeloos C, Lazarev S, Ru M, Kim E, Fischman A, Moshier E, et al. Safety and  
5 Efficacy of Liver Stereotactic Body Radiation Therapy for Hepatocellular Carcinoma  
6 After Segmental Transarterial Radioembolization. *International Journal of Radiation*  
7 *Oncology Biology Physics* 2019;105:968–76.  
8 <https://doi.org/10.1016/j.ijrobp.2019.09.006>.
- 9  
10  
11 [22] Son SH, Choi BO, Ryu MR, Kang YN, Jang JS, Bae SH, et al. Stereotactic body  
12 radiotherapy for patients with unresectable primary hepatocellular carcinoma: Dose-  
13 volumetric parameters predicting the hepatic complication. *International Journal of*  
14 *Radiation Oncology Biology Physics* 2010;78:1073–80.  
15 <https://doi.org/10.1016/j.ijrobp.2009.09.009>.
- 16  
17  
18  
19 [23] Andolino DL, Johnson CS, Maluccio M, Kwo P, Tector AJ, Zook J, et al. Stereotactic  
20 body radiotherapy for primary hepatocellular carcinoma. *International Journal of*  
21 *Radiation Oncology Biology Physics* 2011;81.  
22 <https://doi.org/10.1016/j.ijrobp.2011.04.011>.
- 23  
24  
25  
26 [24] Barney BM, Olivier KR, Miller RC, Haddock MG. Clinical outcomes and toxicity  
27 using Stereotactic Body Radiotherapy (SBRT) for advanced cholangiocarcinoma.  
28 *Radiation Oncology* 2012;7:67. <https://doi.org/10.1186/1748-717X-7-67>.
- 29  
30  
31 [25] Bujold A, Massey CA, Kim JJ, Brierley J, Cho C, Wong RKS, et al. Sequential phase I  
32 and II trials of stereotactic body radiotherapy for locally advanced hepatocellular  
33 carcinoma. *Journal of Clinical Oncology* 2013;31:1631–9.  
34 <https://doi.org/10.1200/JCO.2012.44.1659>.
- 35  
36  
37 [26] Henke L, Kashani R, Robinson C, Curcuru A, DeWees T, Bradley J, et al. Phase I trial  
38 of stereotactic MR-guided online adaptive radiation therapy (SMART) for the  
39 treatment of oligometastatic or unresectable primary malignancies of the abdomen.  
40 *Radiotherapy and Oncology* 2018;126:519–26.  
41 <https://doi.org/10.1016/j.radonc.2017.11.032>.
- 42  
43  
44  
45 [27] Lee MT, Kim JJ, Dinniwell R, Brierley J, Lockwood G, Wong R, et al. Phase I Study  
46 of Individualized Stereotactic Body Radiotherapy of Liver Metastases. *Journal of*  
47 *Clinical Oncology* 2009;27:1585–91. <https://doi.org/10.1200/JCO.2008.20.0600>.
- 48  
49  
50 [28] Bae SH, Kim M-S, Cho CK, Kim KB, Lee DH, Han CJ, et al. Feasibility and Efficacy  
51 of Stereotactic Ablative Radiotherapy for Barcelona Clinic Liver Cancer-C Stage  
52 Hepatocellular Carcinoma. *Journal of Korean Medical Science* 2013;28:213.  
53 <https://doi.org/10.3346/jkms.2013.28.2.213>.
- 54  
55  
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55  
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57  
58  
59  
60  
61  
62  
63  
64  
65
- [29] Maor Y, Malnick S. Liver Injury Induced by Anticancer Chemotherapy and Radiation Therapy. *International Journal of Hepatology* 2013;2013:1–8. <https://doi.org/10.1155/2013/815105>.
- [30] Straub JM, New J, Hamilton CD, Lominska C, Shnayder Y, Thomas SM. Radiation-induced fibrosis: mechanisms and implications for therapy. *Journal of Cancer Research and Clinical Oncology* 2015;141:1985–94. <https://doi.org/10.1007/s00432-015-1974-6>.
- [31] Mohkam K, Golse N, Bonal M, Ledochowski S, Rode A, Selmaji IE, et al. Conformal radiotherapy as a bridge to liver transplantation for hepatocellular carcinoma: is it safe? *Future Oncology* 2016;12:1577–86. <https://doi.org/10.2217/fon-2016-0083>.
- [32] Mourad M, Mabrut J-Y, Chellakhi M, Lesurtel M, Prevost C, Ducerf C, et al. Neoadjuvant conformal radiotherapy before liver transplantation for hepatocellular carcinoma: a propensity score matched analysis of postoperative morbidity and oncological results. *Future Oncology* 2019;15:2517–30. <https://doi.org/10.2217/fon-2019-0127>.
- [33] Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc J-F, et al. Sorafenib in Advanced Hepatocellular Carcinoma. *New England Journal of Medicine* 2008;359:378–90. <https://doi.org/10.1056/NEJMoa0708857>.
- [34] Chu SS, Kuo YH, Liu WS, Wang SC, Ho CH, Chen YC, et al. Effect of radiotherapy on survival in advanced hepatocellular carcinoma patients treated with sorafenib: a nationwide cancer-registry-based study. *Scientific Reports* 2021;11:1–8. <https://doi.org/10.1038/s41598-021-81176-w>.
- [35] Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim T-Y, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. *New England Journal of Medicine* 2020;382:1894–905. <https://doi.org/10.1056/NEJMoa1915745>.
- [36] Su D, Wu B, Shi L. Cost-effectiveness of Atezolizumab Plus Bevacizumab vs Sorafenib as First-Line Treatment of Unresectable Hepatocellular Carcinoma. *JAMA Network Open* 2021;4:e210037. <https://doi.org/10.1001/jamanetworkopen.2021.0037>.
- [37] Vogel A, Rimassa L, Sun H-C, Abou-Alfa GK, El-Khoueiry A, Pinato DJ, et al. Comparative Efficacy of Atezolizumab plus Bevacizumab and Other Treatment Options for Patients with Unresectable Hepatocellular Carcinoma: A Network Meta-Analysis. *Liver Cancer* 2021;10:240–8. <https://doi.org/10.1159/000515302>.
- [38] Salem R, Johnson GE, Kim E, Riaz A, Bishay V, Boucher E, et al. Yttrium-90 Radioembolization for the Treatment of Solitary, Unresectable HCC: The LEGACY Study. *Hepatology* 2021;74:2342–52. <https://doi.org/10.1002/hep.31819>.

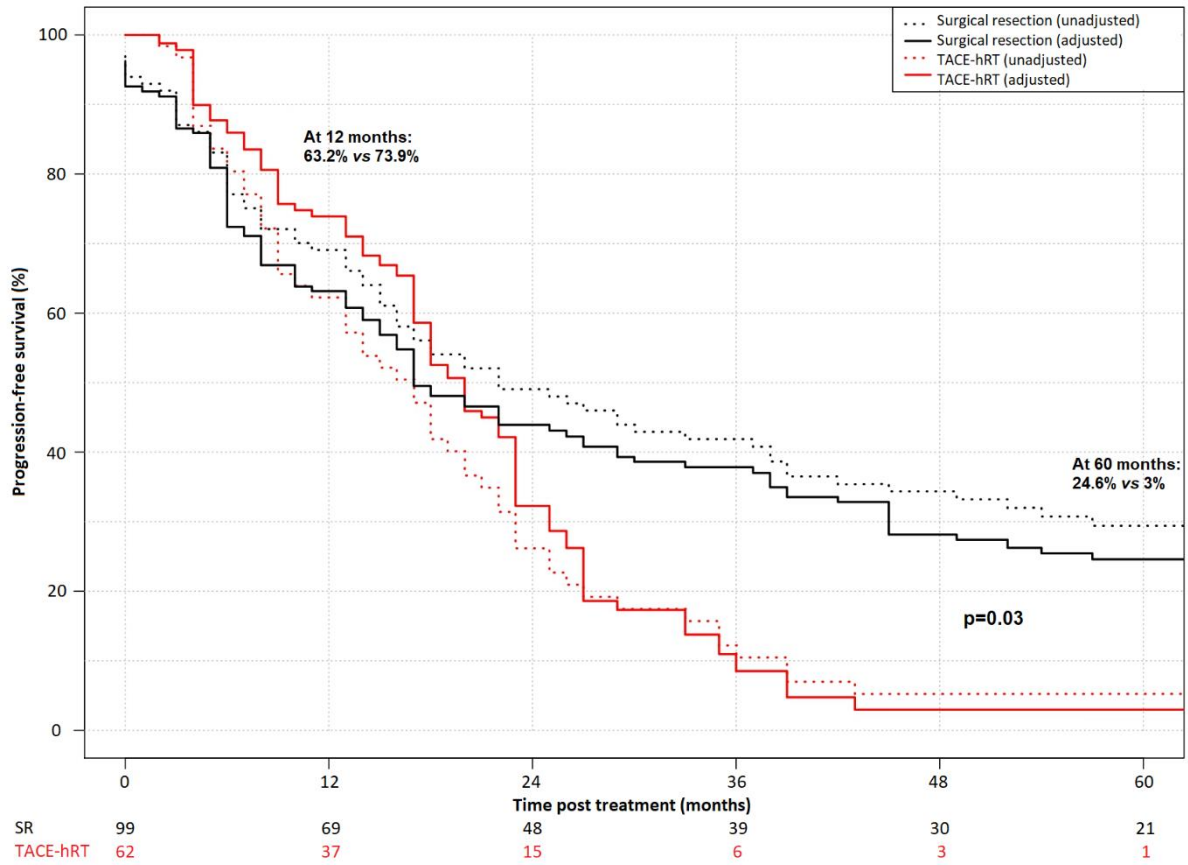
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64  
65
- [39] Pang Q, Qu K, Bi J-B, Liu S-S, Zhang J-Y, Song S-D, et al. Thrombocytopenia for prediction of hepatocellular carcinoma recurrence: Systematic review and meta-analysis. *World Journal of Gastroenterology* 2015;21:7895. <https://doi.org/10.3748/wjg.v21.i25.7895>.
- [40] Bucci L, Garuti F, Camelli V, Lenzi B, Farinati F, Giannini EG, et al. Comparison between alcohol- and hepatitis C virus-related hepatocellular carcinoma: clinical presentation, treatment and outcome. *Alimentary Pharmacology & Therapeutics* 2016;43:385–99. <https://doi.org/10.1111/apt.13485>.
- [41] Costentin CE, Mourad A, Lahmek P, Causse X, Pariente A, Hagège H, et al. Hepatocellular carcinoma is diagnosed at a later stage in alcoholic patients: Results of a prospective, nationwide study. *Cancer* 2018;124:1964–72. <https://doi.org/10.1002/cncr.31215>.
- [42] Schütte K, Bornschein J, Kahl S, Seidensticker R, Arend J, Ricke J, et al. Delayed Diagnosis of HCC with Chronic Alcoholic Liver Disease. *Liver Cancer* 2012;1:257–66. <https://doi.org/10.1159/000343840>.



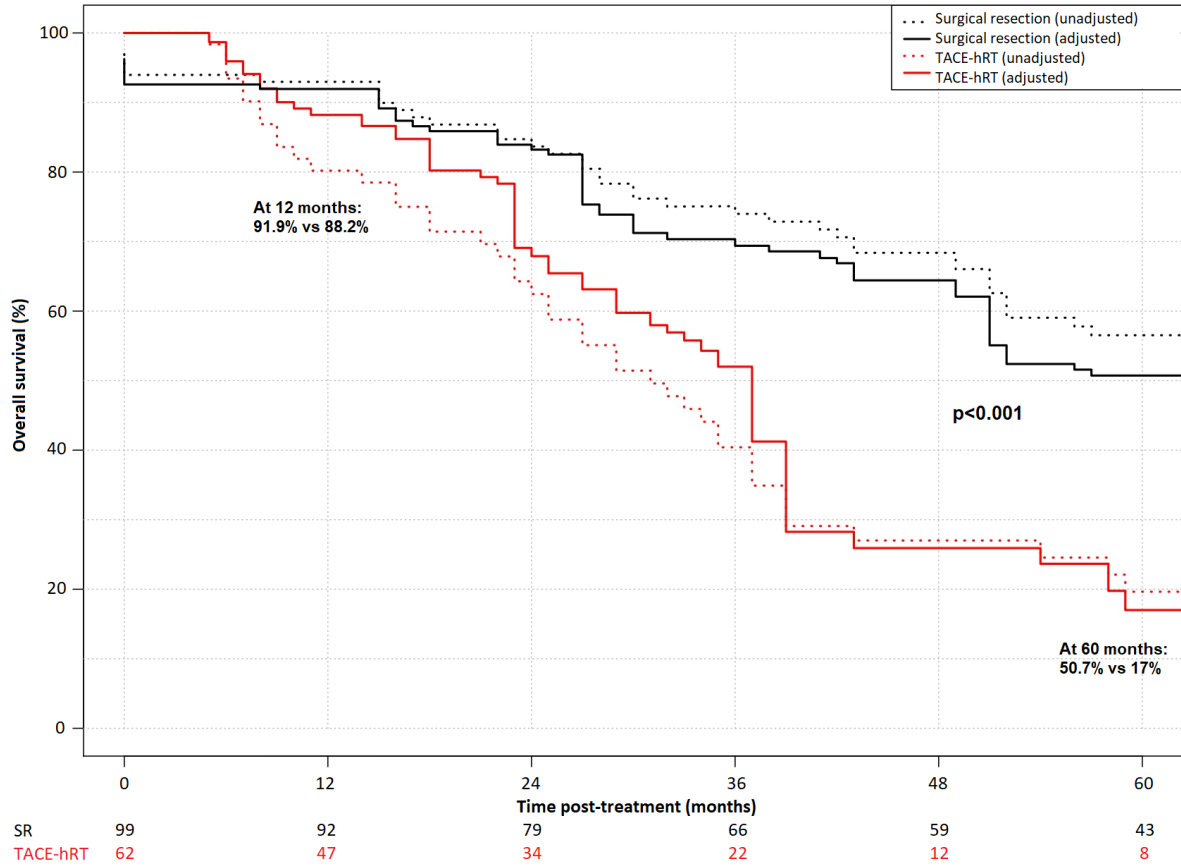
**Figure 1.** Dose distribution of a 3-dimensional conformal radiotherapy treatment, with 10-phase internal target volume motion management. Patient was prescribed 51Gy in 17 fractions on ICRU reference point.



**Figure 2.** Comparison of time-to-progression between surgical resection (SR) and transarterial chemoembolization followed by hypofractionated radiotherapy (TACE-hRT).



**Figure 3.** Comparison of progression-free survival between surgical resection (SR) and transarterial chemoembolization followed by hypofractionated radiotherapy (TACE-hRT).



**Figure 4.** Comparison of overall survival between surgical resection (SR) and transarterial chemoembolization followed by hypofractionated radiotherapy (TACE-hRT).

**Table 1.** Baseline characteristics before inverse probability of treatment weighting.

Variables	SR (n=98)	TACE-hRT (n=62)	<i>p</i> -value
Sex, male	78 (79.6%)	48 (77.4%)	0.74
Age, years	64 (57-71)	70 (61-77)	0.005
Size, mm	50 (40-80)	40 (27-55)	< 0.001
Number of nodules	1 (1-1)	1 (1-1)	0.54
Alpha-Fetoprotein, ng/mL	7 (4-22)	9 (5-70)	0.07
Bilirubin, $\mu$ mol/L	10 (8-15)	14 (10-20)	0.005
Platelets, Giga/L	204 (159-249)	140 (91-199)	<0.001
Albumin, g/L	40 (37-43)	37.3 (34-40)	<0.001
Prothrombin time, %	93 (84-103)	82 (77-94)	<0.001
Portal hypertension	12 (12.1%)	30 (49.2%)	< 0.001
Underlying liver disease			
Hemochromatosis	1 (1%)	3 (4.8%)	0.30
Non-alcoholic fatty liver disease	38 (38.8%)	14 (22.6%)	0.03
Alcohol	47 (48%)	29 (46.8%)	0.88
HBV infection	15 (14.3%)	7 (12.9%)	0.80
HCV infection	15 (15.3%)	11 (17.7%)	0.68
Cryptogenic	18 (18.4%)	6 (9.7%)	0.13
Child-Pugh score			0.003
A5	87 (87.9%)	42 (68.9%)	
A6	12 (12.1%)	19 (31.1%)	
Previous treatment	0 (0-0)	0 (0-0)	< 0.001
Age-adjusted CCI	5 (4-7)	8 (7-9)	< 0.001

Categorical variables are expressed in counts (percentage) and continuous variables in median values (interquartile range)

Abbreviations: CCI, Charlson Comorbidity Index; HBV, Hepatitis B Virus; HCV, Hepatitis C Virus; SR, surgical resection; TACE-hRT, transarterial chemoembolization followed by hypofractionated radiotherapy



**Table 2.** Univariable analysis after inverse probability of treatment weighting.

Variables	TTP		PFS		OS	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Treatment (TACE-hRT vs SR)	1.37 (0.87-2.14)	0.17	1.65 (1.10-2.46)	<b>0.015</b>	2.65 (1.69-4.15)	<b>&lt;0.001</b>
Age (per year)	1.01 (0.99-1.03)	0.29	1.02 (1.00-1.03)	<b>0.041</b>	1.04 (1.02-1.06)	<b>&lt;0.001</b>
Alcohol-related liver disease (yes vs no)	1.64 (1.08-2.48)	<b>0.019</b>	1.65 (1.13-2.40)	<b>&lt; 0.001</b>	1.28 (0.83-1.95)	0.26
Non-alcoholic fatty liver disease	1.18 (0.78-1.78)	0.44	1.08 (0.74-1.57)	0.70	1.06 (0.68-1.63)	0.81
Hepatitis B virus	0.66 (0.34-1.28)	0.22	0.52 (0.27-1.01)	0.06	0.50 (0.21-1.19)	0.12
Hepatitis C virus	1.38 (0.83-2.32)	0.22	1.18 (0.72-1.93)	0.52	1.01 (0.56-1.80)	0.98
AFP (<200 vs ≥200 ng/mL)	1.79 (0.91-3.54)	0.09	1.414 (0.72-2.77)	0.31	0.88 (0.38-2.06)	0.76
Albumin (per g/L)	0.96 (0.91-1.01)	0.14	0.95 (0.90-0.99)	<b>0.017</b>	0.93 (0.87-0.98)	<b>&lt; 0.01</b>
Platelets (<100 vs ≥100 Giga/L)	1.9 (1.01-3.63)	<b>0.048</b>	1.78 (0.97-3.26)	0.061	2.02 (1.09-3.73)	<b>0.026</b>
Size (≥50 mm vs >50 mm)	1.05 (0.7-1.59)	0.80	1.07 (0.74-1.56)	0.71	1.01 (0.66-1.57)	0.95
Number of nodules	0.95 (0.52-1.75)	0.87	1.29 (0.82-2.05)	0.28	1.89 (1.16-3.06)	<b>0.010</b>

Abbreviations: G/L, giga per liter; OS, overall survival; PFS, progression-free survival; SR, surgical resection; TACE-hRT, transarterial chemoembolization followed by hypofractionated radiotherapy; TTP, time-to-progression

**Table 3.** Multivariable analysis after inverse probability of treatment weighting.

Variables	TTP		PFS		OS	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Treatment (TACE-hRT vs SR)	1.30 (0.81-2.07)	0.28	1.55 (1.02-2.35)	<b>0.041</b>	2.33 (1.45-3.74)	<b>&lt;0.001</b>
Age (per years)	1.01 (0.99-1.03)	0.31	1.02 (1.00-1.04)	<b>0.035</b>	1.04 (1.02-1.07)	<b>&lt;0.001</b>
Alcohol-related liver disease	1.60 (1.04-2.45)	<b>0.033</b>	1.65 (1.11-2.44)	<b>0.013</b>	1.34 (0.85-2.11)	0.21
Albumin (per g/L)	0.98 (0.93-1.04)	0.54	0.97 (0.92-1.02)	0.19	0.95 (0.90-1.01)	0.096
Platelets (<100 vs ≥100 Giga/L)	1.59 (0.81-3.11)	0.18	1.38 (0.73-2.61)	0.33	1.54 (0.80-2.97)	0.20
Number of nodules	1.01 (0.55-1.85)	0.97	1.45 (0.92-2.30)	0.11	2.34 (1.43-3.82)	<b>&lt;0.001</b>

Abbreviations: OS, overall survival; PFS, progression-free survival; SR, surgical resection; TACE-hRT, transarterial chemoembolization followed by hypofractionated radiotherapy; TTP, time-to-progression