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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 ≥ 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 (≥ 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.
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56 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

1
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) and unresectable (NCT05096715; source www.clinicaltrials.gov)
13 HCC.
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22 Transarterial radioembolization should further be evaluated in this indication. The aim
23 of the recently published LEGACY study was quite comparable to ours [38]. Salem et al.
24 treated Child-Pugh A patients presenting solitary HCC less than 8 cm delivering high Yttrium-
25 90 doses to the tumor. After achieving median dose in the treated volume of 410 Gy, they
26 reported similar OS with 24- and 36-months rates of 94.8% and 86.6%, respectively. However,
27 grade 3 side effects were much lower at 19.1% [38]. In addition, such “radiation
28 segmentectomy” required only two transarterial procedures, making it a very competitive
29 treatment compared to TACE combined with radiotherapy. Further studies defining the place
30 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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A HCC ($p=0.046$). However, this result is based on a limited sample of 35 patients [42]. In our work, worse prognosis of ALD patients was probably due to worse initial liver function and a possible suboptimal follow-up in this population with socioeconomic issues.

Our study has several limitations, including retrospective data recording. We aimed to limit confusion factors by performing IPTW with a model including patient comorbidities and known prognostic factors, although confounding parameters could remain. Second and most significantly, treatment was not randomly chosen but depended on clear factors: patients who presented larger tumors were more prompt to undergo surgery whereas co-morbidities and advanced underlying hepatopathy inducing thrombocytopenia were more likely to be treated with TACE-hRT. Nevertheless, our study is the first to evaluate TACE-hRT in this frequent situation and report promising TTP.

Conclusion

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

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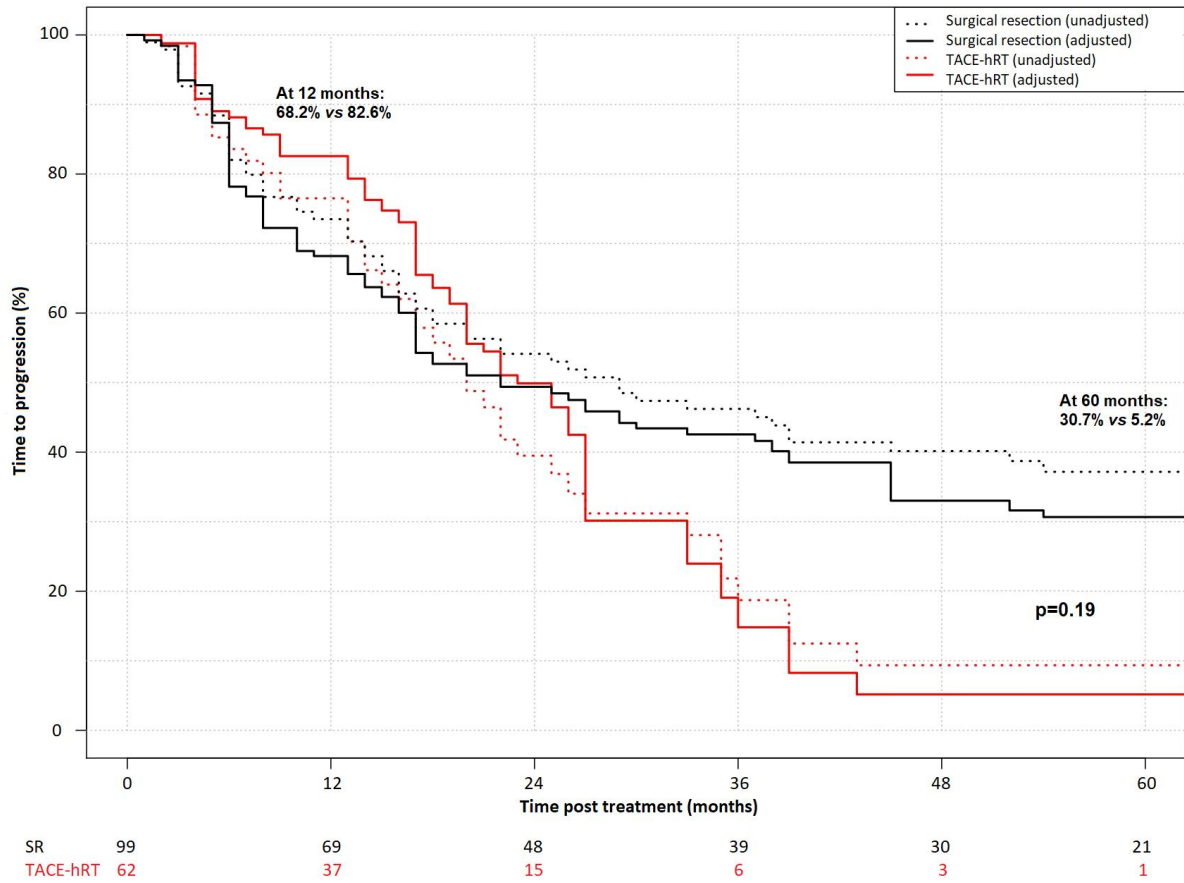


Figure 2. Comparison of time-to-progression between surgical resection (SR) and transarterial chemoembolization followed by hypofractionated radiotherapy (TACE-hRT).

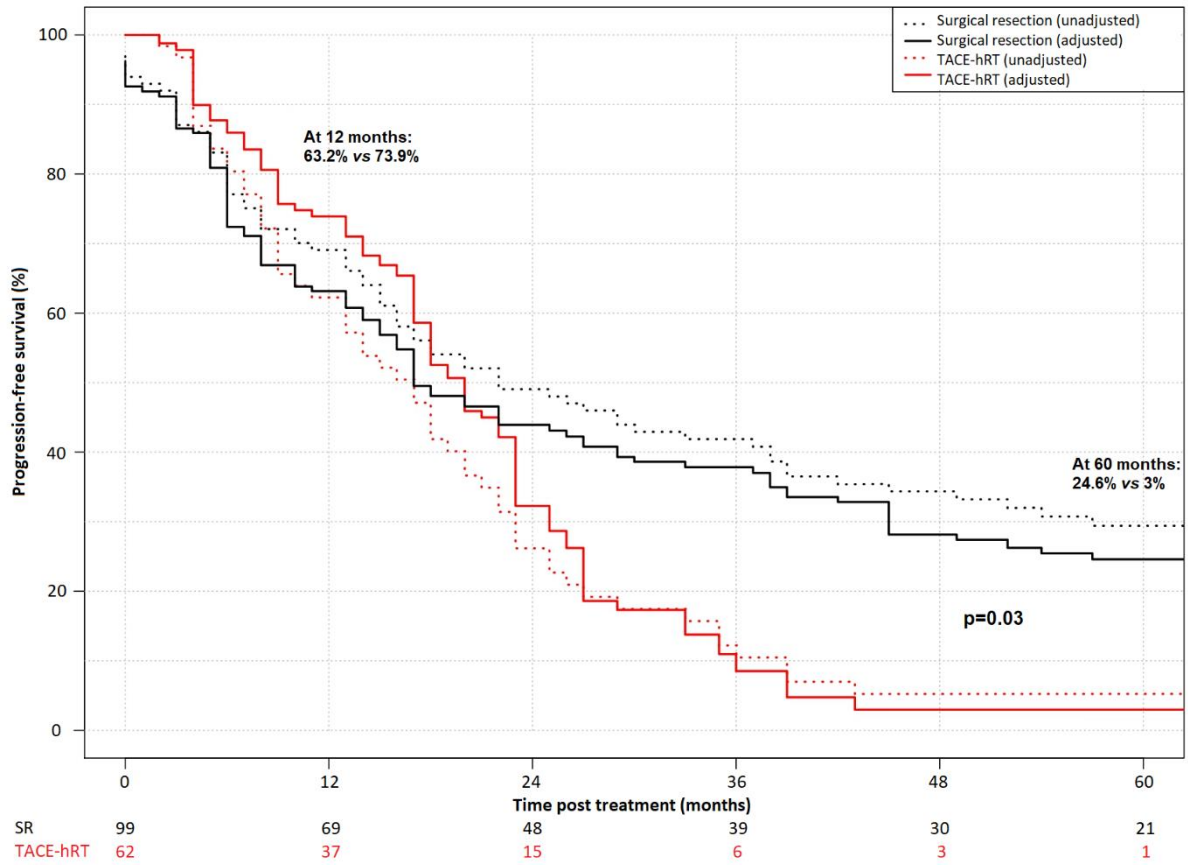


Figure 3. Comparison of progression-free survival between surgical resection (SR) and transarterial chemoembolization followed by hypofractionated radiotherapy (TACE-hRT).

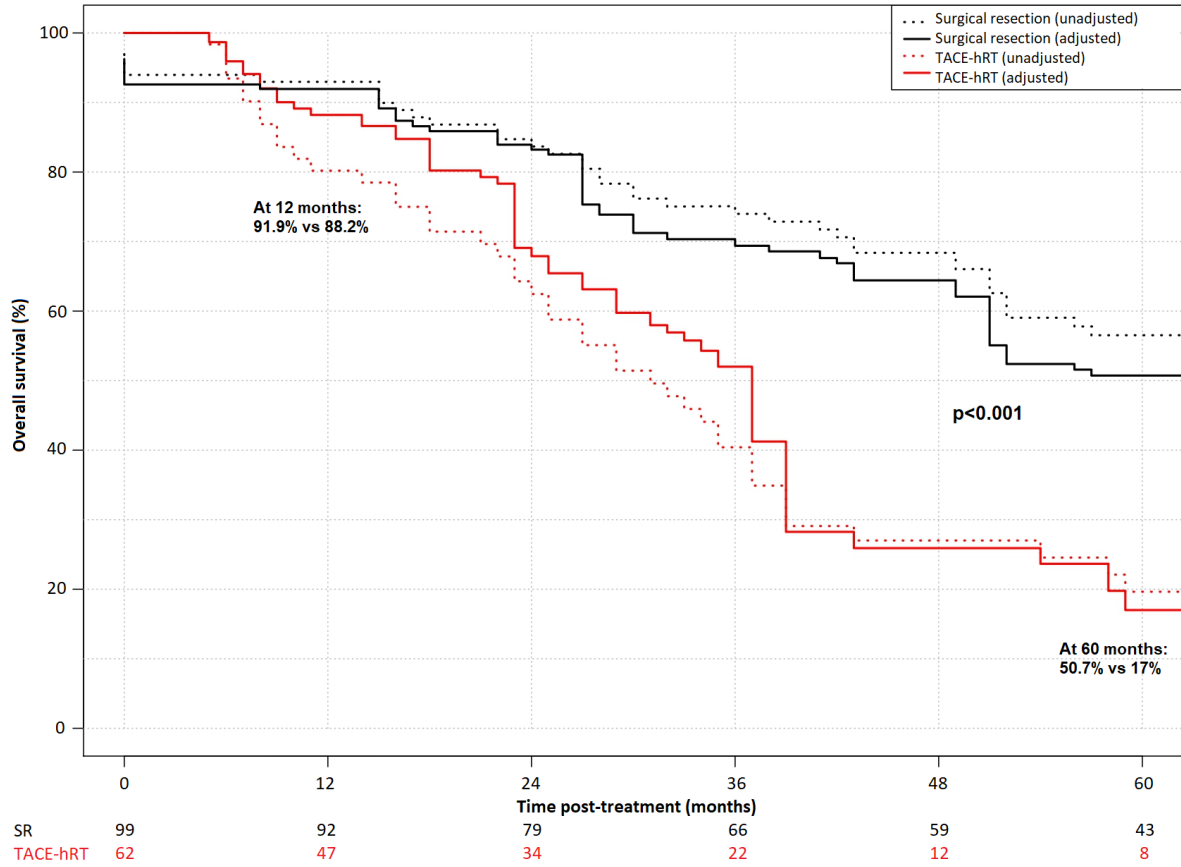


Figure 4. Comparison of overall survival between surgical resection (SR) and transarterial chemoembolization followed by hypofractionated radiotherapy (TACE-hRT).

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, μ 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)	0.015	2.65 (1.69-4.15)	<0.001
Age (per year)	1.01 (0.99-1.03)	0.29	1.02 (1.00-1.03)	0.041	1.04 (1.02-1.06)	<0.001
Alcohol-related liver disease (yes vs no)	1.64 (1.08-2.48)	0.019	1.65 (1.13-2.40)	< 0.001	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)	0.017	0.93 (0.87-0.98)	< 0.01
Platelets (<100 vs ≥100 Giga/L)	1.9 (1.01-3.63)	0.048	1.78 (0.97-3.26)	0.061	2.02 (1.09-3.73)	0.026
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)	0.010

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)	0.041	2.33 (1.45-3.74)	<0.001
Age (per years)	1.01 (0.99-1.03)	0.31	1.02 (1.00-1.04)	0.035	1.04 (1.02-1.07)	<0.001
Alcohol-related liver disease	1.60 (1.04-2.45)	0.033	1.65 (1.11-2.44)	0.013	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)	<0.001

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