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# **Transarterial chemoembolization followed by moderately hypofractionated radiotherapy in hepatocellular carcinoma: Long-term results of RTF3 regimen**

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**English title: Transarterial chemoembolization followed by moderately hypofractionated radiotherapy in hepatocellular carcinoma: long-term results of RTF3 regimen**

**Titre français : Chimioembolisation transartérielle suivie d'une radiothérapie modérément hypofractionnée dans les carcinomes hépatocellulaires : résultats à long terme du schéma RTF3**

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**Abstract**

**Introduction:** In early-stage hepatocellular carcinoma (HCC) patients merely fit for surgery, transarterial chemoembolization (TACE) achieve low long-term disease control. We evaluated the efficacy and safety of its combination with moderately hypofractionated radiotherapy (hRT) using RTF3 regimen.

**Material and Methods:** Between 2006 and 2016, 61 consecutive patients treated in our single expert center for a Barcelona Clinic Liver Cancer (BCLC) A HCC by TACE followed by hRT 3 Gy/fraction were retrospectively included.

**Results:** Sixty of the 61 included presented Child-Pugh A cirrhosis (A5, n=41, 67.2%; A6: n=19, 31.1%). Fourteen patients (22.9%) were already treated for a HCC, mainly by radiofrequency (n=12). All patient received a TACE followed by 3Gy per fraction hRT. Mean radiation dose was 54 Gy (range 48-60). After a median follow-up of 118 months, median time-to-progression, progression-free survival (PFS) and overall survival (OS) was 21.3, 18.1, and 31.5 months, respectively. In univariate analysis, PFS was related to dose >54Gy (HR 2, p=0.036), and OS was correlated to Child-Pugh A6 or B7 (HR 1.93, p=0.03) and overall hRT time (HR 1.06, p=0.015). At progression, orthotopic liver transplantation was performed in 8 patients (13.1%). Severe symptomatic adverse events occurred in 12 patients (19.7%), mainly ascites (n=7).

**Conclusion:** In BCLC-A Child-Pugh A HCC patients ineligible to surgery or thermoablation, TACE-hRT is a safe and effective treatment. Prospective studies are needed to compare this association with radio-embolization, TACE-stereotactic radiotherapy, and systemic treatments combinations.

Keywords: hepatocellular carcinoma; transarterial chemoembolization; hypofractionated radiotherapy; SBRT

## Résumé

**Objectifs de l'étude :** La chimio-embolisation transartérielle (TACE) permet un contrôle tumoral faible à long terme chez les patients présentant un carcinome hépatocellulaire (CHC) récusé à la chirurgie et à la thermoablation. Notre objectif était d'étudier l'efficacité et la tolérance de l'association TACE-radiothérapie modérément hypofractionnée (TACE-hRT) selon le schéma RTF3.

**Matériel et méthode :** De 2006 à 2016, tous les patients traités pour un CHC BCLC-A dans notre centre expert par une TACE-hRT 3Gy/fraction ont été rétrospectivement analysés.

**Résultats :** Soixante des 61 patients inclus présentaient une cirrhose Child-Pugh A (A5, n=41; A6, n=19). Quatorze patients (23%) avaient déjà été traités pour un CHC, majoritairement par radiofréquence (n=12). Tous ont reçu une TACE suivie d'une hRT 3Gy/fraction, de dose totale moyenne 54Gy (étendue 48-60). Après un suivi médian de 118 mois les médianes de TSP, de SSP et de SG était de 21,3 mois, 18,1 mois et 31,5 mois, respectivement. En analyse univariée, la dose >54Gy était associée à une meilleure SSP (HR=2), tandis que la SG était corrélée au Child-Pugh A6/B7 (HR=1,93) et à la durée totale de radiothérapie (HR=1,06). Huit patients (13%) ont bénéficié par la suite d'une transplantation hépatique. Douze patients (20%) ont présenté au moins une toxicité aiguë sévère symptomatique, essentiellement décompensation oedémato-ascitique (n=7).

## Conclusion :

Chez les patients cirrhotiques Child-Pugh A présentant un CHC BCLC-A non éligible aux chirurgie et thermoablations, la TACE-hRT est un traitement sûr et efficace. Des comparaisons prospectives sont nécessaires avec la radio-embolisation, la radiothérapie stéréotaxique et les traitements systémiques.

**Mots-clés:** carcinome hépatocellulaire; chimioembolisation transartérielle; radiothérapie hypofractionnée; SBRT

## **Introduction**

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death and the fifth most frequent neoplasia worldwide [1], with a rising incidence [2]. Improving existing therapies and evaluating new treatment modalities are thus essential. In patients presenting early stage BCLC-A HCC, curative treatments include orthotopic liver transplantation (OLT), surgical resection and thermal ablation [3,4]. Nevertheless, due to comorbidities or to tumor characteristics, only 5 to 20% of patients can be surgically managed.[5,6] In non-curative BCLC-A situations, transarterial chemoembolization (TACE) is usually performed [3,4]. Since it achieves <25% OS at 3 years [7], it is sometimes combined with other local or systemic therapies [8,9].

Combination of TACE and normofractionated radiotherapy have been reported to improve OS compared to TACE alone (OR 1.36 at 1 year).[10] In a randomized controlled trial in patients presenting HCC with macrovascular invasion, Yoon et al. reported that TACE combined with moderately hypofractionated radiotherapy (TACE-hRT) improve time-to-progression (TTP), progression-free survival (PFS) and OS compared to sorafenib (HR 0.28, 0.27, and 0.61, respectively) [11]. Nevertheless, results were not reported after 48 weeks and the population who received TACE-hRT included only 45 patients.

We aimed to assess long-term efficacy and safety of TACE-hRT in patients presenting single or paucinodular HCC.

## **Material and methods**

### ***Study population***

Between May 2005 and October 2016, HCC patients treated in expert centers of Hospices Civils de Lyon (Lyon, France) with TACE followed by hypofractionated RT 3 Gy per daily fraction were retrospectively included. Inclusion criteria were: 18 years or older; BCLC stage A HCC; diagnosis of HCC by CT or MRI using AASLD criteria and/or biopsy; absence of truncular or lobar portal vein invasion, or suprahepatic vein invasion. Exclusion criteria were previous abdominal RT or transplanted liver.

All patient records were presented in an HCC multidisciplinary tumor board including hepatobiliary and transplant surgeons, onco-hepatologists, interventional radiologists and radiation oncologists. Patients with localized HCC were to be treated by TACE-hRT if they had good liver function but were not eligible for thermoablation due to tumor size or location, and if they had predictable elevated risk for surgical complication.

Processing of personal data was performed according to the Informatic and Liberties National Commission (CNIL) and requirement for informed consent was waived. The study was performed in accordance with the 1975 Helsinki declaration and approved by the institutional ethical committee.

### ***Transarterial chemoembolization***

Patients received one single TACE course. Femoral arterial catheterization under local anesthesia was performed using the Seldinger technique with 2.0 to 2.8F microcatheters. To identify tumor arterial supply, an angiography of superior mesenteric artery, coeliac trunk and hepatic artery was performed. A microcatheter was then selectively inserted to inject doxorubicin-loaded beads (DC Beads®; BTG, Farnham, United Kingdom) or an emulsion of

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50 mg of doxorubicin and 10 mL Lipiodol, under fluoroscopic monitoring. Subsequent embolization was performed with mixed absorbable gelatin sponge (Curaspon®; Cura Medical, Amsterdam, The Netherlands).

### ***Irradiation technique***

External beam RT was planned to begin 1 to 3 weeks after TACE and was delivered by a linear accelerator (Varian, Palo Alto, CA). Planning computed tomography (pCT) of 2 to 5 mm slice thickness was performed without contrast agent injection. Acquisition was done either in both expiratory and inspiratory breath hold until 2008, or in free breathing with 10 respiratory phases reconstruction (4D-CT) since 2009. Fiducial placement was rarely performed because TACE usually included a radio-opaque agent.

Gross tumor volume (GTV) was delineated on each respiratory phase on pCT, based on pre-treatment MRI and lipiodol tumor uptake. Internal target volume (ITV) was the sum of the GTV phases. Target volumes were outlined by an experienced radiation oncologist and reviewed and validated by an experienced radiologist. An expansion of 5-15mm from the ITV was generated to create the planning target volume (PTV). Planned dose was 54-60 Gy delivered in 17-20 daily fractions of 3 Gy, 5 fractions a week. To correct translational setup errors, daily pre-treatment cone-beam computed tomography (CBCT) were performed. Uninvolved liver volume was defined as total liver minus PTV and had to be  $\geq 700$  cc. Dose constraints to uninvolved liver volume were  $D_{mean} < 25\text{Gy}$  and  $V_{27\text{Gy}} < 33\%$ , while a  $D_{max}$  of 48 Gy was considered to duodenum and stomach. If those constraints could not be respected, a lower prescribed dose of 45 to 51 Gy was considered.

### ***Follow-up***

Follow-up included clinical evaluation, liver CT or MRI, and biological testing of serum alpha-foetoprotein (AFP) level and liver function. Patients were followed 1 month after

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completion of treatment, then every 3 months for two years, every 4 months for 3 years, and every 6 months thereafter.

### ***Outcomes***

Survival outcomes were evaluated from the day of the TACE. Primary outcome was time-to-progression (TTP), defined as the time between TACE and local or distant progression. Secondary outcomes included PFS, OS and severe acute clinical adverse events (AE). PFS was calculated from TACE to local or distant progression, or death from any cause. Severe acute adverse events were defined as grade 3 or higher AE according to common terminology criteria for adverse events version 4.0 (CTCAE v4.0) occurring within the 4 months after treatment.

### ***Statistical analyses***

Categorical and continuous variables were expressed as counts and percentages, and mean and range, respectively. Median follow-up was calculated using the reverse Kaplan Meier method [12]. Survival rates were estimated using the Kaplan Meier method and compared using the log-rank test. Univariate and multivariate Cox proportional hazard model were performed to evaluate the prognostic value of age over 70, alcohol-related liver disease, non-alcoholic fatty liver disease, hepatitis B virus infection, hepatitis C virus infection, Child-Pugh A6/B7, previous treatment of a HCC, tumor size >5cm, RT dose >54Gy and overall RT time. Two-

sided p-value < 0.05 was considered statistically significant. Statistical analysis was performed using R version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

## Results

### *Patient and treatment characteristics*

Between May 2006 and October 2016, 61 patients were included with mean age 68.6 (range 46-86). The characteristics of the study population are reported in Table 1.

Mean pre-treatment platelets, albumin and prothrombin time were 160 Giga/L (range 44-570), 36.8 g/L (24.8-47.6) and 84.9% (65-117), respectively.

Mean interval between TACE and RT was 23.5 days (range 6-111). Mean RT dose was 54.4 Gy (range 48-60), given in daily fractions of 3 Gy (range 3-3). RT was mainly delivered using motion management techniques (n=52, 85.2%) and by 3D conformational RT (3DCRT; n=42, 68.9%) (see Fig.1) or, more recently, intensity modulated techniques (n=19, 31.1%). Mean maximal tumor diameter, PTV volume and uninvolved liver, was 43 mm (range 16-89), 294 cc (42-1256) and 1564 cc (654-2893).

### *Efficacy*

After a median follow-up of 118.2 months (IQR 97.7-123.8), 1- and 5-year TTP were 72.7% (95%CI 62.1-85.1) and 11.5% (95%CI 4.7-28) (see Fig.2). Median TTP was 21.3 months (95%CI 17.5-27.5). Among the 42 progressions, 31 (73.8%) occurred within 2 years. In univariable analysis, no factor was significantly related to TTP (Table 2).

One-year, 5-year and median PFS were 61.7% (95%CI 50.6-75), 6.67% (95%CI 2.59-17.2) and 18.1 months (95%CI 13.5-23) (see Fig.3). In univariable analysis, PFS was significantly related only to dose >54 Gy (HR 2.02, 95%CI 1.05-3.88, p=0.036) (Table 2).

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One-year, 5-year and median OS were 83.3% (95%CI 74.4-93.3), 23.1% (95%CI 14.4-37.1) and 31.5 months (95%CI 25.8-39) (see Fig.4). In univariate and multivariate analyses, OS was significantly related to Child-Pugh A6/B7 (HR 1.93, 95%CI 1.06-3.52,  $p=0.032$ ) and overall RT time (HR 1.93, 95%CI 1.01-1.12,  $p=0.015$ ) (Table 2).

### ***Adverse events and further treatments***

Mean length of hospital stay after TACE was 6 days (range 2-21). Acute symptomatic grade 3+ AE were experienced by 12 patients (19.7%) and were mostly represented by ascites due to portal hypertension ( $n=7$ , 11.5%). These grade 3+ AE were significantly related to Child-Pugh A6/B7 (OR 2.87, 95%CI 1.04-7.9,  $p=0.046$ ) and tended to be related to the volume of the PTV (OR 1.24 per 100cc,  $p=0.07$ ). Nevertheless, it was not related to uninvolved liver volume ( $p=0.66$ ), uninvolved liver Dmean ( $p=0.99$ ), or radiation dose ( $p=0.82$ ). No death was considered possibly related to treatment. Among the 42 patients who relapsed, 31 (73.8%) could receive further treatment, including orthotopic liver transplantation (OLT;  $n=8$ , 13.1%), radiofrequency ( $n=16$ , 38.1%), systemic treatment ( $n=16$ , 38.1%), or surgical resection ( $n=1$ , 2.4%).

### **Discussion**

In patients ineligible for surgical resection or thermoablation, TACE followed by moderately hypofractionated radiotherapy achieves valuable median TTP, PFS and OS of 21.3, 18.1, and 31.5 months, respectively. Our study is one of the first to report long-term results of this combination. In a randomized single center trial including 90 HCC patients with macrovascular invasion, Yoon et al. reported a prognostic improvement with TACE followed by 45 Gy hRT compared to sorafenib (24-week PFS 55.6 vs 7.4%,  $p<0.001$ ) [11]. The 48-week OS in the TACE-hRT group was 55.4%, inferior to what we report here. Indeed, they evaluated

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a population with poorer prognostic, presenting macrovascular invasion and median tumor size of 9.7 cm.

Because follow-up imaging was frequently performed outside of our institution, we were not able to review them to map locoregional failures according to treated volumes. It is well recognized that after surgery most of intrahepatic recurrences are local or marginal during the first 2 years [13,14]. It might be convenient to extrapolate this distribution to the 31 (73.8%) early recurrences we observed. Nevertheless, the prognosis and the evolutionary profile of HCC patients treated with RT has been reported to differ from surgical series. After SBRT, out-of-field recurrences are much more frequent than in-field ones [15,16], and nearly half of them occur within the first year [16].

TACE-hRT is well tolerated with less than 20% symptomatic grade 3 acute AE. We did not plan to evaluate biological toxicity that did not lead to clinical symptoms. Indeed, the CTCAE version used at that time (version 4) did not consider baseline liver enzymes and thus overestimated adverse events, and many old biological data were missing. We did not plan to evaluate late tolerance neither: due to the retrospective design, to the frequent patient comorbidities, and to the high recurrence rate, it would have been difficult to assess the role of the treatment in the development of late symptoms.

Adding RT to TACE significantly improved complete response and OS in two recent meta-analyses [8,10]. While the combination of TACE with conventional RT still achieved poor long-term results [17], hypofractionated RT significantly improved median OS compared to normofractionated one [18]. Dose delivery technics have been improved during the past decades. Intensity-modulated RT (IMRT) and volumetric-modulated arc therapy (VMAT) enable dose escalation without increased risk of radiation-induced liver disease and could thus improve the prognosis [19]. These technical innovations have allowed the development of highly hypofractionated stereotactic body RT (SBRT). This modality is a valuable alternative

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approach in intermediate stage HCC, even in Child B patients [20]. Its performance seems like that of the TACE with 1-year LC and OS around 83% and 53% [21,22]. Its combination with TACE has already been explored and a recent meta-analysis suggest higher local and disease control rate, and longer OS using this association compared to SBRT alone [23]. A recent phase 2 trial evaluated efficacy and safety of 2 courses of TACE followed by 5 fractions SBRT in 32 patients presenting an unresectable HCC from 4 to 7 cm. Complete response was achieved in 63% cases, with 3-year LC of 85% and a median PFS of 35 months. Nevertheless, 2/33 patients presented grade 5 oesophageal variceal bleeds possibly related to treatment [24]. A randomized phase 3 trial is ongoing comparing TACE with TACE plus SBRT in primary and secondary liver carcinoma (NCT03895359).

Daily target visualization is a key element to avoid geographical miss and local control impairment. Improvement from planar to tomographic pre-treatment image-guided radiotherapy (IGRT) were the first steps. Fiducial placement remained usually necessary due to low contrast on pre-treatment CBCT. It can be avoided when performing TACE-hRT since TACE can include a radio-opaque agent, thus limiting medical and economic burden [25]. All our patients benefited from daily pre-treatment CBCT. Nevertheless, treatment guidance long remained a critical issue in liver irradiation because of tumor intrafraction motion. Recent development of magnetic resonance-guided radiotherapy (MRgRT) allowed both daily adaptive planning and surveillance of intrafraction tumor motion [26]. These major innovations can ensure that target volumes are adequately treated and that organs at risk (OAR) are sufficiently protected [27]. In case of close OAR proximity, MRgRT should be the preferred treatment.

Considering these technical improvements in imaging and dose delivery, it is important to note that most of our patients were treated with old therapeutic standards and that emerging treatments such as SBRT limits the indication of this combination. Nevertheless, TACE-hRT

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guided by daily CBCT and delivered by an intensity-modulated technic (ie. IMRT, VMAT or helical RT) can remain a relevant treatment. It may be a preferred option in centers of developing countries unused to perform liver SBRT, or in case of close OAR proximity without the possibility of referral to a center with MRgRT.

Transarterial radioembolization (TARE) should also be compared to the present association. In the LEGACY trial, Salem et al. performed Yttrium-90 TARE to solitary HCC <8 cm, achieving 3-year OS of 86.6% with 19.1% grade 3 adverse events [28]. Nevertheless only 5.6% of patients had tumor of 5 to 8 cm. A recent individual patient data meta-analysis reported that TARE achieved longer TTP but did not improve OS compared to TACE [29]. A comparison of TARE with TACE-hRT may clarify the place of each of these treatments.

Combination of RT with systemic treatment can also be a valuable way to increase tumor control. In advanced HCC, RT combined with sorafenib was reported to improve OS compared to sorafenib alone [30]. Nevertheless, in this indication, the new standard of care is an association of atezolizumab and bevacizumab [31]. An important issue is that more than half of patients experience grade 3-4 side effects [32]. To the best of our knowledge, this systemic combination has never been compared to TACE-hRT in unresectable HCC. In contrast, a recent phase I trial evaluated a combination of SBRT 40 Gy in 5 fractions, followed by nivolumab with or without ipilimumab in 14 unresectable HCC patients [19]. Overall and hepatic grade 3 adverse events occurred in 61.6% and 30.8% cases, respectively. Nevertheless, patients in SBRT-nivolumab-ipilimumab arm (n=7) achieved promising ORR and 3-year OS of both 57% [19].

Best curative treatment of early-stage HCC remains OLT [4]. Nevertheless, comorbidities, tumor characteristics or disease stage contraindicate surgical management in more than 75% patients [5,6]. In some cases, TACE-hRT could be a bridge to OLT. However, a hypothetical increase of surgical morbidity might be expected, since liver irradiation is known

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to induce fibrosis and vascular damages [33,34]. In the current cohort, 13.1% patients could safely undergo OLT after TACE-hRT, making this association a valuable option in this indication. Those results are consistent with previous publications reporting reassuring post-OLT morbidity after RT [35,36]. We previously reported that pre-OLT RT did not increase severe morbidity (34.8 vs 24.2%,  $p=0.289$ ) while achieving 47.8% complete pathological response [36].

Our study has several limitations, mainly represented by its retrospective and single center design. Furthermore, evaluation of long-term side effects is critically lacking in this comorbid population mostly treated with old 3D-CRT technic. Nevertheless, it is one of the first to evaluate long term efficacy and safety of TACE-hRT in this frequent situation. Furthermore, randomized comparison of TACE alone versus TACE-hRT is unlikely after TACERTE phase II randomized trial (NCT01300143) closed due to low accrual, with 126 out of 174 planned patients.

## **Conclusion**

TACE-hRT is a safe effective treatment in fragile Child-Pugh A BCLC-A HCC patients ineligible to surgery or thermoablation, achieving valuable TTP, DFS and OS. Prospective studies are needed to compare this association with radio-embolization, TACE-SBRT, and systemic treatments combinations.

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**Credit Author statement:**

ALLIGNET B.: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Visualization, Writing- Original draft preparation, Writing- Reviewing and Editing, Project administration.

MERLE P.: Conceptualization, Methodology, Resources, Writing- Reviewing and Editing, Supervision.

RODE A.: Resources, Writing- Reviewing and Editing.

MABRUT J.-Y.: Writing- Reviewing and Editing.

MOHKAM K.: Methodology, Writing- Reviewing and Editing, Supervision.

MORNEX F.: Conceptualization, Resources, Writing- Reviewing and Editing, Supervision.

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**References:**

- [1] Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021;71:209–49.
- [2] Howlader N, Noone A, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2018 National Cancer Institute. Bethesda, MD 2018.
- [3] Marrero JA, Kulik LM, Sirlin CB, et al. Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. *Hepatology* 2018;68:723–50.
- [4] Galle PR, Forner A, Llovet JM, et al. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. *J Hepatol* 2018;69:182–236.
- [5] Bolondi L. Screening for hepatocellular carcinoma in cirrhosis. *J Hepatol* 2003;39:1076–84.
- [6] Wang J, Ha J, Lopez A, et al. Medicaid and Uninsured Hepatocellular Carcinoma Patients Have More Advanced Tumor Stage and Are Less Likely to Receive Treatment. *J Clin Gastroenterol* 2018;52:437–43.
- [7] Zhu S-L, Ke Y, Peng Y-C, et al. Comparison of Long-Term Survival of Patients with Solitary Large Hepatocellular Carcinoma of BCLC Stage A after Liver Resection or Transarterial Chemoembolization: A Propensity Score Analysis. *PLoS One* 2014;9:e115834.
- [8] Xie H, Yu H, Tian S, et al. What is the best combination treatment with transarterial chemoembolization of unresectable hepatocellular carcinoma? A systematic review and network meta-analysis. *Oncotarget* 2017;8:100508–23.
- [9] Cai Y, Chang Q, Xiao E, et al. Transcatheter arterial chemoembolization (TACE) combined with  $\gamma$ -knife compared to TACE or  $\gamma$ -knife alone for hepatocellular carcinoma. *Medicine (United States)* 2018;97.

Allignet et al., Long-term results of RTF3 regimen

- [10] Huo YR, Eslick GD. Transcatheter arterial chemoembolization plus radiotherapy compared with chemoembolization alone for hepatocellular carcinoma a systematic review and meta-analysis. *JAMA Oncol* 2015;1:756–65.
- [11] Yoon SM, Ryoo BY, Lee SJ, et al. Efficacy and safety of transarterial chemoembolization plus external beam radiotherapy vs sorafenib in hepatocellular carcinoma with macroscopic vascular invasion : A randomized clinical trial. *JAMA Oncol* 2018;4:661–9.
- [12] Shuster JJ. Median follow-up in clinical trials. *Journal of Clinical Oncology* 1991;9:191–2.
- [13] Yamamoto Y, Ikoma H, Morimura R, et al. Optimal duration of the early and late recurrence of hepatocellular carcinoma after hepatectomy. *World J Gastroenterol* 2015;21:1207–15.
- [14] Imamura H, Matsuyama Y, Tanaka E, et al. Risk factors contributing to early and late phase intrahepatic recurrence of hepatocellular carcinoma after hepatectomy. *J Hepatol* 2003;38:200–7.
- [15] Huang WY, Jen YM, Lee MS, et al. Stereotactic body radiation therapy in recurrent hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys* 2012;84:355–61.
- [16] Gerum S, Heinz C, Belka C, et al. Stereotactic body radiation therapy (SBRT) in patients with hepatocellular carcinoma and oligometastatic liver disease. *Radiation Oncology* 2018;13:100.
- [17] Zhou ZH, Liu LM, Chen WW, et al. Combined therapy of transcatheter arterial chemoembolisation and three-dimensional conformal radiotherapy for hepatocellular carcinoma. *British Journal of Radiology* 2007;80:194–201.

Allignet et al., Long-term results of RTF3 regimen

- [18] Wang C, Li S, Sun A, 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.
- [19] Yoon HI, Lee IJ, Han K-H, et al. Improved oncologic outcomes with image-guided intensity-modulated radiation therapy using helical tomotherapy in locally advanced hepatocellular carcinoma. *J Cancer Res Clin Oncol* 2014;140:1595–605.
- [20] Culleton S, Jiang H, Haddad CR, 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.
- [21] Sapir E, Tao Y, Schipper MJ, et al. Stereotactic Body Radiation Therapy as an Alternative to Transarterial Chemoembolization for Hepatocellular Carcinoma. *Int J Radiat Oncol Biol Phys* 2018;100:122–30.
- [22] Bettinger D, Gkika E, Schultheiss M, et al. Comparison of local tumor control in patients with HCC treated with SBRT or TACE: a propensity score analysis. *BMC Cancer* 2018;18:807.
- [23] Zhao J, Zeng L, Wu Q, et al. Stereotactic Body Radiotherapy Combined with Transcatheter Arterial Chemoembolization versus Stereotactic Body Radiotherapy Alone as the First-Line Treatment for Unresectable Hepatocellular Carcinoma: A Meta-Analysis and Systematic Review. *Chemotherapy* 2019;64:248–58.
- [24] Buckstein M, Kim E, Özbek U, et al. Combination Transarterial Chemoembolization and Stereotactic Body Radiation Therapy for Unresectable Single Large Hepatocellular Carcinoma: Results From a Prospective Phase 2 Trial. *International Journal of Radiation Oncology\*Biography\*Physics* 2022;114:221–30.

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- [25] Chan M, Chiang CL, Lee V, et al. Target localization of 3D versus 4D cone beam computed tomography in lipiodol-guided stereotactic radiotherapy of hepatocellular carcinomas. *PLoS One* 2017;12:e0174929.
- [26] Boldrini L, Corradini S, Gani C, et al. MR-Guided Radiotherapy for Liver Malignancies. *Front Oncol* 2021;11.
- [27] Henke L, Kashani R, Robinson C, et al. Phase I trial of stereotactic MR-guided online adaptive radiation therapy (SMART) for the treatment of oligometastatic or unresectable primary malignancies of the abdomen. *Radiotherapy and Oncology* 2018;126:519–26.
- [28] Salem R, Johnson GE, Kim E, et al. Yttrium-90 Radioembolization for the Treatment of Solitary, Unresectable HCC: The LEGACY Study. *Hepatology* 2021;74:2342–52.
- [29] Brown AM, Kassab I, Massani M, et al. TACE versus TARE for patients with hepatocellular carcinoma: Overall and individual patient level meta analysis. *Cancer Med* 2022.
- [30] Chu SS, Kuo YH, Liu WS, et al. Effect of radiotherapy on survival in advanced hepatocellular carcinoma patients treated with sorafenib: a nationwide cancer-registry-based study. *Sci Rep* 2021;11:1–8.
- [31] Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. *New England Journal of Medicine* 2020;382:1894–905.
- [32] Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. *New England Journal of Medicine* 2020;382:1894–905.
- [33] Maor Y, Malnick S. Liver Injury Induced by Anticancer Chemotherapy and Radiation Therapy. *Int J Hepatol* 2013;2013:1–8.
- [34] Straub JM, New J, Hamilton CD, et al. Radiation-induced fibrosis: mechanisms and implications for therapy. *J Cancer Res Clin Oncol* 2015;141:1985–94.

Allignet et al., Long-term results of RTF3 regimen

- [35] Mohkam K, Golse N, Bonal M, et al. Conformal radiotherapy as a bridge to liver transplantation for hepatocellular carcinoma: is it safe? *Future Oncology* 2016;12:1577–86.
- [36] Mourad M, Mabrut J-Y, Chellakhi M, 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.

**Table 1.** Baseline characteristics.**Table 1.** Caractéristiques initiales.

Variables	TACE-hRT (n=61)
Age, years	68.6 (46-86)
Sex	
Male	48 (78.7%)
Female	13 (21.3%)
Size, mm	43.1 (16-89)
Number of nodules	1.1 (1-3)
Platelets, Giga/L	160 (44-570)
Alpha-Fetoprotein, ng/mL	501 (1-11000)
Bilirubin, $\mu$ mol/L	15.5 (4-32)
Albumin, g/L	36.8 (24.8-47.6)
Prothrombin time, %	84.9 (65-117)
Portal hypertension	
No	32 (52.5%)
Yes	29 (47.5%)
Child-Pugh score	
A5	41 (67.2%)
A6	19 (31.1%)
B7	1 (1.6%)
Underlying liver disease	
Alcohol	29 (47.5%)
Non-alcoholic fatty liver disease	16 (26.2%)
HBV infection	8 (13.1%)
HCV infection	11 (18%)
Hemochromatosis	2 (3.3%)

Cryptogenic	6 (9.8%)
Previous treatment	0.5 (0-4)
RT dose	54.4 (48-60)
EQD <sub>2</sub> <sub>10</sub>	59 (52-65)
RT technique	
3DCRT	42 (68.9%)
IMRT	12 (19.7%)
VMAT	7 (11.5%)

Notes: Categorical variables are expressed in counts (percentage) and continuous variables in mean (range)

Abbreviations: 3D-CRT, 3-dimensional conformal radiation therapy; EQD<sub>2</sub><sub>10</sub>, equivalent dose in 2 Gy fractions with alpha/beta ratio=10; HBV, Hepatitis B Virus; HCV, Hepatitis C Virus; IMRT, intensity modulated radiation therapy; RT, radiotherapy; TACE-hRT, transarterial chemoembolization followed by hypofractionated radiotherapy; VMAT, volumetric modulated arc-therapy

**Table 2.** Uni- and multivariate analyses of time to progression, progression-free survival, and overall survival.

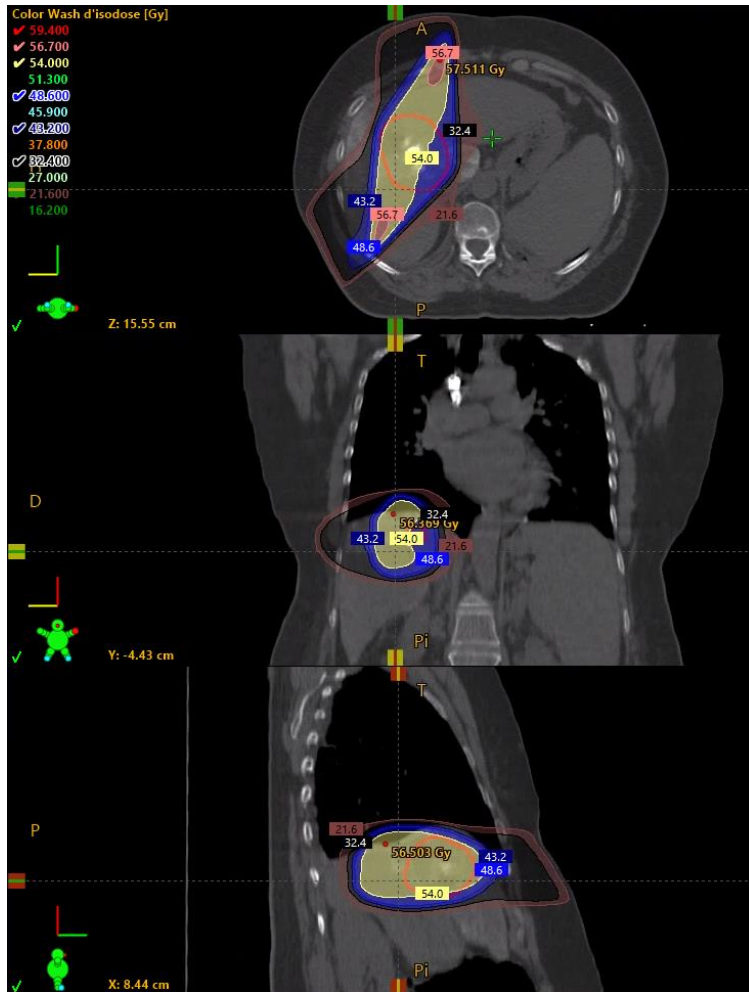
**Table 2.** Analyses uni- et multivariées des temps jusqu'à progression, survie sans progression et survie globale

Variables	TTP		PFS		OS			
	Univariate		Univariate		Univariate		Multivariate	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	P
Age (>70 vs ≤70)	1.23 (0.66- 2.3)	0.5	1.14 (0.66- 1.95)	0.6	1.37 (0.78- 2.42)	0.3	-	-
Child-Pugh cirrhosis (A6 or B7 vs A5)	1.15 (0.57- 2.32)	0.7	1.50 (0.84- 2.69)	0.2	1.82 (1.00- 3.30)	<b>0.048</b>	1.93 (1.06- 3.52)	<b>0.032</b>
Alcohol-related liver disease (yes vs no)	1.34 (0.72- 2.49)	0.4	1.49 (0.87- 2.55)	0.14	1.02 (0.58- 1.78)	0.96	-	-
Non-alcoholic fatty liver disease (yes vs no)	1.56 (0.81- 3.01)	0.2	1.28 (0.71- 2.31)	0.4	1.15 (0.61- 2.13)	0.7	-	-
Hepatitis B virus (yes vs no)	0.68 (0.28- 1.67)	0.4	0.51 (0.21- 1.2)	0.12	0.58 (0.23- 1.46)	0.2	-	-
Hepatitis C virus (yes vs no)	0.7 (0.31- 1.6)	0.4	0.68 (0.33- 1.4)	0.3	0.66 (0.3- 1.41)	0.3	-	-
Previous treatment of a HCC (yes vs no)	1.28 (0.65- 2.51)	0.5	1.11 (0.6- 2.03)	0.7	1.14 (0.6- 2.15)	0.7	-	-
Size (>50 vs ≤50 mm)	0.89 (0.44- 1.78)	0.7	0.95 (0.53- 1.71)	0.9	1.40 (0.75- 2.61)	0.3	-	-

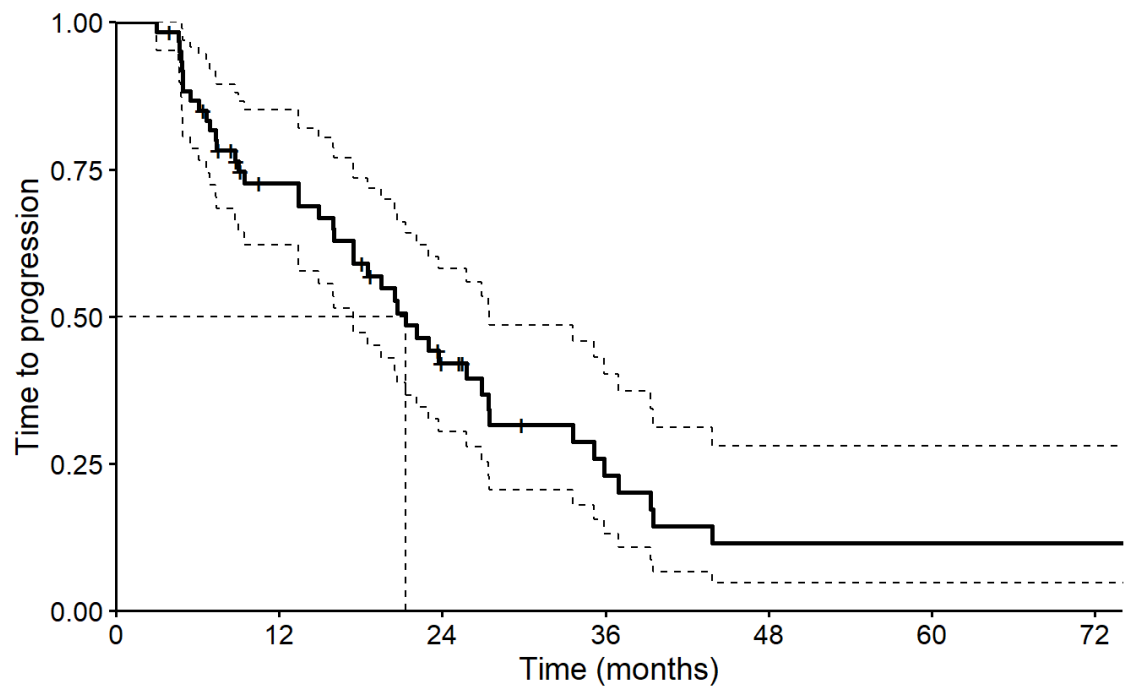
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RT dose	1.87 (0.94-	0.075	2.02 (1.05-	<b>0.036</b>	1.87 (0.94-	0.075	-	-
(>54 Gy vs ≤54 Gy)	3.71)		3.88)		3.71)			
Overall RT time	1.02 (0.97-	0.5	1.03 (0.99-	0.2	1.06 (1.01-	<b>0.024</b>	1.06 (1.01-	<b>0.015</b>
(per day)	1.08)		1.08)		1.11)		1.12)	

Abbreviations: G/L, giga per liter; HCC, hepatocellular carcinoma; OS, overall survival; PFS, progression-free survival; RT, radiation therapy; TTP, time-to-progression

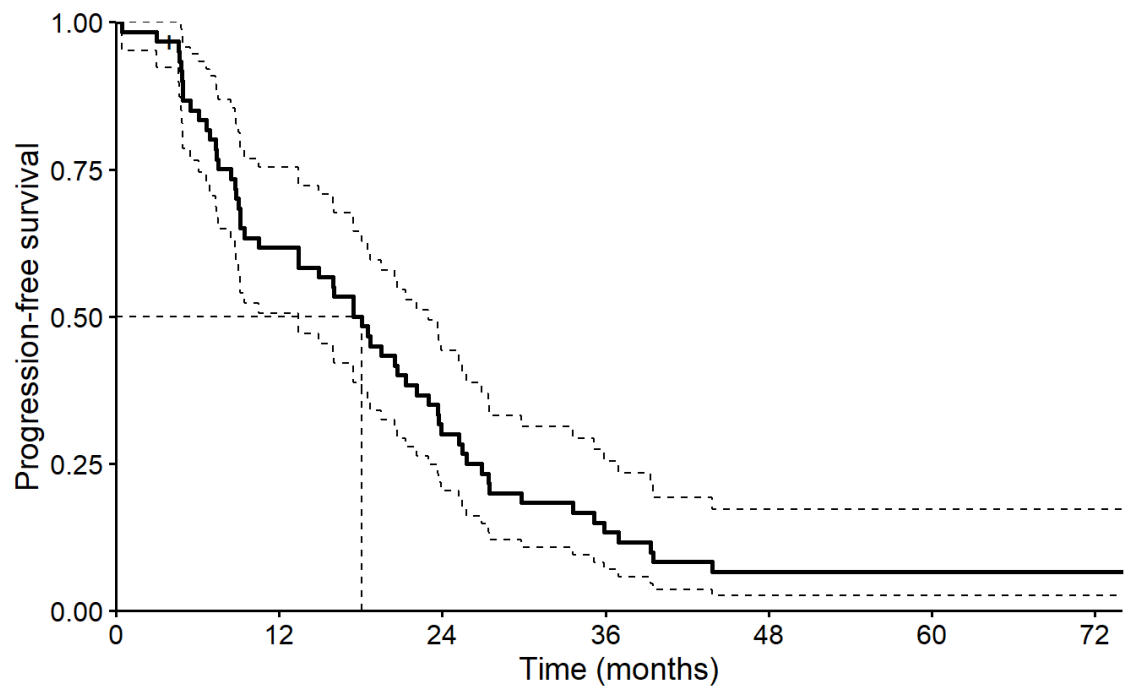


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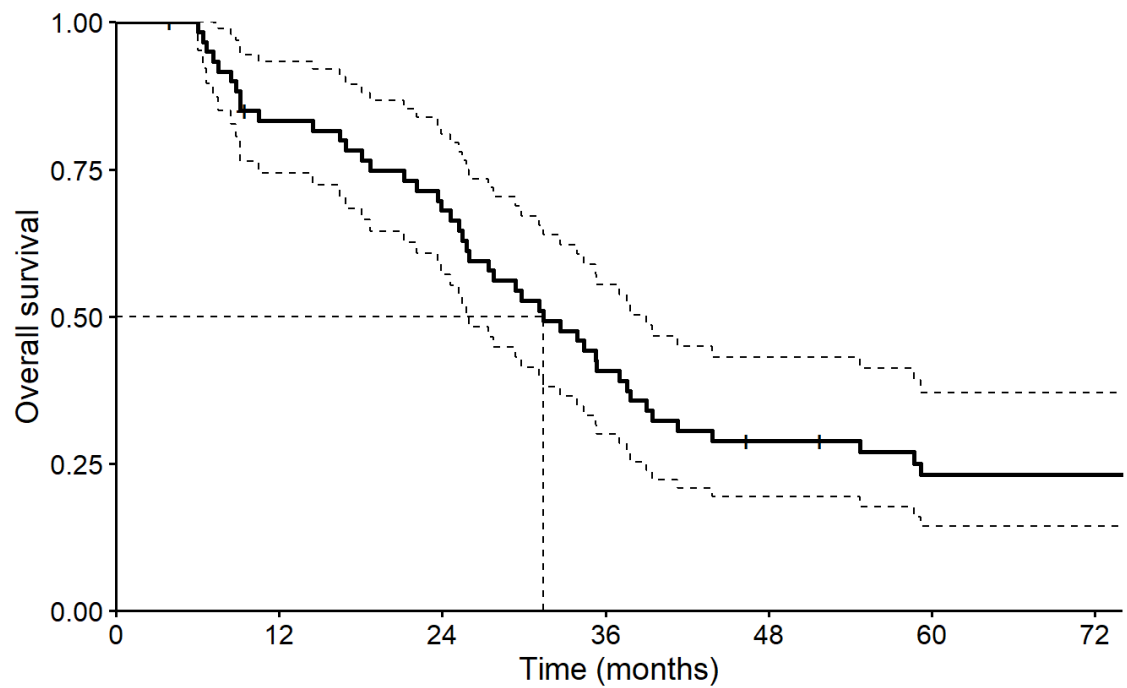
Number at risk

All	61	37	18	8	4	4	4
	0	12	24	36	48	60	72



		Number at risk						
	All	61	37	18	8	4	4	4
	0	12	24	36	48	60	72	
	0	61	37	18	8	4	4	4
	12		37	18	8	4	4	4
	24			18	8	4	4	4
	36				8	4	4	4
	48					4	4	4
	60						4	4
	72							4

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Number at risk

All	61	49	40	24	16	12	12
	0	12	24	36	48	60	72

**Fig. 1.** Typical dose distribution of a treatment performed in three-dimensional conformal radiotherapy, 51 Gy in 17 daily fractions.

**Fig. 1.** Distribution de dose typique d'un traitement réalisé en radiothérapie conformationnelle tridimensionnelle, 51 Gy en 17 fractions quotidiennes.

**Fig. 2.** Time to progression

**Fig. 2.** Temps jusqu'à progression

**Fig. 3.** Progression-free survival

**Fig. 3.** Survie sans progression

**Fig. 4.** Overall survival

**Fig. 4.** Survie globale