Hospices Civils de Lyon

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INSTITUT DE CANCÉROLOGIE
DES HOSPICES CIVILS DE LYON

CHC et thrombose porte néoplasique : Actualités 2021 en Radiothérapie

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**Journée Multidisciplinaire d'Hépatologie et
transplantation hépatique, Lyon, 2 décembre 2021**

Liens d'intérêt

**Consulting: Roche, Boehringer Ingelheim,
Lilly, Astra Zeneca.**

Foie et Radiothérapie

Une association difficile mais réussie

Organe mobile,

Pts fragiles, parenchyme radiosensible,

Le « foie sain » n'est pas sain : *non tumoral*

Organes creux environnants, radiosensibles

Repérage difficile (isodensité)

Autres traitements peu compatibles + RT

Traitement du CHC :

Place de la Radiothérapie.

~~Transplantation
Résection chirurgicale
Radiofréquence~~

T < 5 cm

T > 5 cm

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CLINICAL INVESTIGATION

Liver

FEASIBILITY AND EFFICACY OF HIGH-DOSE THREE-DIMENSIONAL-CONFORMAL RADIOTHERAPY IN CIRRHOTIC PATIENTS WITH SMALL-SIZE HEPATOCELLULAR CARCINOMA NON- ELIGIBLE FOR CURATIVE THERAPIES—MATURE RESULTS OF THE FRENCH PHASE II RTF-1 TRIAL

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• CHC et Radiothérapie : Etude française RTF1

Purpose: Hepatocellular carcinoma (HCC) is a poor prognosis tumor, and only 20% of patients will benefit from curative therapies (surgery, liver transplantation, percutaneous ablation). Although conventional radiotherapy has been traditionally regarded as inefficient and toxic for cirrhotic patients, three-dimensional conformal radiotherapy (3DCRT) has provided promising preliminary data for the treatment of HCC.

Methods and Materials: Prospective phase II trial including Child-Pugh A/B cirrhotic patients with small-size HCC (1 nodule ≤ 5 cm, or 2 nodules ≤ 3 cm) nonsuitable for curative treatments, to assess tolerance and efficacy of high-dose (66 Gy, 2 Gy/fraction) 3DCRT.

Results: Twenty-seven patients were enrolled. Among the 25 assessable patients, tumor response was observed for 23 patients (92%), with complete response for 20 patients (80%), and partial response for 3 patients (12%). Stable disease was observed in 2 patients (8%). Grade 4 toxicities occurred in 2 of 11 (22%) Child-Pugh B patients only. Child-Pugh A patients tolerated treatment well, and 3/16 (19%) developed asymptomatic Grade 3 toxicities.

Conclusion: High-dose 3DCRT is a noninvasive, well-tolerated modality that is highly suitable for the treatment of small HCCs in cirrhotic patients, with promising results. However, additional trials are needed to optimize this technique and formally compare it with the usual curative approaches. © 2006 Elsevier Inc.

Hepatocellular carcinoma, Conformal radiotherapy, Cirrhosis.

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92% contrôle local

● Conformal Radiation for HCC. Phase II trials

Author	n	CRT	OR	Acute toxicity grade ≥ 3	Infield failure rate	Multifocal failure rate	Disease-free survival	Survival
Robertson 1993	11	BF 48-72 Gy	100 %	16 %	-	-	72% (2-year)	-
Dawson 2000	27	BF 30-90 Gy	45 %	-	-	-	-	11 months (median)
Park 2000	158	MF 40-60 Gy	67 %	-	7 %	34 %	-	42% (1-year) 20% à 2-year
Liu 2004	44	MF 40-60 Gy	61 %	0 %	0 %	43 %	-	15 months (median) 61% (1-year) 40% (2-year)
Mornex 2005	27	MF 66 Gy	92 %	11 % Late 1%	26 %* > 2 yrs	43 %	34 months (median)	-

Le CHC est une tumeur très radiosensible

Efficacy and safety of transarterial chemoembolization combined to conformal radiotherapy for uninodular hepatocellular carcinoma

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Original Article

Chimio-embolisation-RT: Conclusions

**L'association chimio-embolisation-RT
est efficace et bien tolérée.**

**Elle permet d'améliorer le contrôle local
et la survie chez des patients présentant
des facteurs de mauvais pronostic.**

Overview: Where Does Radiation Therapy Fit in the Spectrum of Liver Cancer Local-Regional Therapies?

Laura A. Dawson, MD^{*,†}

Experience with radiation therapy for the treatment of hepatocellular carcinoma (HCC) and liver metastases has increased rapidly in the past decade. This is principally because of advances in imaging and radiation techniques that can conform high doses to focal cancers and to a better understanding of how to avoid radiation-induced liver toxicity. Guidelines on how to use radiation therapy safely are becoming more clearly established, and reports of tumor control at 2 to 5 years show the potential for cure after radiation therapy for early-stage HCC and liver metastases. For both HCC and liver metastases, the best outcomes after radiation therapy are found in patients with fewer than 3 lesions that are <6 cm in size, with intact liver function and no extrahepatic metastases. There is a strong rationale for using radiation therapy in patients unsuitable for or with expected poor outcomes after standard local-regional therapies. These patients tend to have advanced tumors (large, multifocal, or invading vessels) and/or impaired liver function, reducing the chance of cure and increasing the chance of toxicity. In these patients, the benefits of radiation therapy over systemic therapy or best supportive therapy should be established in randomized trials.

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SBRT hépatique

2 situations cliniques très différentes :

- CHC : RT à visée curative, pts fragiles**
- MTS : Statut oligoMTS, visée « curative »**

**Dans les 2 situations, haute dose SBRT,
mais prendre en compte l'état hépatique,
l'espérance de vie longue et le cumul des traitements**

Stéréotaxie: SBRT/SABR

Réduire le volume à irradier

Augmenter la dose de RT

**2005 RT 3D
Conformation**

**2012 SBRT
Stéréotaxie**

SBRT hépatique

- **Dose très “conformée”, moulée sur la forme de la T**
- **Dose totale très élevée, dose par fraction élevée**
- **Peu de fractions**
- **Prise en compte du mouvement**
- **Radiothérapie guidée par l’image**
- **Traitement non invasif et ambulatoire, rapide, “entre 2 chimios”, pas d’anesthésie**
- **Taux de contrôle local élevé, > 90%, bonne tolérance.**

SBRT hépatique pour CHC

Seconde cause de mort par cancer dans le monde

- **Lésion < 5 cm, 1-3 lésions, pas de MTS ?** **OMS ≤ 2**
- **Attention à l'état du parenchyme :**
volume foie "sain" > 700 cc
- **BH, CHILD P < B7 si cirrhose.** Bilirub, Album, Prothromb, ascite, encéphalopathie
- **Attention aux traitements précédents**
- **Penser aux traitements futurs**
- **Attention aux organes creux environnants, Rxsensibles**
- **Validation de la SBRT en RCP**

CHC, SBRT-Résultats

16, Vol. 108, No. 9

REVIEW

Radiotherapy for Hepatocellular Carcinoma: New Indications and Directions for Future Study

Nitin Ohri, Laura A. Dawson, Sunil Krishnan, Jinsil Seong, Jason C. Cheng, Shiv K. Sarin, Milan Kinkhabwala, Mansoor M. Ahmed, Bhadrasain Vikram, C. Norman Coleman, Chandan Guha

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Table 1. Results from selected series of stereotactic radiotherapy for hepatocellular carcinoma reporting local control rates at two to three years

First author (country)	Sample size	SBRT schedule	Prescription point/volume	Median follow-up (range)	Local control
Andolino (United States)	60 patients	24–48 Gy, 3–5 fx	PTV (80% IDL)	27 mo	90% at 2 y
Dewas (France)	42 patients*, 48 lesions*	Median 45 Gy, 3 fx	PTV (80% IDL)	15 mo	91% at 2 y
Honda (Japan)	30 patients*	Median 48 Gy, 4 fx	Isocenter	12 mo (6–38)	94% at 2 y
Jang (Korea)	82 patients, 95 lesions	<45 Gy, 3 fx (n = 11) 45–54 Gy, 3 fx (n = 47) >54 Gy, 3 fx (n = 57)	PTV (70%–80% IDL)	30 mo (4–81)	87% at 2 y
Kang (Korea)	47 patients	Risk-adapted, 3 fx	PTV (70%–80% IDL)	17 mo (6–38)	95% at 2 y
Kwon (Korea)	42 patients	Median 33 Gy, 3 fx	PTV (70%–85% IDL)	29 mo (8–49)	68% at 3 y
Sanuki (Japan)	185 patients	35 Gy, 5 fx (n = 48) 40 Gy, 5 fx (n = 137)	PTV (70%–80% IDL)	25 mo† (3–80)	91% at 3 y
Wahl (United States)	63 patients, 83 lesions	27–60 Gy, 3–5 fx	PTV (75%–85% IDL)	13 mo	84% at 2 y

*Subset of larger cohort with hepatocellular carcinoma. fx = fractions; IDL = isodose line; PTV = planning target volume; SBRT = stereotactic body radiotherapy.

†Estimate.

EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma[☆]

European Association for the Study of the Liver^{*}

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National Comprehensive Cancer Network^{*}
**NCCN Guidelines Version 3.2018
Hepatocellular Carcinoma**

[NCCN Guidelines Index](#)
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[Discussion](#)

PRINCIPLES OF LOCOREGIONAL THERAPY

Radiation Therapy

- EBRT is a treatment option for patients with unresectable disease, or for those who are medically inoperable due to comorbidity.
- All tumors irrespective of the location may be amenable to radiation therapy (3D conformal radiation therapy, intensity-modulated radiation therapy [IMRT], or stereotactic body radiation therapy [SBRT]). Image-guided radiotherapy is strongly recommended when using EBRT, IMRT, and SBRT to improve treatment accuracy and reduce treatment-related toxicity.
- Hypofractionation with photons²⁵ or protons^{26,27} is an acceptable option for intrahepatic tumors, though treatment at centers with experience is recommended.
- SBRT is an advanced technique of hypofractionated EBRT with photons that delivers large ablative doses of radiation.
- Dosing for SBRT is generally 30–50 Gy in 3–5 fractions, depending on the ability to meet normal organ constraints and underlying liver function. Other hypofractionated schedules >5 fractions may also be used if clinically indicated.
- There is growing evidence for the usefulness of SBRT in the management of patients with HCC.^{18,19} SBRT can be considered as an alternative to the ablation/embolization techniques mentioned above or when these therapies have failed or are contraindicated.
- SBRT (1–5 fractions) is often used for patients with 1 to 3 tumors. SBRT could be considered for larger lesions or more extensive disease, if there is sufficient uninvolved liver and liver radiation tolerance can be respected. There should be no extrahepatic disease or it should be minimal and addressed in a comprehensive management plan. The majority of data on radiation for HCC liver tumors arises from patients with Child-Pugh A liver disease; safety data are limited for patients with Child-Pugh B or poorer liver function. Those with Child-Pugh B cirrhosis can be safely treated, but they may require dose modifications and strict dose constraint adherence.²⁰ The safety of liver radiation for HCC in patients with Child-Pugh C cirrhosis has not been established, as there are not likely to be clinical trials available for Child-Pugh C patients.^{21,22}
- Proton beam therapy (PBT) may be appropriate in specific situations.^{23,24}
- Palliative EBRT is appropriate for symptom control and/or prevention of complications from metastatic HCC lesions, such as bone or brain.

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ScienceDirect

journal homepage: www.jfma.com

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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References

HCC-E
2 OF 3

Original Article

Management consensus guideline for hepatocellular carcinoma: 2016 updated by the Taiwan Liver Cancer Association and the Gastroenterological Society of Taiwan

Surveillance group, Diagnosis group, Staging group, Surgery group, Local ablation group^{*}, TACE/TARE/HAI group, Target therapy/systemic therapy group, Radiotherapy group, Prevention group, Drafting group

Consensus Guidelines

Consensus for Radiotherapy in Hepatocellular Carcinoma from The 5th Asia-Pacific Primary Liver Cancer Expert Meeting (APPLE 2014): Current Practice and Future Clinical Trials

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Wan-Yee Lau^k Kwang Hyub Han^l Pierce Kah-Hoe Chow^m
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Original article

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Stereotactic body radiotherapy for liver tumors

Principles and practical guidelines of the DEGRO Working Group on Stereotactic Radiotherapy

Attention au tube digestif et aux ATCD

Table 7 Dose constraints for stomach and duodenum in liver SBRT

	Bae et al. [5]	Kavanagh et al. [36]	Rusthoven et al. [63]
Number of fx	3	3	3
Gy/fx	15 (11–20)	12–20	20
Prescribed isodose	70–87% covering PTV (CyberKnife) 92–98% covering PTV (Rapid Arc)	PTV	80–90% covering PTV
Stomach		$D_{\max} \leq 30$ Gy	$D_{\max} \leq 30$ Gy
Duodenum			$D_{\max} \leq 30$ Gy
≥ 3 gastroduodenal toxicity	$D_{\max} 35$ Gy: 5% $D_{\max} 38$ Gy: 10%	No	No

Thrombose porte néoplasique (PVTT)

Thrombose porte néoplasique (PVT)

Situation clinique rare en oncologie

**Pronostic sombre (BCLC C), hétérogénéité pts
risque d'essaimage, pronostic vital engagé**

Place pour un traitement local agressif ?

**RT : Forme tumorale spécifique : vaisseaux
Quel volume irradier ? Dose ?
Associations thérapeutiques ?**

BCLC staging. Update 2022

BCLC strategy for prognosis prediction and treatment recommendation Barcelona Clinic Liver Cancer (BCLC) staging system. The 2022 update

M. Reig, A. Forner, J. Rimola, J. Ferrer-Fàbrega, M. Burrel, A. Garcia-Criado, R.K. Kelley, P.R. Galle, V. Mazzaferro, R. Salem, B. Sangro, A.G. Singal, A. Vogel, J. Fuster, C. Ayuso, J. Bruix

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 Reference: JHEPAT 8515

To appear in: *Journal of Hepatology* **FIGURE 1**

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Quel traitement local ?

Associations ?

Table 1. Locoregional therapies for HCC with PVTT.

Study	Type	Size	PVTT	Treatment	Outcomes
Luo 2011 [17]	Prospective	164	Vp1-Vp4	TACE	12- and 24-mos. OS of 30.9% and 9.2%, downstaging in 10.7%
Zhu 2014 [18]	Retrospective	91	Vp2, Vp3	TACE + sorafenib	OS 14 mos
Yoon 2018 [19]	RCT	90	Vp 2-Vp4	TACE + ERBT	OS 13.8 mos, downstaging in 11.1%
Venerito 2020 [15]	Meta-analysis	1243	Vp 2-Vp4	TARE	Non-inferiority of TACE to sorafenib
Garin 2015 [20]	RCT	41	Vp 2-Vp4	Personalized Dosimetry TARE	OS 22.9 mos, downstaging in 12.2%
Yang 2012 [21]	RCT	104	Vp 1-Vp4	Cryotherapy + sorafenib	OS 12.5 mos
Giorgio 2016 [22]	RCT	99	Vp4	RFA + sorafenib	1-, 3-, and 5-year OS: 63%, 30%, and 20%
Ding 2020 [23]	Prospective	80	Vp1-Vp3	RFA + TACE + sorafenib	OS 15.3 mos
Long 2016 [24]	Prospective	109	Vp2-Vp4	MWA after TACE	OS 13.5 mos

PVTT = portal vein tumor thrombus; RCT = randomized, controlled trial; TACE = transarterial chemoembolization; ERBT = external beam radiotherapy; TARE = transarterial radioembolization; RFA = radiofrequency embolization; MWA = microwave ablation; downstaging refers to the percentage of patients who were able to undergo resection or ablation following treatment.

SBRT pour thrombose porte tumorale

Advanced radiotherapy technique in hepatocellular carcinoma with portal vein thrombosis: Feasibility and clinical outcomes

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Fig 1. Kaplan-Meier analysis of overall survival.

Table 4. Tumor, PVTT and overall response after the completion of the RT.

Response	Tumor Response (n = 81)	PVTT Response (n = 117)	RR 84% Tox G>3 14%
CR	16 (19.8%)	26 (22.2%)	
PR	44 (54.3%)	72 (61.5%)	
SD	12 (14.8%)		
PD	9 (11.1%)	19 (16.2%)	
Responder (CR + PR)	60 (74.1%)	98 (83.8%)	
Non-responder (SD + PD)	21 (25.9%)	19 (16.2%)	

Table 2. Univariate and multivariate analyses of potential prognostic factors for overall survival.

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P-value	HR	95% CI	P-value
Age (< 60 yr vs ≥ 60 yr)	1.35	0.96–1.91	0.09	1.03	0.66–1.60	0.90
ECOG-PS (2 vs 0–1)	2.08	1.39–3.09	< 0.001	1.41	0.79–2.52	0.24
Child-Pugh score (B or C vs A)	1.85	1.28–2.67	0.001	1.07	0.64–1.79	0.79
Hepatitis B/C infection (yes vs no)	1.02	0.69–1.49	0.94			
Tumor size (≥ 10 cm vs < 10 cm)	2.62	1.82–3.77	< 0.001	2.00	1.27–3.14	0.003
PVTT location (main/bilateral first branch vs others)	1.22	0.86–1.73	0.26			
BED10 (< 56 Gy vs ≥ 56 Gy)	2.64	1.81–3.83	< 0.001	1.83	1.15–2.90	0.01
Overall response (SD/PD vs CR/PR)	2.04	1.31–3.19	0.002	2.00	1.26–3.17	0.003
RT technique (non-SBRT vs SBRT)	1.18	0.71–1.96	0.53			

Taille tumeur
Dose RT
Répondeur

La SBRT peut permettre une restauration du flux portal : Aspect dynamique de l'efficacité

Stereotactic body radiotherapy based
treatment for hepatocellular carcinoma
with extensive portal vein tumor
thrombosis

Yongjie Shui¹, Wei Yu^{1,4}, Xiaoju Ren^{1,4}, Yinglu Guo^{1,4}, Jing Xu^{1,4}, Tao Ma², Bicheng Zhang¹, Jianjun Wu³,
Qinghai Li³, Qiongge Hu¹, Li Shen¹, Xuelli Bai², Tingbo Liang² and Qichun Wei^{1,4*}

**Un traitement
local devient
possible après
SBRT**

Taux de réponse Taux de réponse complète

79% à 3 mois

10% 3 mois

84% à 6 mois

32% 6 mois

50% 9 mois

SBRT puis TACE

**Hoon Sik Choi,
Asia Pacific Journal
of Clinical Oncology,
Aug 2020**

Radio-embolisation / SIRT / TARE + SBRT

Combination of yttrium-90 radioembolization with stereotactic body radiation therapy in the treatment of portal vein tumor thrombosis

Jason Liu¹, Colton Ladbury¹, Arya Amini¹, Scott Glaser¹, Jonathan Kessler², Aram Lee², Yi-Jen Chen¹

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**Y90: 104 Gy, 846 ml
pour le parenchyme**

**SBRT: 30 Gy en 5 Fx, 91 ml
pour thrombus, PVTT
1 mois d'intervalle
12 pts**

Fig. 2. Local control for all patients.

Fig. 4. Example of a SBRT plan to the PVTT and near CR after treatment. Patient #12 was an 83-year-old Asian male with hepatocellular carcinoma who received surgery, transarterial chemoembolization, and sorafenib, but progressed with worsening PVTT. Patient was treated with ⁹⁰Y radioembolization 107.3 Gy followed by SBRT 27.5 Gy in 5 fractions. Patient had near CR 3 months after SBRT. SBRT, stereotactic body radiation therapy; PVTT, portal vein tumor thrombosis; CR, complete response.

MRI-Guided Radiotherapy

- Meilleure visualisation de la tumeur (important pour CHC)
- Contourage plus précis
- Intégration des mouvements tumoraux,
- Suivi de la cible en temps réel,
- Faibles marges (épargne parenchyme)

IRM unity Elekta 1,5T Lyon Sud

Journal of Cancer Research and Clinical Oncology
<https://doi.org/10.1007/s00432-021-03788-z>

ORIGINAL ARTICLE – CLINICAL ONCOLOGY

MRI-guided radiotherapy for PVTT in HCC patients: evaluation of the efficacy and safety

So Jung Lee¹ · Myungsoo Kim¹ · Yoo-Kang Kwak¹ · Hye Jin Kang¹

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Fig. 1 Example of plan of stereotactic body radiation therapy for portal vein tumor thrombi. The patient received stereotactic body radiation therapy of 50 Gy in 5 fractions for portal vein tumor thrombus. Prescription dose was planned to cover more than 95% of the PTV volume (D_{95%} = 100%). The volume of normal liver that irradiated

less than 15 Gy was more than 700 cm³. *Orange line—95% isodose line, yellow line—90% isodose line, green line—80% isodose line, cyan line—42% isodose line (21 Gy), blue line—30% isodose line (15 Gy)

12 Pts, 83% contrôle local
8 TACE post RT

Conclusion MRI-guided tumor tracking HFRT and SBRT was a feasible, effective, and safe treatment option in HCC patients with tumor thrombi in the main trunk or first branch of the portal vein.

Mr FE DE A

CHC chez un patient de 63 ans envahissant la veine cave inférieure et la branche portale droite

**Radiothérapie 60Gy/20fr puis ATEZOLIZUMAB et BEVACIZUMAB
Excellente tolérance du traitement**

Couverture dosimétrique

Coupe supérieure

Coupe moyenne

Coupe inférieure

Isodose 95%

Mr C.P

Récidive de CHC chez un patient de 54 ans au niveau du dôme hépatique avec thrombose cave inférieure tumorale remontant jusqu'à l'oreillette droite.

Avant

Après (délai 3 mois)

**Résultat après RT (68 Gy/17 fr) puis ATEZOLIZUMAB BEVACIZUMAB
Toxicité: Œsophagite grade 2**

Couverture dosimétrique

Coupe supérieure

Coupe moyenne

Coupe inférieure

Isodose 95%

Au total

**PVTT fréquente (50%), pronostic sombre (C)
Chirurgie, TACE difficiles**

Sélection des patients nécessaire, RCP

Approche multidisciplinaire

SBRT: efficacité, tolérance

Rôle majeur à jouer, en association **ATZ Bev...**

Permet traitements locaux (Xie, TACE, TARE)