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Original article

Long-term outcome of Stereotactic Body Radiation Therapy for patient with unresectable liver metastases from colorectal cancer

Radiothérapie stéréotaxique des métastases hépatiques des cancers colorectaux : résultats à long terme d'une étude rétrospective monocentrique

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ABSTRACT

Purpose. – To investigate clinical outcome and predicting factors of local failures in patients with colorectal cancer treated for unresectable liver metastases with stereotactic body radiation therapy (SBRT).
Methods and materials. – We restrospectively reviewed the medical records of 67 patients treated with the Cyberknife SBRT system for 99 hepatic metastases between January 2007 and December 2015 in our center. In total, 37.5 to 54.0 Gy in 3 to 5 fractions were prescribed to the 80% isodose line. Local control (LC), intrahepatic progression incidence, Progression-Free Survival (PFS), Overall Survival (OS) and toxicity were evaluated.
Results. – The median follow-up was 47 months (IQR, 28–59 months). The median OS was 53 months, the 2-year OS and PFS rates were 81.4% and 54.0%. The 1- and 2-year LC rates were 86.6% and 72.4%. In the multivariate analysis, the degree of differentiation was the only prognostic factor for LC (HR 0.31, 95% CI, 0.10–0.98, $P = 0.046$). Margin expansion > 5 mm was not associated with a better LC (HR 0.72, 95% CI, 0.38–1.37, $P = 0.317$). Performans Status ≥ 2 (HR 3.27, 95% CI, 1.07–9.98, $P = 0.038$), chemotherapy for metastases before SBRT (HR 0.36, 95% CI, 0.18–0.75, $P = 0.006$) and regional lymph node at diagnosis (HR 2.19, 95% CI, 1.09–4.43, $P = 0.029$) were independent prognostic factors for OS. We report 2 cases of grade ≥ 3 toxicity (3.0%) – one grade 3 acute nausea and one grade 3 late gastric ulcer.
Conclusion. – Stereotactic body radiation therapy is an effective and well-tolerated treatment that allow high LC for liver metastases from colorectal cancer during the first two years. A prescription dose of 45 Gy in 3 fractions to the 80% isodose line with a risk adapted schedule to respect Organ At Risk constraints allows a low rate of toxicity.
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RÉSUMÉ

Objectif de l'étude. – Évaluer les résultats cliniques et les facteurs prédictifs de récidive locale des patients traités pour des métastases non résécables de cancer colorectal par par irradiation stéréotaxique par Cyberknife®.
Matériel et méthodes. – Nous rapportons rétrospectivement les données de 67 patients traités par Cyberknife® pour 99 métastases hépatiques entre janvier 2007 et décembre 2015 dans notre centre. Des doses de prescription de 37,5 à 54 Gy en trois à cinq fractions ont été prescrites sur l'isodose 80 %. Les taux de contrôle local, de progression intrahépatiques, de survie sans progression, de survie globale et la toxicité sont rapportés.

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Résultats. – Le suivi médian était de 47 mois (IQR, 28–59 mois). La survie globale médiane était de 53 mois, les probabilités de survies globale et sans progression à 2 ans étaient de 81,4 % et 54,0 %, celles de contrôle local à 1 et 2 ans étaient de 86,6 % et 72,4 %. En analyse multifactorielle, le degré de différenciation était le seul facteur prédictif indépendant pour le contrôle local (HR [*Hazard Ratio*] : 0,31 ; intervalle de confiance à 95 % [IC 95 %] : 0,10–0,98 ; $p = 0{,}046$). Des marges d'extension du CTV (volume cible anatomoclinique) de plus de 5 mm n'étaient pas associées à un meilleur taux de contrôle local (HR : 0,72 ; IC 95 % : 0,38–1,37 ; $p = 0{,}317$). Un indice de performance de 2 ou plus (HR : 3,27 ; IC 95 % : 1,07–9,98 ; $p = 0{,}038$), l'administration de chimiothérapie avant la radiothérapie stéréotaxique (HR : 0,36 ; IC 95 % : 0,18–0,75 ; $p = 0{,}006$) et l'atteinte ganglionnaire initiale (HR : 2,19 ; IC 95 % : 1,09–4,43 ; $p = 0{,}029$) étaient des facteurs indépendants prédictifs pour la survie globale. Nous rapportons deux cas de toxicité de grade ≥ 3 (3,0 %).

Conclusion. – La radiothérapie stéréotaxique est un traitement efficace, sécurisé permettant l'obtention de taux contrôle local importants dans les deux premières années de suivi dans le traitement des métastases hépatiques des cancers colorectaux. Un schéma de 45 Gy en trois fractions sur l'isodose 80 %, possiblement adapté pour respecter les contraintes dans les organes à risque, est associé à un faible taux de toxicité sévère.

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1. Introduction

1.1. Background

Colorectal cancer is one of the most common cancers, representing an incidence of almost 10% [1]. The proportion of patients with synchronous liver metastases from colorectal cancer (CRLM) was 14% and the 5-year cumulative metachronous CRLM rate was 15% in a large French population-based cancer registry [2,3]. Surgery is the gold standard treatment with 5 and 10-year survival rate of 38% and 26% respectively [4]. However, only 10 to 25% of patients are amenable to resection due to impaired general health status, unfavorable anatomical location or an insufficient anticipated functional parenchyme [5]. In this situation, thermal ablation including radiofrequency ablation (RFA) is the most widely used alternative [6–8] and an ongoing phase III trial is comparing the two approaches for small CRLM [9]. However, thermal ablation has some limitation such as the proximity with vasculature or major bile duct (heat sinks) and large lesions ($\geq$ 2–3 cm) [10,11]. Advances in radiation therapy technology made it possible to deliver ablative doses to limited volume of the liver with high precision in a few sessions. Stereotactic Body Radiation Therapy (SBRT) was prospectively reported to provide a safe treatment with a high local control rate [12–15]. A survival benefit is observed if local control of individual metastases has been achieved [16]. The optimal fractionation schedule and margins remain unclear. The aim of this study was to report the long-term effectiveness and tolerance of SBRT in CRLM.

2. Methods and materials

2.1. Study design

Our research was a retrospective cohort study.

2.2. Setting

We collected the data of all the patients treated with SBRT for liver metastases of CCR from January 2007 to December 2015 in our institution.

2.3. Data sources/measurement

All consecutive patients were retrieved from the Comprehensive Cancer Centers of Lorraine–Alexis Vautrin database. Data were collected in 2017 and analyzed in first half of 2018.

2.4. Population

CRLM management was discussed in a multidisciplinary tumor board on a weekly basis. We included adult patients with an Eastern Cooperative Oncology Group (ECOG) score inferior or equal to 2, one to four liver metastases from an histological proven colorectal adenocarcinoma, radical resection of the primary tumor, inoperable metastasis or patient, a maximum individual tumor diameter inferior to 6 cm. Patients with ascites and/or biliodigestive derivation were recused. Extrahepatic disease was allowed, provided it was potentially treatable with surgery or ablative local therapy. Previous treatments were allowed (surgery, thermal ablation, chemoembolization, chemotherapy).

2.5. Intervention

Patients underwent standard pretreatment staging including history, physical examination, a blood test including liver exploration, a contrast-enhanced dynamic liver magnetic resonance imaging (MRI) or an abdominal contrast enhanced computerized tomography scan when MRI was not feasible.

Patients underwent implantation of 2–4 gold fiducial seeds into- or adjacent to the liver tumor using either Computed Tomography (CT) or ultrasound guidance.

Radiation planning was performed 7 days after seed placement to accommodate for potential migration. Patients were immobilized during CT simulation and treatment with a customized, external vacuum mattress type contention. Planning CT-scan included two acquisitions of one millimeter thick slices, 40 and 80 seconds after contrast agent injection.

The Gross Tumor Volume (GTV) was defined on the best of either the contrast-enhanced planning CT or pre-treatment MRI, using image fusion, depending on image quality. The Clinical Target Volume (CTV) was obtained adding a 3 to 10 millimeters isotropic margin to the GTV. During the first period of this study (2007–2011) we applied an isotropic 3 mm margin, increased to 5–10 mm depending on the proximity of stomach or duodenum during the second period (2012–2015). The Planning Target Volume (PTV) was obtained adding a 3 mm isotropic margin to the CTV. Organs at risk (OAR) included whole liver, healthy liver (total liver minus GTV), esophagus, duodenum, bowels, stomach, kidney, spinal cord, lungs and heart. Table 1 present dosimetric constraints to OAR, according to QUANTEC recommendations [17–22].

Standard dose prescription was 45 Gy in 3 fractions corresponding to a Biologically Effective Dose (BED) of 112.5 Gy_{10}, 2 fractions

Table 1
Characteristics of the 67 patients and the 99 colorectal liver metastases.

Patient characteristics ($n = 67$)	No. (%) or median [IQR]
Age at time of SBRT (y)	66.0 [57.5–79.5]
Sex (male)	47 (70.1)
ECOG Performance Status	
0	27 (40.3)
1	34 (50.7)
2–3	6 (9.0)
Degree of differentiation	
Well differentiated	14 (20.9)
Moderately differentiated	51 (76.1)
Poorly differentiated	2 (3.0)
Tumor site	
Right colon	14 (20.9)
Transverse colon	1 (1.5)
Left colon	9 (13.4)
Sigmoid	22 (32.8)
Rectosigmoid junction	7 (10.5)
Rectum	14 (20.9)
Tumor staging (missing data = 1)	
T1-T2	7 (10.6)
T3	50 (75.8)
T4	9 (13.6)
Node staging (missing data = 2)	
N0	19 (29.2)
N1	26 (40.0)
N2	20 (30.8)
LVI (yes)	45 (70.3)
Extra-hepatic metastases (yes)	12 (17.9)
Time from initial diagnosis to liver metastases	
Synchronous (DFI $\leq$ 3 months)	29 (43.3)
Metachronous (DFI > 3 months)	38 (56.7)
Number of treated metastases	
1	42 (62.7)
$\geq$ 2	25 (37.3)
Primary tumor treatment	
Surgery alone	14 (20.9)
CT and surgery	37 (55.3)
Concomitant CRT and surgery	8 (11.9)
Other	8 (11.9)
Metastases characteristics ($n = 99$)	**No. (%) or median [IQR]**
Synchronous metastasis	41 (41.4)
Tumor size (mm)	23.0 [16–33]
Tumor volume (cm^3)	6.9 [2.6–17.0]
Focal liver treatment before SBRT	
Nil	53 (53.5)
Surgery alone	35 (35.3)
RFA alone	3 (3.0)
Surgery and RFA	8 (8.0)
MRI before treatment (yes)	79 (79.8)
Number of CT lines before SBRT treatment	
0	29 (29.3)
1	46 (46.5)
2	21 (21.2)
3–4	3 (3.0)

BRT: Stereotactic Body Radiation Therapy; ECOG: Eastern Cooperative Oncology Group; LVI: Lymphovascular Invasion; DFI: Disease-Free Interval; CT: Chemotherapy; CRT: Chemo-Radiation Therapy; RT: Radiation Therapy; RFA: Radiofrequency Ablation; MRI: Magnetic Resonance Imaging.

weekly, reported to the 80% isodose, encompassing at least 95% of the PTV. Dose and fraction schedule could be adapted to respect dosimetric constraints of the OAR (BED from 59.5 to 112.5 Gy_{10}, in 3 to 5 fractions).

Treatments were delivered with the Cyberknife® (Accuray, Sunnyvale, California, U.S.A.), delivering 6MV photons. Synchrony® Respiratory Tracking System was used, enabling the tracking of tumor movement in real time.

For synchronous metastases, treatment of both metastases was done in the same plan if possible, and in sequential with a dose summation of the two treatment plans when not achievable.

Based on the linear quadratic model of cell survival following radiation therapy, the BED was calculated ($BED = nd\,[1 + d/\alpha/\beta]$), with n = the number of fractions, d = the dose per fraction and α/β value = 10 for tumor), allows for the comparison of the effects of different dose fractionation schemes.

Quality of treatment plan was assessed by reporting the PTV coverage defined as the volume of the PTV receiving at least the prescription dose divided by the total volume of the target multiplied by 100. Conformality index was defined as the prescribed isodose volume divided by the tumor volume encompassed by the prescription isodose line and dose heterogeneity index as the maximum dose divided by prescribed dose.

2.6. Patients' follow-up

Patients were evaluated weekly during radiation with physical examination. After the completion of SBRT, physical exam was performed quaterly the first year and at least every 6 months thereafter combined with hepatic contrast-enhanced MRI (or CT-scan when MRI not feasible) and a thoracic-abdominal-pelvic CT-scan or 18F-fluoro-deoxyglucose (18F-FDG) positron emission tomography-computed tomography (PET-CT).

2.7. Variable collected

The following variables were retrospectively collected from medical charts:

- patient-related variables (gender, age, ECOG score, hepatopathy);
- primitive tumor related variables (tumor stage [T], clinical node stage [N], degree of differentiation, location, treatment);
- extrahepatic associated metastases (location, number of metastases, treatment);
- number of liver metastases and sum of all lesions;
- metastasis-related variables (target diameter, location, volume, location, prior treatments);
- dosimetric-related variables (dose and fraction schedule, BED, isodose line prescription, GTV, CTV, PTV, coverage index, conformity index, heterogeneity index, mean dose to the liver (Dmean), liver volume receiving 10 Gy (V10), 15 Gy (V15), 21 Gy (V21), 30 Gy (V30), maximum dose (Dmax) and V21 to stomach and to duodenum;
- Toxicity-related variables (time from treatment, type, grade).

2.8. End point and statistical methods

Primary end point:

- the primary end point was local control evaluated independently for each lesion using Response Evaluation Criteria in Solid Tumors (RECIST) criteria v1.1 [23]. Complete response (CR) was defined as the disappearance of the target lesion; partial response (PR), as at least a 30% decrease of diameter of the target lesion and progressive disease (PD) as at least a 20% increase of diameters of the target lesion. Time to local progression was measured from the first day of radiation to the day PD of the irradiated tumor was first noticed.

Secondary end points:

- toxicity was evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Acute toxicity was defined as adverse effect occurring within the 3 months after the end of the treatment. Classic and non-classic Radiation induced liver disease (RILD) were defined according to Lawrence's

criteria [21] and to QUANTEC [14], and hepatic toxicity was defined as RILD or ascites;
- overall Survival (OS) and Progression Free Survival (PFS) were measured from the first day of the first (or only) treatment until the date of progression or death;
- intrahepatic progression incidence was defined as the incidence of in-field or out-of-field hepatic progression.

2.9. Statistical methods

The results were expressed as mean and standard deviations for quantitative variables or as median and interquartile range (IQR) according to the normality of the distribution, assessed by the Kolmogorov–Smirnov test. Qualitative variables were expressed as frequencies and percentages.

The local failure was described by the cumulative incidence method since out-of-filed hepatic recurrences, extrahepatic recurrences and death were considered as competing risk events. The proportional subdistribution hazards regression method proposed by Fine and Gray was used to investigate each prognostic factor. The same model was applied for hepatic progression incidence in order to considered extrahepatic progression and death as competing event.

The description of OS and PFS was performed by the Kaplan–Meier method. The association between OS or PFS and each prognostic factor was first investigated using univariate Cox proportional hazards models. The validity of the proportional hazard (PH) assumption was checked by determining the scaled Schoenfeld residuals (SSR).

All variables with a P-value < 0.1 in the bivariate survival models were introduced in a multivariate model (Cox proportional hazard regression analysis or proportional subdistribution hazards regression method according to the presence of competing risk) with backward selection at $P = 0.05$. The results were presented as a hazard ratio (HR) [95% confidence interval (CI)].

Statistical analysis was performed using SAS software (SAS Institute Inc., Cary, NC). The threshold for statistical significance was set to $P < 0.05$.

2.10. Ethics

All patients have been managed in the Lorraine Comprehensive Cancer Center according to the standards of good clinical practice. This retrospective study was approved by the local institutional review board and has been declared to the "*Commission national informatique et libertés*" (CNIL), i.e., the French Data Protection Authority.

3. Results

3.1. Participants

We retrospectively reviewed 67 consecutive patients with 99 CRLM treated with SBRT from January 2007 to December 2015 in our center.

3.2. Descriptive date

Patient and metastasis characteristics are summarized in Table 2. The median follow-up was 47 months (IQR, 28–59 months), 42 patients (62.7%) were treated with SBRT for 1 CRLM, 19 patients (28.4%) for 2 CRLM, 5 patients (7.5%) for 3 CRLM and 1 patient (1.5%) for 4 CRLM. Twenty-nine (43.3%) patients had one or more synchronous liver metastases while 38 (56.7%) had metachronous disease. For 46 (46.5%) treatments, patients had undergone prior liver-directed focal therapy (35 surgery, 3 RFA and 8 both surgery and RFA) to other lesions than the ones that were targeted in this study. A contrast-enhanced dynamic liver magnetic resonance imaging was performed before treatment for 79 (79.8%) CRLM to help delineation of GTV. Prescription dose summary and dosimetric characteristics are described in Table 3. Seventy-nine (79.8%) CRLM were treated with the schedule 45 Gy in 3 fractions (BED = 112.5 Gy), 2 (2.0%) CRLM received 54 Gy in 3 fractions (BED = 151.2 Gy), 18 (18.2%) metastases received a dose and fractionation adapted schedule to match OAR constraints. Treatment was delivered in 8 days (interquartile range from 7 to 10 days).

Table 2
Treatment characteristics of the 99 colorectal liver metastases.

Treatment characteristics ($n = 99$)		No. (%) or median [IQR]
Fiducial markers		
0[a]		3 (3.0)
1–2		26 (26.3)
3–4		70 (70.7)
Fractions – dose (Gy)	BED (Gy_{10})	
3 fractions: 45 Gy	112,5 Gy	79 (79.8)
3 fractions: 37.5–43.5 Gy	84.4–106.6 Gy	7 (7.1)
3 fractions: 54 Gy	151.2 Gy	2 (2.0)
4 fractions: 40–50 Gy	80.0–112.5 Gy	7 (7.1)
5 fractions: 35–50 Gy	59.5–100.0 Gy	4 (4.0)
BED (Gy_{10})		
< 112.5 Gy		16 (16.1)
≥ 112.5 Gy		83 (83.4)
Isodose line prescription		
65%		2 (2.0)
80%		92 (92.9)
85%		5 (5.1)
Target volume		
GTV (cm^3)		6.9 [2.6–17.0]
< 30		85 (87.6)
≥ 30		12 (12.4)
CTV (cm^3)		20.8 [14.0–44.1]
PTV (cm^3)		34.7 [22.6–63.4]
< 80		81 (83.5)
≥ 80		16 (16.5)
PTV/GTV		4.5 [3.0–9.6]
GTV to CTV expansion (mm)		5 [3–10]
< 5		46 (47.2)
≥ 5		51 (52.6)
Heterogeneity index		1.3 [1.3–1.3]
Conformality index		1.3 [1.2–1.5]
CTV prescription dose coverage (%)		99.8 [99.0–100.0]
PTV prescription dose coverage (%)		99.2 [95.8–99.7]

BED: Biologically Effective Dose; GTV: Growth Tumor Volume; CTV: Clinical Target Volume; PTV: Planning Target Volume.
[a] In cases of contraindications to fiducial marker implant, use of a 4D CT-scan with the X-sight spine tracking system®.

3.3. Local control

Fifty (50.5%) treated CRLM exhibited imaging in-field progression at the time of analysis with a median time to local failure of 23 months (interquartile range, 12–40 months). One-, two- and five-year LC rates were 86.6% [95% CI, 79.0-92.5%], 72.4% [95% CI, 63.0–81.0%] and 45.3% [95% CI, 35.0–57.0%]. Univariate analysis showed that maximum GTV size ≥ 40 mm (HR 2.21, 95% CI, 1.04–4.68, $P = 0.038$), GTV ≥ 30 cm^3 (HR 2.27, 95% CI, 1.01–5.08, $P = 0.045$), PTV ≥ 80 cm^3 (HR 2.43, 95% CI, 1.11–5.32, $P = 0.027$) were associated with local failure whereas a well differentiated tumor had a better LC (HR 0.31, 95% CI, 0.10–0.98, $P = 0.046$). In multivariate analysis, only the well differentiation remained significant (Table 4). Out of the 12 metastases with a GTV ≥ 30 cm^3, 11 (91.7%) where moderately or poorly differentiated. The local failure

Table 3
Prognostic factors affecting local control in univariate and multivariate analyses for the 99 colorectal liver metastases.

Variables*	Bivariate analysis		Multivariate analysis*	
	HR 95% CI	*P*	HR 95% CI	*P*
Gender (female)	1.27 [0.64–2.52]	0.489		
Age (> 60 years)	1.77 [0.81–3.86]	0.149		
Time from diagnosis (synchronous)	0.73 [0.37–1.41]	0.343		
Previous focal treatment: RFA or surgery (yes)	1.20 [0.60–2.42]	0.599		
Previous chemotherapy for metastases (yes)	1.75 [0.72–4.29]	0.217		
Histology (well differentiated)	0.31 [0.10–0.98]	0.046	0.31 [0.10–0.98]	0.046
T staging (T3-4)	0.57 [0.23–1.41]	0.227		
LVI (yes)	1.36 [0.66–2.83]	0.403		
MRI before SBRT (yes)	1.24 [0.49–3.09]	0.649		
Number of fiducial markers (≥ 3)	1.68 [0.84–3.36]	0.145		
Maximum tumor size (> 40 mm)[a]	2.21 [1.04–4.68]	0.038		
GTV (> 30 cm^3)	2.27 [1.01–5.08]	0.045		
PTV (> 80 cm^3)[a]	2.43 [1.11–5.32]	0.027		
GTV to CTV expansion (> 5 mm)	0.72 [0.38–1.37]	0.317		
BED (> 110 Gy)	0.66 [0.29–1.49]	0.316		

MRI: Magnetic Resonance Imaging; PTV: Planning Target Volume; GTV: Gross Tumor Volume; BED: Biologically Effective Dose; LVI: Lymphovascular Invasion. *: variables with *P*-value less than 0.1 were introduced into multivariate analysis with backward selection.
[a] Not included in the multivariate analysis due to strong correlation with GTV

Table 4
Prognostic factors affecting progression-free survival and overall survival for the 67 patients with colorectal liver metastases.

Variables*	Progression-free survival				Overall survival			
	Bivariate analysis		Multivariate analysis		Bivariate analysis		Multivariate analysis	
	HR 95% CI	*P*	HR 95% CI	*P*	HR 95% CI	*P*	HR 95% CI	*P*
Gender (female)	0.65 [0.36; 1.17]	0.149			0.80 [0.41; 1.56]	0.511		
Age (> 60 years)	1.27 [0.72; 2.24]	0.406			1.48 [0.74; 2.95]	0.270		
ECOG Performance Status (≥ 2)	3.88 [1.44; 10.44]	0.007	3.88 [1.44; 10.44]	0.007	6.31 [2.26; 17.6]	< 0.001	3.27 [1.07; 9.98]	0.038
Primary tumor (rectum)	1.53 [0.78; 3.00]	0.213			2.06 [0.95; 4.48]	0.069		
Histology (well differentiated)	1.22 [0.63; 2.35]	0.558			1.24 [0.57; 2.70]	0.589		
LVI (yes)	1.07 [0.64; 1.96]	0.820			1.25 [0.65; 2.41]	0.501		
Time from diagnosis (synchronous)	1.01 [0.62; 1.71]	0.963			1.07 [0.58; 1.96]	0.838		
Extrahepatic metastases at time of SBRT (yes)	0.93 [0.47; 1.81]	0.821			0.73 [0.32; 1.65]	0.454		
N staging (N1-2)	1.23 [0.69; 2.17]	0.482			1.81 [0.91; 3.61]	0.090	2.19 [1.09; 4.43]	0.029
T staging (T3-4)	0.74 [0.32; 1.75]	0.494			0.81 [0.32; 2.07]	0.655		
Number of liver metastases treated (≥ 2)	1.26 [0.72; 2.22]	0.424			1.26 [0.66; 2.39]	0.485		
Sum of diameters of the treated metastases (> 30 mm)	0.98 [0.58; 1.63]	0.93			1.17 [0.64; 2.16]	0.609		
Previous chemotherapy for metastases before SBRT (yes)	0.51 [0.29; 0.89]	0.017			0.39 [0.21; 0.72]	0.003	0.36 [0.18; 0.75]	0.006
Previous focal treatment: RFA or surgery (yes)	0.66 [0.39; 1.11]	0.116			0.48 [0.26; 0.87]	0.017		
Recurrence (yes)	–	–	–	–				
Local (in-field) (*n* = 34)	–	–	–	–	1.35 [0.73; 2.51]	0.339		
Intrahepatic out-of-field (*n* = 42)	–	–	–	–	1.35 [0.73; 2.66]	0.372		
Intrahepatic (both) (*n* = 48)	–	–	–	–	1.22 [0.58; 2.55]	0.598		
Extrahepatic (*n* = 33)	–	–	–	–	0.85 [0.47; 1.54]	0.594		

ECOG: Eastern Cooperative Oncology Group; LVI: Lymphovascular Invasion; SBRT: Stereotactic Body Radiation Therapy; RFA: Radiofrequency Ablation. *: variables with *P*-value less than 0.1 were introduced into multivariate analysis with backward selection.

according to GTV, differentiation and the interaction between GTV and differentiation is represented on Fig. 1.

3.4. Hepatic progression incidence

At the time of analysis, 48 patients had intrahepatic recurrences: 6 patients had only local failure, 14 patients had only out-of-field recurrence and 28 patients had local recurrence associated with out-of-field recurrence. One, two and five-year cumulative incidence of hepatic progression was 10.6% (95% CI, 4.6–19.5%), 35.5% (95% CI, 24.0–47.2%) and 72.3% (95% CI, 58.2–82.3%). By univariate analysis, age > 60 years (HR 1.98, 95% CI, 1.09–3.59, $P = 0.02$) was the only significant factor associated with hepatic progression incidence (Online material Table E1).

3.5. Survival

PFS rates were 81.9% [95% CI, 70.2%; 89.2%], 54.0% [95% CI, 41.2%; 65.2%] and 13.1% [95% CI, 6.0–23.0%] at 1, 2 and 5 years (Fig. 2a). In multivariate analysis, an OMS ≥ 2 was the only parameter associated with a poorer PFS (HR 3.88, 95% CI, 1.44–10.44, $P = 0.007$) (Online material Table E2).

Median OS was 53 months (95 CI, 38–66 months). At the time of analysis, 45 patients had died. Overall survival was 95.5% [95% CI, 86.7%; 98.5%], 81.4% [95% CI, 69.6%; 90.0%] and 43.5% [95% CI, 30.1%; 56.1%] at 1, 2 and 5 years respectively (Fig. 2b). In multivariate analysis, ECOG performans status ≥ 2 (HR 3.27, 95% CI, 1.07–9.98, $P = 0.038$) and a node stage ≥ N1 (HR 2.19, 95% CI, 1.09–4.43, $P = 0.029$) were associated with a poorer OS where a previous chemotherapy for metastasis (HR 0.49, 95% CI, 0.26–0.89,

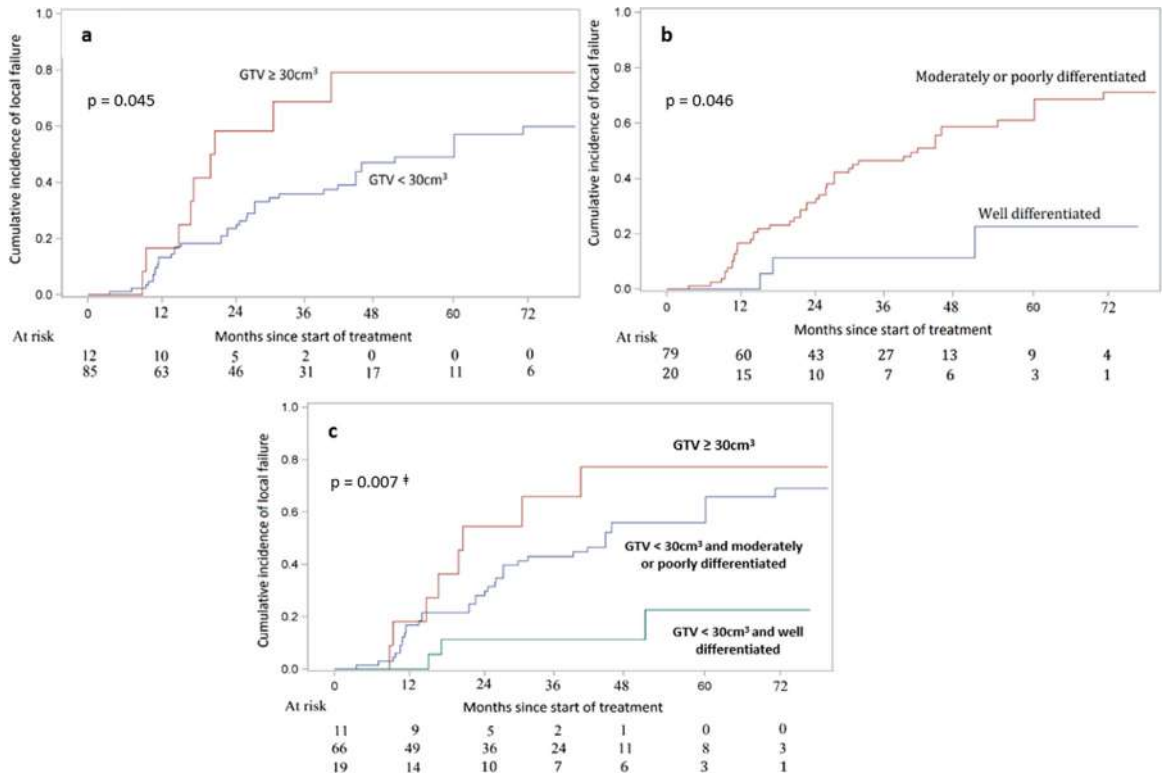

Fig. 1. Cumulative incidence of local failure for the 99 colorectoral liver metastases since the first day of treatment according to: (a) GTV; (b) degree of differentiation; (c) interaction between GTV and degree of differentiation.

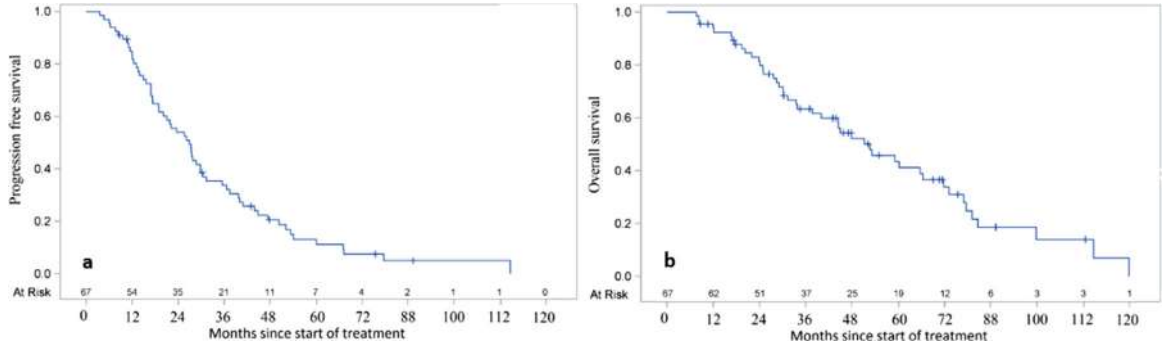

Fig. 2. Kaplan–Meir curve for Progression-Free Survival and Overall Survival for the 67 patients since the first day of treatment for colorectoral liver metastases.

$P = 0.02$) was a protective factor of death (HR 0.36, 95% CI, 0.18–0.75, $P = 0.006$) (Online material Table E2).

3.6. Toxicity

One patient (1.5%) presented a grade 1 hematoma following gold fiducial implantation without need for transfusion or embolization. One patient (1.5%) presented grade 3 acute nausea that required the use of setron. One patient (1.5%) presented grade 3 late gastric ulcer that required parenteral nutrition for 6 months. We did not report another grade ≥ 3 toxicity.

4. Discussion

While management of metastatic tumours has historically focused on systemic therapy, local treatment of CRLM has become standard of care following results from surgical resection [25,26].

We report the long-term follow-up of 67 patients with 99 unresectable CRLM treated with SBRT. The median GTV of the CRLM was 6.9 cm^3 (IQR, 2.6–17.0 cm^3) and most of the patients analyzed in this study were pretreated and had limited treatment options; 47% had already received focal treatment such as surgery or RFA and 69% had received at least one line of chemotherapy.

We confirmed that SBRT is a safe treatment of CRLM if dose constraints to OAR are respected with only 2 patients who experienced grade 3 toxicity after a median follow-up of 47 months [13–15,27–29]. However, due to the retrospective nature of this study, toxicity is probably underestimated.

The LC rate we obtained is consistent with the report by Chang et al. who modeled that a dose of 46–52 Gy in 3 fractions offered a 1-year LC of 90% [30]. Several predictive factors of LC after SBRT are discussed: histology and differentiation of the primary, tumor volume and dose intensity. Takeda et al. reported a worse LC of CRLM compared to other primary locations [31]. In our study, we are first to report that the degree of differentiation of the primary colorectal cancer is the strongest prognostic factor associated with LC, even for small tumors (Fig. 1). We confirm the results of Mahadevan et al. [27] who showed that smaller tumor

volumes < 40 cm^3 correlated with an improved LC. Biologically effective dose has been described as an independent prognosis factor for LC [27,30,32]. We did not found significant association between LC and BED probably in part because of the homogeneity of dose prescriptions in this study, only 2 (2.0%) metastases received a BED > 115 Gy_{10} and 18 (18.2%) received an adapted schedule to match OAR constraints (BED from 59.5 to 112.5 Gy_{10}).

We also aimed to evaluate wether larger margin expansion from GTV to CTV had an impact on LC. The absolute value of the margin applied around the GTV to take into account the microscopic peritumoral extension has never been evaluated to our knowledge. In most studies, the value of that margin ranged from 0 to 8 mm [27,28,32–39]. Margins greater than 5 mm did not improve LC ($P = 0.317$) in our study. These preliminary results suggest that we should not apply margin superior to 5 mm margin but this must be confirmed by larger studies.

We must stress that only 6 patients (9%) exhibited local recurrence without out-of-field intrahepatic or extrahepatic progression leading to a two-year PFS of 54%. The major pattern of failure remained out-of-field intrahepatic progression. The combination of SBRT with systemic therapy has not been evaluated yet and could improve PFS as did perioperative chemotherapy in relation with surgery [40]. One of the major challenges is to select patients who will benefit the most from SBRT. In accordance with our results and the reported studies, we could propose the following screening factors: ECOG Performans Status 0–1, absence of metastatic regional lymph nodes and extrahepatic disease.

PFS seemed to plateau at about 15% at 4 years pointing out a substantial number of patients who remain long-term disease-free after SBRT. These findings illustrates the concept of oligometastatic disease and the benefit of aggressive local therapy on survival [41,42].

Our study presents with several limitations. Our study reports a limited number of patients in a retrospective cohort. Scorsetti et al. reported a comparable sized prospective clinical trials [15] while several larger cohort studies have also been reported like Andratschke et al. who reported 623 liver oligometastasis [16,43,44]. Retrospective, single-institution studies are prone to selection biases. Furthermore, over the study period, additional systemic therapy have emerged with an unmeasured impact on survival.

We must stress that evaluation of local control after SBRT in liver metastases is limited with RECIST criteria especially in case of underlying cirrhosis [45].

While a phase III single-blind prospective randomized controlled trial is ongoing to compare radiofrequency ablation to surgery for CRLM < 3 cm [9], randomized trials are needed to establish whether SBRT improves PFS or OS. The NCT01233544 clinical trial was designed to compare RFA to SBRT in CRLM but, unfortunately, stopped early due to insufficient recruitment. In most cases, the indication of SBRT in management of non operable CRLM is infuenced by thermal ablation limitations and local policies: (i) tumors abutting vasculature or major bile duct (heat sinks); (ii) large size CRLM (≥ 2–3 cm); and (iii) tumours that are poorly visible on ultrasonography. Two recent non randomized studies compared RFA to SBRT and showed a trend towards longer LC for tumours > 2 cm and disease free survival in favor of SBRT [10,46], these results have to be confirmed.

5. Conclusion

In this study, we have investigated the long term outcome of 3 to 5 fractions SBRT for CRLM. We observed high rate of LC and a low incidence of toxicity, supporting that high-dose SBRT is an effective and safe option for unresectable liver metastases from colorectal cancer. We found that degree of differentiation of the tumour was a significant factor for local control. Despite improved LC, PFS at 2 and 5 year remains low, the combination of SBRT with an adjuvant systemic therapy could improve survivals and should be evaluated. Moreover, randomized trials to evaluate the efficacy of SBRT versus surgery and versus thermal ablation are needed.

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Disclosure of interest

The authors declare that they have no competing interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.canrad.2021.01.004.

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