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Original article

Does prior radiotherapy impact the acute cellular liver graft rejection?

Une radiothérapie préalable a-t-elle un impact sur le rejet cellulaire aigu de la transplantation hépatique ?

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ABSTRACT

Purpose. – Radiotherapy can be used as a bridge therapy prior to liver transplantation. Radiotherapy generates immune reactions involving T cells, which are the main effectors of acute cellular rejection after transplantation. Here, we investigated the impact of radiotherapy on acute cellular rejection.
Materials and methods. – We retrospectively reviewed the data of oncological patients who benefited from liver transplantation. Patients who received radiotherapy prior to liver transplantation ("RT cohort", $n = 17$) were compared to a matched cohort ("$NoRT_{matched}$ cohort", $n = 17$) obtained through propensity score-matching analysis of the total non-irradiated cohort ("$NoRT_{all}$" cohort, $n = 136$). The acute cellular rejection was evaluated using the Banff score for rejection (mild: < 5, moderate: 5–6, and severe: 7–9) obtained on an early post-transplantation biopsy. Overall and disease-free survival were reported for patients with hepatocellular carcinoma.
Results. – Median Banff scores was significantly lower for the RT cohort compared to the $NoRT_{all}$ cohort (2.5 versus 5, respectively, $P = 0.043$) but this statistical difference was eliminated after comparison with the $NoRT_{matched}$ cohort (median: 4, $P = 0.62$). The 5-year overall and disease-free survival rates were 62 % and 69 %, respectively, for hepatocellular carcinoma patients of the RT cohort ($n = 14$) and did not differ from the 5-year overall (83 %, $P = 0.15$) and disease-free survival rates (90 %, $P = 0.05$) of those of the $NoRT_{matched}$ cohort ($n = 16$).
Conclusion. – Radiotherapy given prior to liver transplantation did not impact the rate or severity of acute cellular rejection. Furthermore, overall and disease-free survival rates were not impacted by radiotherapy.

Mots clés :
Transplantation hépatique
Radiothérapie hépatique
Radiothérapie prégreffe
Rejet cellulaire aigu
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RÉSUMÉ

Objectif de l'étude. – La radiothérapie peut être utilisée à visée de contrôle local avant transplantation hépatique. Elle génère des réactions immunitaires impliquant les lymphocytes T, qui sont les principaux médiateurs du rejet cellulaire aigu post-transplantation. Nous avons étudié l'impact de la radiothérapie sur le rejet cellulaire aigu.
Méthodes utilisées. – Nous avons inclus rétrospectivement les patients oncologiques ayant bénéficié d'une transplantation hépatique. Ceux ayant reçu une radiothérapie avant la transplantation hépatique (« cohorte RT », $n = 17$) ont été comparés à une cohorte appariée (« cohorte $NoRT_{matched}$ », $n = 17$) obtenue

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après analyse d'appariement par score de propension de la cohorte totale non irradiée (« cohorte $NoRT_{all}$ », $n = 136$). Le rejet cellulaire aigu a été évalué à l'aide du score de rejet de Banff (léger : < 5, modéré : 5–6, et sévère : 7–9) obtenu sur une biopsie post-transplantation précoce. La survie globale et la survie sans maladie ont été rapportées pour les patients atteints de carcinome hépatocellulaire.

Résultats. – La médiane des scores de Banff était significativement plus basse dans la cohorte RT que dans la cohorte $NoRT_{all}$ (respectivement 2,5 contre 5, $p = 0,043$), mais cette différence statistique a été éliminée après comparaison avec la cohorte $NoRT_{matched}$ (médiane : 4, $p = 0,62$). La probabilité de survie globale à 5 ans et celle survie sans maladie étaient respectivement de 62 % et 69 % pour les patients atteints de carcinome hépatocellulaire de la cohorte RT ($n = 14$) et ne différaient pas celle de survie globale à 5 ans (83 %, $p = 0,15$) et de celle de survie sans maladie (90 %, $p = 0,05$) des patients de la cohorte $NoRT_{matched}$ ($n = 16$).

Conclusion. – La radiothérapie administrée avant la transplantation hépatique n'a pas eu d'impact sur le taux ou la sévérité du rejet cellulaire aigu. En outre, la radiothérapie n'a pas eu d'impact sur la survie globale et la survie sans maladie.

1. Introduction

Liver transplantation is the recommended first-line curative treatment for localised hepatocarcinoma and could be an option in early stage unresectable peri hilar cholangiocarcinoma [1,2]. However, the availability of grafts remains an important limitation for these patients and leads to a long time between diagnosis and transplantation. To control the tumour until liver transplantation, "bridge" treatments such as transarterial chemoembolisation or radiofrequency ablation could be indicated [1,3,4]. Liver stereotactic ablative radiotherapy is another bridge strategy that has been recently demonstrated to be feasible with good local control and poor toxicities in localised hepatocellular carcinoma [5]. Conventional radiotherapy in combination with chemotherapy has been evaluated as neoadjuvant treatment before liver transplantation in selected cholangiocarcinoma patients according to the Mayo Clinic protocol [6]. Therefore, it is not uncommon for liver transplanted patients to have previously been irradiated. In addition to tumoral cell death induction, radiotherapy also mediates local and systemic immune reactions [7,8]. Particularly, lymphopenia is a well-known effect of irradiation that can be long lasting and is a poor prognosis factor for overall survival in several malignancies [9–11]. These radiation-induced immune reactions could potentially impact the outcome of liver transplanted patients, who require immunosuppressive drugs to avoid liver graft rejection. Acute cellular rejection occurs in 15 to 25 % after tacrolimus-based scheme. As T cells are the main mediators of acute cellular rejection, the radiation effects on these cells could potentially impact its frequency and severity [12]. This could have a detrimental impact on oncological outcomes, since acute cellular rejection requires further immunosuppressive treatments such as steroids and other immunosuppressive drugs, and increased immunosuppression has been associated with a higher hepatocellular carcinoma recurrence rate after liver transplantation [13,14]. The aim of this retrospective propensity score-matching analysis was to evaluate if prior liver radiotherapy has a predictive value for acute cellular rejection.

2. Methods

This research was conducted in accordance with the Strengthening the reporting of observational studies in epidemiology (STROBE) criteria for case-control studies [15].

2.1. Patient selection

Patients who underwent liver transplantation for an oncological indication were retrospectively included from January 2015, the date of liver radiotherapy implementation at our institution, until January 2023. Paediatric patients, patients with a history of prior non-liver radiotherapy, and patients with a history of prior liver transplantation before liver radiotherapy were excluded. The first cohort included liver transplanted patients with previous liver radiotherapy ("RT cohort"). For the comparative group, we used a propensity score-matching analysis to select patients sharing similar baseline characteristics with those from the RT cohort ("$NoRT_{matched}$ cohort") among the whole cohort of liver transplanted patients without radiotherapy history ("$NoRT_{all}$ cohort"). All patients meeting these criteria were included regardless of follow-up time.

2.2. Procedures

Included patients received initial tacrolimus after liver transplantation, as described in a previous study by our group [16]. We also included patients from a randomised protocol (EudraCT number 2006–004830–34) comparing initial tacrolimus monotherapy and combination of tacrolimus with a single intraoperative high-dose of rabbit anti-lymphocytic serum (r-ATG) [17]. The serum level of tacrolimus was regularly assessed, and a dose adaptation was performed to reach the recommended range of 4 to 6 ng/mL. A liver biopsy was routinely performed seven days after liver transplantation or earlier in cases of unexplained liver enzyme perturbation. Acute cellular rejection severity was classified by one experienced pathologist specialised in liver diseases (more than 80 liver transplantations per year in our centre) using Banff criteria as mild (score < 5), moderate (5–6), and severe (7–9) [18]. In case of moderate or severe rejection, the tacrolimus dose was first adapted. If insufficient, further immunosuppressive drugs (steroids, mycophenolate mofetil, etc.) were added. Regular follow-up was performed to assess liver transplantation outcomes and oncological recurrence.

Patients with progression after alternative bridge treatment (transarterial chemoembolisation or radiofrequency ablation) as well as those with anatomical considerations that contraindicated invasive bridge therapy were referred to the radiotherapy department for liver stereotactic ablative radiotherapy. Liver stereotactic ablative radiotherapy was delivered using intensity-modulated technique. Prescribed doses ranged from 36 Gy to 50 Gy in three to six fractions (biological effective dose [BED] range with an α/β ratio = 10: 57.6–124.8 Gy). For unresectable peri hilar cholangiocarcinoma, neoadjuvant radiotherapy was performed in combination with 5-fluorouracil or capecitabine chemotherapy according to the Mayo Clinic protocol [6]. The liver hilum and associated lymph

node regions received a prophylactic dose of 45 to 50 Gy in 25 o 30 fractions, and a 60 Gy simultaneous integrated boost to the gross tumour volume (GTV) was delivered in some cases. For all patients, we performed a planning 4D-computed tomography (CT) under audio coaching and, if required to limit respiration motion, we applied abdominal compression. The GTV was delineated on the planning CT after its co-registration with a planning magnetic resonance imaging. An isotropic clinical target volume (CTV) margin of 5 mm was added around the GTV for stereotactic ablative radiotherapy. The planning target volume margin was calculated according to the institutional standard mid-position strategy [19]. Daily cone-beam CT was realised for the image-guided radiotherapy process.

2.3. Endpoints

To assess the impact of prior radiotherapy on liver graft acute cellular rejection, anatomopathological reports from the first early liver biopsy were screened. A comparison was made between Banff scores of the RT- and the $NoRT_{matched}$ cohorts. Survival endpoints were reported only for patients with hepatocellular carcinoma, since the oncological outcomes of cholangiocarcinomas are not similar. Time zero for overall survival and disease-free survival corresponds to the liver transplantation procedure date. Overall and disease-free survival were calculated until the date of the patient's death and the date of diagnosis of recurrent disease, respectively.

2.4. Statistical analysis

We performed a propensity score-matching to minimise the risk of imbalance between the RT cohort and the liver transplanted patients without radiotherapy. A logistic regression model considering covariables predictive of acute cellular rejection was used for the propensity score determination. Included covariables were: age, gender, body mass index (BMI), preoperative diabetes mellitus, autoimmune disease, preexisting liver disease, tumour histology, Child-Pugh score class, Model for End-stage Liver Disease (MELD) score, cytomegalovirus status, warm and cold ischemia times, initial immunosuppressive therapy, blood levels of tacrolimus, and heart-beating/non-heart-beating donor status. Patients with missing data for these covariables were excluded from the propensity score-matching analysis. A one-to-one nearest neighbour method without replacement was performed to find, among the $NoRT_{all}$ cohort, patients that had the closest propensity score. After matching, baseline characteristics were compared between the $NoRT_{matched}$ and the RT cohorts. The comparison of continuous variables (expressed as the mean ± standard deviation or the median and interquartile range when appropriate) was made using the Wilcoxon signed-rank test. Chi^2 and Fisher's exact tests were performed to compare discrete variables when appropriate. Overall and disease-free survival were analysed according to the Kaplan–Meier method, and the log-rank test was used for comparison. A P-value < 0.05 was considered significant. All these statistical analyses were performed on RStudio (R version 4.2.1) using the "tidyverse", "rstatix", "survival" and "MatchIt" packages.

3. Results

3.1. Population

During the evaluation period, a total of 160 patients underwent liver transplantation for an oncological indication. Of these, seven patients were excluded due to missing data ($n = 3$), prior radiotherapy for another indication ($n = 2$), and second liver transplantation ($n = 2$). Among the 153 remaining patients, 17 were included in the RT cohort and 136 in the $NoRT_{all}$ cohort. Baseline characteristics were balanced for both cohorts except for body mass index and tumour histology. After matching, there was no further difference between the RT cohort and the $NoRT_{matched}$ cohort (Table 1). In the RT cohort, 14 patients receive radiotherapy as a bridge therapy before liver transplantation for a localised hepatocellular carcinoma. For the three others, radiotherapy was part of the neoadjuvant treatment before transplant for an unresectable peri hilar cholangiocarcinoma (Table 2).

3.2. Acute cellular rejection

The early liver biopsy was missing for three patients in the RT cohort, 42 in the $NoRT_{all}$ cohort, and four patients in the $NoRT_{matched}$ cohort. Banff scores were significantly lower for the RT cohort (median: 2.5 [2–5.5]) compared to the $NoRT_{all}$ cohort (median: 5 [3.25–6], $P = 0.043$). However, no significant difference was demonstrated after matching (median $NoRT_{matched}$ cohort: 4 [1–5], $P = 0.62$). The number of patients experiencing acute cellular rejection and level of severity are reported in Fig. 1. Further immunosuppressive treatment was required in a total of 17 patients with moderate or severe acute cellular rejection. Among these 17 patients, two were in the RT cohort and two in the $NoRT_{matched}$ cohort. Total bilirubin levels were increased in eight out of ten patients with moderate or severe ACR in the RT and $NoRT_{matched}$ cohorts. In most cases, total bilirubin normalised rapidly, except for one patient in the RT cohort who developed chronic graft rejection (Table 3).

3.3. Oncological outcomes

Fourteen patients from the RT cohort, 110 from the $NoRT_{all}$ and 16 from the $NoRT_{matched}$ cohort were included in the survival analysis. The median follow-up was 4.4 years [2.2–6.3]. The 5-year overall survival probability in the RT cohort was not significantly different compared to both the $NoRT_{all}$ cohort and the $NoRT_{matched}$ cohort (Fig. 2A). The median overall survival was not reached for all cohorts at the time of the last follow-up (Fig. 2A). Two patients in the RT cohort died prematurely following the liver transplantation (one due to haemorrhagic shock following hepatic artery dissection, one due to humoral graft rejection). In the $NoRT_{all}$ cohort, 13 patients died in the immediate aftermath of the graft (three haemorrhagic shock, two humoral graft rejection, two septic shock, two hepatic failure following hepatic artery thrombosis, one vasoplegic shock, one respiratory failure, and two undetermined causes) in which one death due to hepatic failure following hepatic artery thrombosis occurred in the $NoRT_{matched}$ cohort. The oncological progression caused two and eleven deaths in the RT cohort and the $NoRT_{all}$ cohorts, respectively (none in the $NoRT_{matched}$ cohort). The 5-year disease-free survival probability in the RT cohort was significantly lower than that of the $NoRT_{all}$ cohort (Fig. 2B). However, after comparison with the $NoRT_{matched}$ cohort, this statistical difference with the RT cohort no longer existed (Fig. 2B). The median disease-free survival probability was not reached for all cohorts (Fig. 2B). In the RT cohort, all oncological recurrences occurred within the first two years following radiotherapy, while no recurrence occurred during this time interval in the $NoRT_{matched}$ cohort.

4. Discussion

In this study, a cohort of 17 patients who underwent radiotherapy before liver transplantation was compared with a paired cohort of patients who did not have radiotherapy before liver transplantation, obtained after propensity score-matching analysis. To our knowledge, this is the first study evaluating the impact of liver

Table 1
Results of a retrospective study on the impact of radiotherapy on acute cellular liver graft rejection baseline characteristics of studied cohorts.

Characteristics	RT cohort ($n = 17$)	$NoRT_{all}$ cohort ($n = 136$)		$NoRT_{matched}$ cohort ($n = 17$)	
			P		*P*
Age (years)	59.6 ± 10.2	60.4 ± 9.8	0.67	62.0 ± 8.4	0.46
Gender (n)			0.99		0.99
Male	14	111		13	
Female	3	25		4	
Body mass index (kg/m²)	30.5 ± 5.6	27.5 ± 5.2	**0.024**	28.3 ± 4.8	0.23
Preoperative diabetes mellitus (n)			0.99		0.99
Absent	9	76		10	
Present	8	60		7	
Autoimmune disease (n)			0.51		0.99
Absent	16	131		17	
Present	1	5		0	
Preexisting liver disease (n)			0.23		0.78
Alcoholic steatohepatitis	6	59		7	
Hepatitis C virus	3	19		4	
Absent	2	19		1	
Multifactorial	1	16		1	
Non-alcoholic steatohepatitis	2	10		2	
Hepatitis B virus	1	7		2	
Hemochromatosis	0	3		0	
Other	2	3		0	
Tumour histology (n)			**0.003**		0.60
Hepatocellular carcinoma	14	110		16	
Hepatocholangiocarcinoma	0	7		0	
Cholangiocarcinoma	3	1		1	
Colorectal metastases	0	7		0	
Neuroendocrine tumour metastases	0	9		0	
Other	0	2		0	
Child-Pugh score class (n)			0.71		0.89
Absence of cirrhosis	1	20		1	
A	9	74		9	
B	5	31		5	
C	2	11		2	
Model for End-stage Liver Disease score	12 [8–15]	10 [7.75–15]	0.42	12 [10–18]	
Cytomegalovirus status (n)			0.38		0.90
Donor −/Recipient −	2	32		3	
Donor +/Recipient −	4	42		5	
Donor +/Recipient +	6	40		3	
Donor −/Recipient +	5	21		6	
Cold ischemia time (min)	411 ± 107	390 ± 163[a]	0.51	420 ± 169	0.85
Warm ischemia time (min)	41 ± 11	46 ± 14[a]	0.22	38 ± 12	0.44
Initial immunosuppressive therapy (n)			0.43		0.99
Tacrolimus	17	124		17	
Tacrolimus + r-ATG	0	12		0	
Tacrolimus blood level (ng/mL)	7.6 ± 2.6	7.3 ± 3.2	0.61	7.6 ± 2.5	0.97
Donor status (n)			0.46		0.43
Alive	1	19		2	
Domino transplant	0	1		0	
Heart-beating donor	8	76		6	
(Non-)heart-beating cadaveric donor	8	40		9	

RT cohort: patients who received radiotherapy prior to liver transplantation; $NoRT_{matched}$ cohort: matched patients obtained through propensity score-matching analysis of the total non-irradiated patients; $NoRT_{all}$ cohort: total non-irradiated patients; r-TAG: rabbit anti-lymphocytic serum.
Significant *P*-value (< 0.05) are in bold.
[a] Three missing data.

radiotherapy on acute cellular rejection. We showed that radiotherapy given before liver transplantation does not impact the occurrence nor the severity of acute cellular rejection, based on the Banff score on the early liver biopsy. None of the included patients required emergency liver transplantation or died because of acute cellular rejection.

Radiotherapy can induce a local and systemic immune response that mainly involves T cells. Its effect on T cells is complex and depends on multiple factors, including the site and the dose of radiation [20]. Radiation can activate T cells by releasing neoantigens from dying tumoral cells that will be processed by dendritic cells in the tumour-draining lymph nodes. T cells are then activated by these dendritic cells, migrate to distant tumoral sites, and can induce immunogenic cell death [21]. Additionally, following irradiation, tumoral cells generate damage-associated molecular patterns [22]. These damage-associated molecular patterns are similarly released in response to ischemia-reperfusion injury or infections that are associated with liver transplantation [12]. In liver transplantation, damage-associated molecular patterns can produce an adaptive immune reaction through activation of alloreactive T cells, resulting in a proinflammatory environment that favours transplant rejection [12]. Radiation can also induce systemic lymphopenia and, therefore, an increase in the neutrophils-to-lymphocytes ratio, which can be long lasting and associated with poor oncological outcomes [23]. While preoperative lymphocyte count seems not to be correlated with acute cellular rejection in liver transplanted patients, an increased preoperative neutrophils-to-lymphocytes ratio is associated with a higher rate of graft loss and poorer oncological outcomes in patients with hepatocellular carcinoma [24–27]. However, focusing only on T cells is probably inappropriate to establish the real impact of radiation on acute cellular rejection in liver transplanted

Table 2
Results of a retrospective study on the impact of radiotherapy on acute cellular liver graft rejection: tumour and treatment characteristics of the matched cohorts.

Tumour and treatment characteristics	RT cohort ($n = 17$)	$NoRT_{matched}$ cohort ($n = 17$)
Hepatocellular carcinoma,n	14	16
T stage (TNM 8th edition),n		
T1a	5	5
T1b	2	2
T2	7	9
Barcelona-Clinic Liver-Cancer stage,n		
0	3	2
A	2	5
B	5	1
C	2	7
D	2	1
Bridge therapy (before radiotherapy in RT cohort),n		
None	4	4
Single TACE	2	2
Multiple TACE	5	7
Other modalities	3	3
Radiotherapy scheme,n		
6×6 Gy	1	
6×8 Gy	2	
5×8 Gy	4	
5×10 Gy	5	
3×15 Gy	1	
3×16 Gy	1	
Cholangiocarcinoma,n	3	1
Radiotherapy scheme,n		
30×1.5 Gy (+15 Gy boost)	2	
25×2 Gy	1	
Concomitant chemotherapy,n		
5-fluorouracile	2	
Capecitabine	1	

RT cohort: patients who received radiotherapy prior to liver transplantation; $NoRT_{matched}$ cohort: matched patients obtained through propensity score-matching analysis of the total non-irradiated patients; TACE: transarterial chemoembolization.

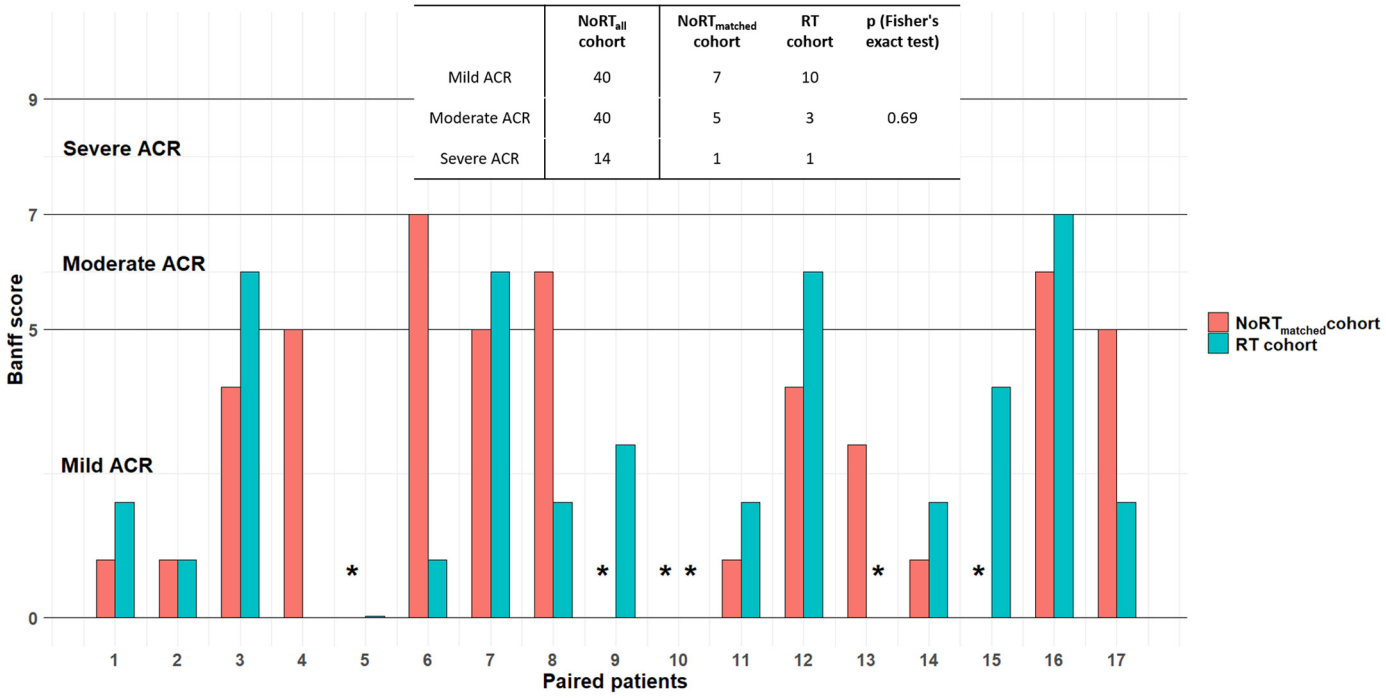

Fig. 1. Results of a retrospective study on the impact of radiotherapy on acute cellular liver graft rejection: occurrence and severity of acute cellular rejection for paired patients from the RT cohort and the $NoRT_{matched}$ cohort. ACR: acute cellular rejection; RT: radiotherapy; RT cohort: patients who had radiotherapy prior to liver transplantation ($n = 17$); $NoRT_{matched}$ cohort: matched patients obtained through propensity score-matching analysis of the total non-irradiated cohort ($n = 17$); $NoRT_{all}$ cohort: total non-irradiated patients ($n = 136$); * missing early liver biopsy.

patients because both phenomena involve many other immune cells [8,12].

Liver stereotactic ablative radiotherapy is an alternative to other local bridge therapies before liver transplantation. It can be achieved with a low rate of toxicity, including mainly abdominal discomfort, nausea/vomiting and liver function worsening. Reported stereotactic ablative radiotherapy-induced grade ≥ 3 adverse events are rare in this indication [5,28,29]. In our RT cohort,

Table 3
Results of a retrospective study on the impact of radiotherapy on acute cellular liver graft rejection: details of patients with moderate/severe acute rejection based on Banff score in the study cohorts.

Patient identification number	Cohort	Banff score[a]	Rejection treatment	Maximum total bilirubin level during acute rejection (mg/dL)	Time from transplant to bilirubin normalisation (days)	Chronic rejection evolution	Follow-up duration (years)
1	$NoRT_{matched}$	5	None	5.5	7	No	5.1
6	$NoRT_{matched}$	7	Tacrolimus increase	4.9	60	No	3.5
7	$NoRT_{matched}$	5	Tacrolimus increase	8.8	86	No	2.9
8	$NoRT_{matched}$	6	None	3.0	8	No	3.9
16	$NoRT_{matched}$	6	None	2.6	9	No	4.1
17	$NoRT_{matched}$	5	None	9.4	169	No	7.0
25	RT	6	Tacrolimus increased, addition of mycophenolate mofetil, methylprednisolone, and ATG	31.5	265	Yes	4.0
27	RT	7	None	No bilirubin increase		No	1.7
32	RT	6	None	2.3	11	No	1.9
33	RT	6	Tacrolimus increase	No bilirubin increase		No	2.3

RT cohort: patients who received radiotherapy prior to liver transplantation; $NoRT_{matched}$ cohort: matched patients obtained through propensity score-matching analysis of the total non-irradiated patients; ATG: antithymocyte globulin.
[a] Acute cellular rejection, mild: < 5, moderate: 5–6, severe: 7–9.

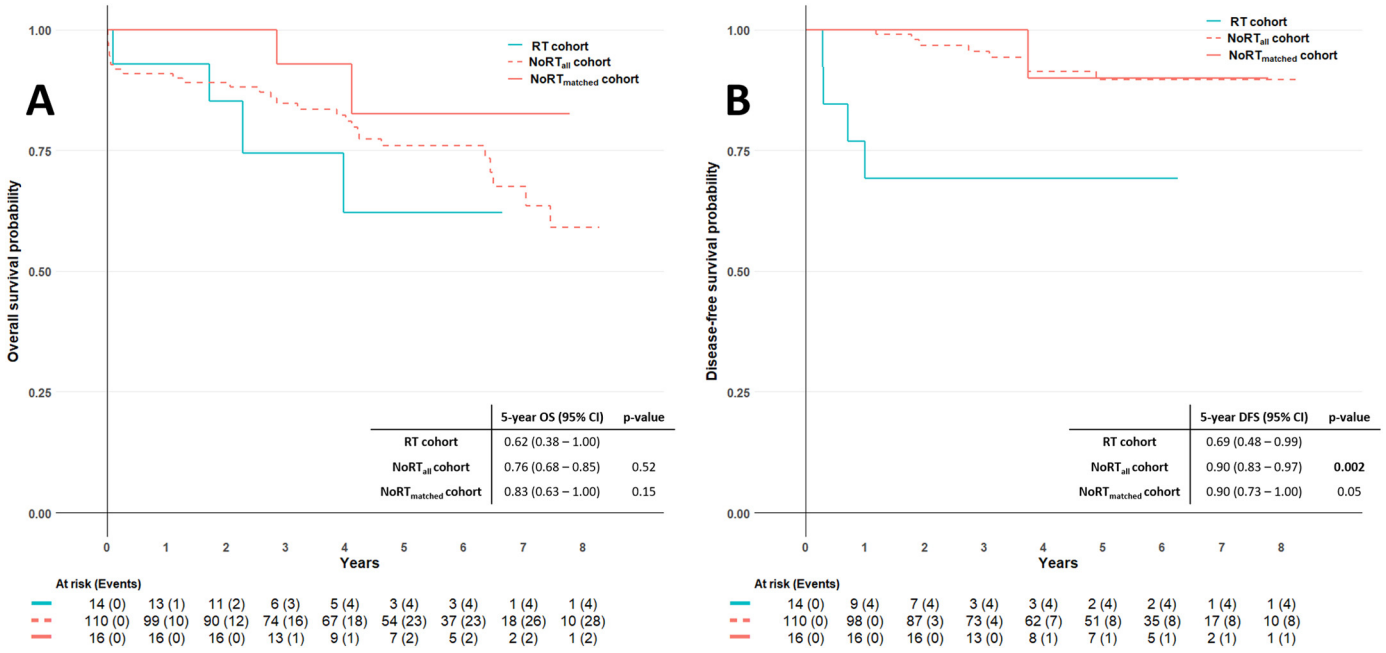

Fig. 2. Results of a retrospective study on the impact of radiotherapy on acute cellular liver graft rejection: oncological outcomes. A. Overall survival. B. Disease-free survival. RT cohort: patients who had radiotherapy prior to liver transplantation; $NoRT_{matched}$ cohort: matched patients obtained through propensity score-matching analysis of the total non-irradiated cohort; $NoRT_{all}$ cohort: total non-irradiated patients; CI: confidence interval; DFS: disease-free survival; OS: overall survival.

5-year overall survival probability in patients with hepatocellular carcinoma reached 62.1 %, which is inferior compared to other series, in which 5-year overall survival probability ranged from 65 % to 100 % [5,28,29]. It is probably due to a selection bias related to our institutional policy reserving liver stereotactic ablative radiotherapy as bridge therapy mainly when the patient has comorbidities that contraindicate other local bridge therapy, or when the tumour is not controlled after transarterial chemoembolisation or radiofrequency ablation. We report a 5-year disease-free survival probability of 69.2 % in our RT cohort, which is also inferior compared to other published reports (74 %–100 %) [5,28,29]. However, all of the four oncological recurrences in our series occurred during the first year following liver transplantation. It suggests a more advanced oncological disease in these patients, who should not have been considered eligible for liver transplantation.

Our results have several limitations due to the retrospective design of this study and the small number of patients included in our RT cohort leading to a potential lack of power to highlight a differential effect between irradiated and non-irradiated patients. PSM analysis allows us to select patients in the $NoRT_{all}$ cohort that have similar baseline characteristics compared to the RT cohort for a more appropriate comparison between groups. With the rising role of radiotherapy as a bridge therapy before liver transplantation for patients with hepatocellular carcinoma, further studies on

larger populations will be required to confirm our results. Additionally, the heterogeneity in the radiotherapy indication and scheme (biological equivalent dose ranging from 57.6 Gy to 124,8 Gy in the RT cohort) prevents drawing definitive conclusions about the real impact of radiotherapy on acute cellular rejection after liver transplantation. Particularly, different radiotherapy fraction doses can have opposite effects on immune effectors [8,30]. The systematic use of tacrolimus as immunosuppressive therapy and the systematic liver biopsy at around 7 days post-liver transplantation allows for reducing other bias linked to the surgery and immunosuppressive procedure.

5. Conclusion

Liver radiotherapy can be given as a bridge therapy for hepatocellular carcinoma or as part of the neoadjuvant chemoradiotherapy for cholangiocarcinoma before liver transplantation. Despite its potential effect on the local and systemic immune systems, liver radiotherapy has no impact on acute cellular rejection based on the Banff score reported in the early liver biopsy. Additionally, liver transplanted patients with liver radiotherapy before transplantation present similar overall and disease-free survival probabilities compared to a matched cohort of non-irradiated liver transplanted patients. Based on these results, and subject to analysis of larger cohorts, liver radiotherapy could be performed safely in patients requiring liver transplantation.

Institutional Review Board approval and patient consent

This monocentric study was conducted in accordance with the declarations of Helsinki and Istanbul and was approved by the ethics committee of cliniques universitaires Saint-Luc (reference number: 2023/17JUL/325). None of the subjects refused to consent to the publication of their data.

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Data availability statement

The data that support the findings of this study are available upon request from the authors.

Author contributions

JP: conceptualization, methodology, formal analysis, investigation, writing – original draft, visualization; MF, PB, EBR, LC, OC, GD, BD: investigation, writing – review & editing; GVO: writing – original draft, writing – review & editing, supervision.

Disclosure of interest

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