Multimodal Therapy including Yttrium-90 Radioembolization as a Bridging Therapy to Liver Transplantation for a Huge and Locally Advanced Intrahepatic Cholangiocarcinoma

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ABSTRACT

Treatment of intrahepatic cholangiocarcinoma remains a major challenge. For an unresectable lesion without extrahepatic spread, liver transplantation could be a potential solution but it is still associated with poor oncologic results owing to the absence of effective neoadjuvant treatment. We report the case of a young man with locally advanced intrahepatic cholangiocarcinoma presenting with multiple intrahepatic metastases and vascular structure involvement. The lesion was significantly downstaged by a multimodal therapy including intra-arterial Yttrium-90 radioembolization, systemic chemotherapy and external radiotherapy, allowing liver transplantation. Three years after the procedure, oncologic outcome is excellent with no sign of recurrence. Multimodal therapy including Yttrium-90 radioembolization could be relevant as neoadjuvant treatment before liver transplantation for unresectable intrahepatic cholangiocarcinoma.

Key words: liver transplantation – intrahepatic cholangiocarcinoma – radioembolization – Yttrium.

INTRODUCTION

Intrahepatic cholangiocarcinoma (ICC) is the second primary liver malignancy after hepatocellular carcinoma (HCC) and accounts for 10%-15% of primary liver malignancies [1]. Its incidence and mortality are increasing worldwide [2] and complete surgical resection remains the only potential curative treatment with a 5-year survival rate of 30%-40% [3]. Since these tumors are clinically silent, patients are usually diagnosed with bulky lesions, infiltrating vascular structures or intra- or extrahepatic metastases. Few patients can therefore benefit from surgery and the resection rate remains low [4]. For unresectable tumors without extrahepatic dissemination, liver transplantation (LT) can be an alternative option. However, recurrence is frequent and the survival rate remains disappointing [5].

Radioembolization with Yttrium-90 (Ytt-90) is a promising method that has already demonstrated its efficacy as a palliative treatment for HCC or ICC, and is an effective therapy for downstaging to resection or LT for HCC [6, 7]. Recently, we showed its interest in downstaging huge and unresectable ICCs which enabled secondary resection [8].

Here, we report the case of a 35-year-old patient presenting a huge ICC with multiple intrahepatic lesions, significantly downstaged after Ytt-90 radioembolization combined with systemic chemotherapy and eventually transplanted. The patient still presents no sign of recurrence three years after the procedure.

CASE PRESENTATION

A 35-year-old man with no medical history initially presented with epigastric pain. He was a non-smoker and did not drink alcohol abusively. The physical examination revealed a right subcostal abdominal mass and superficial abdominal venous distension. Imaging (CT scan and MRI) revealed a huge liver tumor 12 cm in diameter arising from the right liver involving the three
hepatic veins and the portal vein bifurcation. The intrahepatic bile ducts were moderately dilated due to external compression of the biliary confluence by the lesion. The tumor presented at least three tumoral satellite nodules in segments 2, 4 and 7 (Fig. 1). No extrahepatic spread was found on radiological investigations as well as on FDG-PET.

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Four months after radioembolization, imaging showed significant tumoral shrinkage (Fig. 1-C), but the lesion was still considered as unresectable owing to vascular involvement and persistent tumoral satellite nodules.

Since the patient was young with a controlled disease limited to the liver, a compassionate liver transplantation (LT) option was evaluated. A staging laparotomy was first performed in order to confirm the absence of both lymph node invasion around the portal pedicle or abdominal carcinosis. Additional external radiotherapy targeting the tumor (50 Grays delivered over 25 sessions) without oral chemotherapy was performed.

As no exception points were allowed for this indication, LT was eventually performed with a graft discarded by all other transplant teams (due to elevated cholestasis and liver enzyme) seven months after Yt-90 radioembolization (i.e. one year after diagnosis of the tumor). The transplant procedure went smoothly but required a partial resection of the retrohepatic inferior vena cava. A total of two red blood cell packs and three fresh frozen plasmas were transfused. The graft was implanted orthotopically using the modified piggyback technique (i.e. latero-lateral anastomosis). Total cold ischemic time was 8 hours. The postoperative course was uneventful except for urinary and cytomegalovirus infections which were both easily controlled.

Immunosuppression therapy was standard, associating low doses of tacrolimus, mycophenolate mofetil and prednisolone [9]. The patient was discharged from the hospital on postoperative day 20 with normal liver function. Three months after LT, tacrolimus was switched to everolimus owing to its potential anti-tumoral effect [10].

Pathology revealed an ICC 9 cm in diameter with 70% necrosis or fibrosis. Multiple intrahepatic secondary lesions were observed. After multidisciplinary discussion, no adjuvant treatment was indicated.

Two years after LT, the patient presented with biliary anastomotic stricture requiring surgical repair. At the time of laparotomy, complete exploration of the abdominal cavity showed no signs of recurrence.

Three years after LT, the patient is doing perfectly well. Liver function and CA19.9 blood level have remained within normal range and no sign of recurrence was found on imaging.

**DISCUSSION**

Liver transplantation is a well-recognized treatment for selected HCC in cirrhotic liver [11] and early-stage perihilar cholangiocarcinoma (PHC) [12]. Conversely, ICC is still considered as a contraindication for LT by most transplant authorities.
centers. Indeed, previous studies have reported poor oncologic outcomes with high recurrence rates and 5-year survival at approximately 30% and identified lymph node invasion, advanced TNM stage, microvascular invasion and multifocality as poor prognostic factors [5, 13, 14].

These disappointing results could be partly explained by the absence of effective neoadjuvant therapy as opposed to PHC. Indeed, LT for PHC became relevant when associated with aggressive preoperative treatment [15]. Nowadays, the Mayo Clinic protocol which associates rigorous selection criteria, preoperative chemotherapy with external radiotherapy followed by staging laparotomy to confirm the absence of extrahepatic spread and then liver transplantation, has increased the 5-year survival rate of patients with unresectable PHC to over 50% [12].

As for ICC, Hong et al. promoted the role of neoadjuvant chemotherapy prior to LT and proposed a neoadjuvant protocol including systemic chemotherapy associated with stereotactic body radiation for lesions ≤ 6cm or TACE for lesions > 6cm [14, 16]. Despite such preoperative treatment, the 5-year survival rate has remained low even for small tumors and has not been evaluated prospectively or confirmed by other teams. Therefore, the most effective neoadjuvant combination therapy before LT remains to be found and represents a major challenge for treatment of unresectable ICC.

To our knowledge, we report the first case of huge (>10cm) unresectable ICC with multiple tumoral satellite nodules transplanted with good oncologic outcome 3 years after the procedure. The lesion presented many poor prognostic factors such as its size, presence of macrovascular invasion and multiple tumoral satellite nodules. Given these observations, the prognosis was expected to be poor and according to the Wang et al. nomogram [17], this type of lesion is associated with a dismal (i.e. <10%) 3-year survival rate. In our case, the oncologic outcome is still good 3 years after transplantation. We believe that pre-transplant Yttrium-90 radioembolization enabled such a good result. Indeed, while systemic chemotherapy enabled disease stabilization, Yttrium-90 radioembolization allowed significant tumoral shrinkage and necrosis.

Yttrium-90 radioembolization, a pure beta emitter, is an emerging therapy that has already proved its interest in palliative treatment and downstaging before resection or transplantation for HCC [6]. Its interest in the palliative treatment of ICC has been demonstrated [7, 18, 19] and our team recently reported its utility for downstaging huge initially unresectable lesions, thereby enabling secondary resection [8].

In this case, the patient received a modified LV5FU2-cisplatin regimen chemotherapy while the actual standard for palliative treatment is an association of Gemcitabine and Cisplatin [20]. Moreover, one can discuss the interest of the external radiotherapy performed after radioembolization, especially as it could be incriminate in the biliary Anastomotic stricture observed two years after LT procedure.

Although we can report only one case, we suggest that further studies should be conducted testing Gemcitabine and Cisplatin chemotherapy associated with Yttrium-90 radioembolization without external radiotherapy before liver transplantation for unresectable ICC.

CONCLUSION

We report the first case of a huge and locally advanced ICC transplanted after neoadjuvant treatment combining systemic chemotherapy and Yttrium-90 radioembolization with a good oncologic result at 3 years. We believe that the association of Yttrium-90 radioembolization and systemic chemotherapy could be relevant in the treatment of ICC similarly to the Mayo Clinic protocol in the treatment of unresectable PHC and could open the door to curative treatment for patients with locally advanced ICC.

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REFERENCES


Tratamentul multimodal, incluzând radioembolizarea cu Yttrium-90, ca terapie intermediară înainte de transplantul hepatic pentru un colangiocarcinom intrahepatic voluminos și avansat local

ABSTRACT / REZUMAT

Tratamentul colangiocarcinomului intrahepatic rămâne o provocare majoră. Pentru o leziune nerezecabilă și fără extindere extrahepatică, transplantul hepatic poate reprezenta o soluție posibilă, dar este încă asociat cu rezultate oncologice slabe datorită absenței unui tratament neoadjuvant eficient. Raportăm cazul unui tânăr cu colangiocarcinom intrahepatic avansat, care prezenta multiple metastaze intrahepate și interesare vasculară. Leziunea a fost semnificativ diminuată printr-un tratament multimodal, incluzând radioembolizare intraarterială cu Yttrium-90, chimioterapie sistemică și radioterapie externă, ceea ce a permis efectuarea transplantului hepatic. La trei ani după transplant, rezultatul oncologic este excelent, și nu există semne de recurență. Terapia multimodală, incluzând radioembolizarea cu Yttrium-90, poate fi relevantă ca tratament neoadjuvant înainte de de efectuarea transplantului hepatic pentru colangiocarcinomul intrahepatic nerezecabil.