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Case-report: Metastases in a low-stage middle-graded HCC in cleared HCV infection, non-cirrhotic liver: Surgical therapy

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ABSTRACT

INTRODUCTION: Hepatocellular carcinoma (HCC) is rare in non-cirrhotic liver. Achievement of sustained virological response (SVR) reduces even more the risk.

PRESENTATION OF CASE: Liver resection for small HCC was performed in cleared HCV infection non-cirrhotic 62-year-old man. Methachronous oligometastatic recurrences in intolerant to Nexavar® side-effects patient, were treated by multiple innovative microinvasive approaches: bilateral laparoscopic adrenalectomy, thoracic wall resection, laparoscopic sacrum cryoablation combined with hadron-therapy.

DISCUSSION: Therapies allowed the patient to lead 6 years satisfying QoL with only a small residual presacral disease stable at 8 months.

CONCLUSION: Microinvasive surgery may be a valid resource of therapy in indolent HCC limited distant recurrences.

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1. Introduction

Hepatocellular carcinoma (HCC) represents worldwide 5,4% of all cancers, mainly associated with chronic HCV or HBV infection. It is commonly diagnosed in cirrhotic liver and only 10% in non-cirrhotic parenchyma. HCC incidence after HCV Sustained Virological Response (SVR) in non-cirrhotic liver is not currently widely accepted in scientific medical community [1–3]. Incidence rates in patients with low to moderate liver fibrosis after SVR are highlighted only by few Japanese works [1,2].

HCC-related metastatic disease has a very poor survival rate, chemotherapy is unable to increase overall survival [3] and patients suffer for very poor quality of life [4,5].

Nowadays the opportunity of surgery with non-invasive approach widens the possibilities to submit fit patients to repeated surgical interventions.

This work has been reported in line with the SCARE criteria [6].

2. Case presentation

We present the case of a fit 62-year-old man referred to our Hepatobiliopancreatic Unit in July 2012. He cleared the HCV infection (Genotype 1b) in 2007 by conventional therapy (Peg-Interferon α + Ribavirin) [7].

HCC-nodule of 3 cm in diameter in VI liver segment and non-signs of cirrhosis were founded by RM-scan and CT-scan with an α FP serum level of 360,9 ng/mL. Hepatic Resection was administered in September 2012. Histology revealed trabecular HCC T1 N0 M0 graded G2 (stage I) in moderately fibrotic liver tissue (IASL score F2) and with little immune infiltration (IASL score A1) [8]. The lesion, encapsulated, with no signs of vascular invasions or portal thrombosis, was staged as an early HCC. In December 2013, a mass in left adrenal gland and a simultaneous thoracic-wall metastasis were showed by CT-scan while serum α FP level had been raising (>1000 ng/mL). We planned surgical treatment for the adrenal metastasis, high intensity focus ultrasound (HIFU) therapy for the thoracic-wall one. Left laparoscopic adrenalectomy was performed in March 2014; histology confirmed it as secondary lesion. Since HIFU therapy failed, in April the patient underwent thoracic wall metastasis excision. A team of neuro and thoracic surgeons resected IV, V and VI posterolateral right ribs with D4, D5 and D6 transverse processes, dorsal muscles and parietal pleura en-bloc. Adjuvant radiotherapy (52 Grays) was administered.

Abbreviations: HCC, hepatocellular carcinoma; SVR, sustained virological response; HCV, hepatitis C virus; HBV, hepatitis B virus; HIFU, high intensity focused ultrasound; IASL, international association for the study of the liver; QoL, quality of life; CTCAE, common terminology criteria for adverse events; OAR, organ at risk.

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In June 2015 serum α FP level dropped to 30,29 ng/mL but raised again in September without CT showing evidence of newer metastasis. The patient was sent to the oncology department.

In November 2015 he started chemotherapy with Nexavar[®], however he had to suspend it after 6 weeks for intolerance to side effects. In May 2016 right laparoscopic adrenalectomy was necessary for a new contralateral adrenal gland metastasis. Medical therapy was administered and in this period the patient maintained an active and sporty life. In January 2017, for a serum α FP level of 3464 ng/mL, PET-scan and CT- total body were performed and, in absence of other sites' recurrences, a paramedian anterior right sacral lesion with partial infiltration of the bone's cortical was found. The patient lamented for right leg impairment and pain.

The 4 cm diameter mass was approached laparoscopically, and then cryoablated. Histological exam confirmed invariance of HCC origin.

In June, RM-scan showed a little malignant residue in former cryotherapy site. The patient was then scheduled for carbon-ions hadrontherapy at CNAO centre in Pavia.

Presacral lesion, after Hadrontherapy, showed a significant volumetric reduction at three months follow-up. A further lesion's reduction and the maintenance of local control in all other sites were noted at eight months [9].

All masses removed, at histology turned out to be trabecular hepatocellular carcinoma G2 graded metastases.

Currently, after 6-years history of metastatic disease, the patient maintains a sporty life and no pain treatments are requested for the residual lesion. However, as we expect further disease progression, a very close follow-up is needed.

3. Discussion

Surgical resections for metastatic disease have increased over last decades.

It is now part of multidisciplinary oncological approaches, leading to considerable improvement in long-term survival and quality of life. Minimally invasive procedures expanded the enrollable patients for repeated surgery.

Japanese studies find out a significant correlation between liver fibrosis before interferon therapy and HCC development. These observations make our report interesting and enforce the thesis that cirrhosis is not strictly necessary to develop HCC. HCV infection alone may induce enough alterations to cell cycle control thus to lead to malignant switch [10,11].

We do believe metastatic cells followed a strange migration pathway; all metastases were in retroperitoneal organs so tumour possibly spread through Retzius venous system. This is quite unconventional since the patient underwent a radical excision of an early HCC in a moderate-fibrotic liver.

HCC metastases are more frequently found in lungs (58%), lymph nodes (53%) and bone (28%). Adrenal glands are uncommon sites of HCC metastases (11%) [12]. In our case we had recurrences in this gland, first contralateral then omolateral ones. All malignant recurrences showed a raised serum α FP level allowing us to use it as a recurrence predictor. Adrenalectomy performed by laparoscopic approach allows to lower post-operative pain, length of stay and costs compared to open adrenalectomy. As a result, it has become the preferred approach for benign tumours. Recently, however, some series of studies report safety and absence of oncologic recurrences with minimally invasive approach even in malignant and metastatic adrenal lesions [13,14]. Careful patient selection, pre-operative staging, respect for oncologic principles are important considerations in choosing laparoscopic surgery for primary and secondary adrenal malignancies. Reduction of post-operative hos-

pitalization, fast recovery, durable disease-free and overall survival are factors which can significantly influence the choice.

The refusal of the patient to chemotherapy (Nexavar[®]) due to heavy side effects (CTCAE grade 3 for skin and respiratory system) [15] made the indication to minimally invasive surgery.

Another unusual laparoscopic approach with curative/palliative intent is cryotherapy of the sacrum. Many studies [16] have shown that ablation of painful bone metastases can significantly and sustainably reduce symptoms. This laparoscopic approach with mobilization of adjacent vessels and structures allowed performing safely the bone metastasis cryoablation.

The patient was also treated with carbon-ions hadron-therapy, proved to be far more effective than classical radiotherapy in HCC phase II clinical trials. Moreover, hadron-therapy showed astonishing result in HCC control, both in primary and metastatic lesions with local control rates at 81% at 5 years [2] and low organ at risk (OAR) damage.

Primitive malignancy control, absence of cirrhosis, non HCV-RNA detectability, good physical conditions and the will of the patient led to his enrolment into surgical treatments. Surgical multidisciplinary treatments by minimally invasive approach allowed to low surgical stress, fast post-operative recovery and rapid return to normal living activities.

The introduction of less and less invasive procedures allows multiple methachronous surgical resections.

4. Conclusion

This case report contributes to raise awareness on the possible development of HCC in patients who cleared HCV infection without cirrhotic liver.

Thus, after SVR, we suggest continuing a long-term follow-up.

Although the treatment of extrahepatic metastases from primary liver tumour is essentially palliative, multimodal aggressive therapy, including surgery, may be considered in very carefully selected patients to achieve benefits in both survival and QoL.

Conflicts of interest

There are not any potential conflicts of interest (financial, professional, or personal) relevant to the manuscript.

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Ethical approval

This case report is exempt from ethic committee approval.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request

Author contribution

Stefania Brozzetti – study concept, writing and revision.
Simone Bini – paper writing and revision.
Katia Fazzi – paper writing.
Leonardo Luca Chiarella – paper revision.
Virginia Ceccarossi – paper revision.

Chiara De Lucia – paper revision.
Giorgio De Toma – study concept.

Registration of research studies

Our case report does not need registration. Even though the procedures applied were innovative, intolerance of the patient to palliative therapy forced a different approach.

Guarantor

Professor Stefania Brozzetti.

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