



# Multi–detector Computed Tomography (MDCT) Findings of Seven Cases with Spontaneous Regression of Hepatocellular Carcinoma

Adel El–Badrawy

Radiology Department, Mansoura Faculty of Medicine, Mansoura, Egypt

## Abstract

**Purpose:** To review Multi–detector CT findings of seven cases with spontaneous regression of hepatocellular carcinomas (HCC).

**Materials and methods:** This retrospective study included 7 patients confirmed with diagnosis of HCC. Triphasic CT scan using multi–detector CT scanner was done for all patients. They were 2 women and 5 men. 1st patient presented with metastatic HCC underwent fine needle aspiration cytology (FNAC) from vertebral metastasis. 2nd patient underwent only one session of trans–arterial chemo–lipiodol. 3rd patient exposed to blunt trauma with rib fissure fracture. 4th patient presented with two HCCs underwent radio–frequency ablation of one lesion. 5th patient underwent FNAC from HCC and exposed to fracture acetabulum. 6th and 7th patients underwent FNAC from hepatic focal lesions.

**Results:** Complete regression of primary HCC and metastases occurred in 1st patient. 2nd patient showed partial lipiodol uptakes of HCC with complete regression of HCC on follow up. Incomplete regression of HCC detected in 3rd, 6th and 7th patients. Partial regression of non–ablated lesion detected in the 4th patient. Complete regression of HCC occurred on 5th patient.

**Conclusion:** Spontaneous regression of HCC is an interesting phenomenon. It has been hypothesized that invasive techniques and trauma may be linked. They may initiate immunologic mechanisms that may be involved in the regression. More reports and accumulation of such cases should help to clarify the mechanisms, contribute to a further understanding of this phenomenon and may lead to a new treatment strategy for HCC.

**Keywords:** computed tomography, spontaneous regression, hepatocellular carcinoma

## Introduction

Primary liver cancer is a major health problem worldwide. It is the fifth most common neoplasm in the world and the third most common cause of cancer–related death <sup>(1)</sup>. In hepatocellular carcinoma, liver transplantation is an alternative to surgical resection and requires lifetime immunosuppression. Locoregional ablation approaches are used with both curative and palliative intent in hepatocellular carcinoma. RFA is the most commonly applied ablative procedure. Transarterial chemoembolization (TACE) is a palliative treatment option for those with liver–confined disease not amenable to potentially curative ablation or surgery <sup>(2)</sup>.

Spontaneous regression of cancer is a phenomenon that has been observed since antiquity <sup>(3)</sup>. Spontaneous regression of a malignant tumor, which was defined by Everson and Cole, is a partial or complete involution of a malignant tumor without specific therapy being applied <sup>(4)</sup>. The present study review seven cases with spontaneous

regression of hepatocellular carcinoma aiming to determine the underlying etiology of regression.

## Materials and Methods

### Patients

The study was approved by the institutional research ethics review committee. This retrospective study included seven patients. They were 2 women and 5 men with a mean age of 47.5 years. The most common presenting symptom was abdominal pain and discomfort

**Corresponding Author:** Adel El–Badrawy, MD.

Radiology Department, Mansoura Faculty of Medicine,  
Mansoura, Egypt. Tel.: 002–0100–5785751,  
002–050–2234683. Fax: 002–050–2315280.

Address: 1 Omar Ben Abdel–Aziz from  
Gehan Street – Mansoura–Egypt.

Email: adelelbadrawy@hotmail.com

in 5 patients. Symptoms of liver cell failure were present in 2 patients. Three patients presented with more than one symptom. Clinical examination revealed the presence of an enlarged liver in 4 cases. All seven patients had ultrasonography. All patients satisfied the criteria of hepatocellular carcinomas. All seven patients were hepatitis C virus positive. 1<sup>st</sup> and 3<sup>rd</sup> patients were hepatitis B virus positive. 1<sup>st</sup> patient underwent fine needle aspiration cytology (FNAC) from vertebral metastases. The remaining 6 patients underwent FNAC from hepatic focal lesions. 5<sup>th</sup> patient underwent FNAC from two lesions. There were no major immediate complications from FNAC. All patients were observed for 4 hours following the procedure and then discharged with no patients requiring a blood transfusion. Four patients had transient pain at the puncture site that eventually subsided without medications. No delayed complications were reported on routine clinic review 2 weeks following biopsy. Laboratory abnormalities were detected in all cases. These abnormalities on admission showed the following results: mild elevated total bilirubin 1.3 – 3 mg/dL (normal 0.1–1.1), aspartate aminotransferase (AST) 70– 130 IU/mL (up to 40) and alanine aminotransferase (ALT) 55– 120 IU/L (up to 40). Alpha fetoprotein (AFP) titer was, 4253, 850, 1223, 250, 145, 35 and 945 ng/ml (normal range 0–10ng/ml) in 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup> & 7<sup>th</sup> patients respectively. Pathological diagnosis of HCC was confirmed in all 7 cases. 2<sup>nd</sup> patient underwent of session of trans–arterial chemo–lipidol. 3<sup>rd</sup> patient exposed to blunt trauma with fracture rib. 4<sup>th</sup> patient had two HCCs and underwent RFA for one lesion. Pathology revealed infected HCC in 5<sup>th</sup> & 7<sup>th</sup> cases. 5<sup>th</sup> patient exposed to trauma with fracture acetabulum. 7<sup>th</sup> patient exposed

to fracture neck femur with prosthetic hip replacement (Table 1).

### CT technique

Triphasic CT scanning was performed on one of two systems (Brilliance 64; Philips Healthcare, Best, The Netherlands) in 3 patients and (SOMATOM Emotion6, Siemens, Germany) in 4 patients. The pre–contrast and post–contrast series were taken by using a 5 mm slice thickness. The post–contrast study was performed using 120 ml of low osmolar non–ionic contrast medium (Ioversol, Optiray 350) at a flow rate of 5 ml/sec. Patients were requested to hold their breath during the pre–contrast phase and the three phases of acquisition. Automated bolus tracking with bolus detection at the level of the descending aorta above the diaphragm ensured accurate timing of the data acquisition in an early arterial phase. Portal venous phase was performed with an effective delay of 55–60 seconds after initiation of the contrast material injection. The delayed phase was performed with effective delay of 3–6 minutes. All images were transferred to the workstation Extended Brilliance Workspace V3.5.0.2254 (EBW) for post processing.

### Image interpretation

Data interpretation and image analysis focused on the following aspects on the initial CT scan: pre–contrast attenuation of the lesions, density in all phases (arterial, portal and delayed phases), number of lesions, vascular invasion, lymph node involvement and other abdominal organs as well as metastatic spread. On follow up, in addition to previous aspect, we focused on reduction in tumor size, residual tumor enhancement and necrosis.

<b>Patients</b>	<b>Invasive procedure</b>	<b>mRECIST response</b>	<b>Inciting event</b>
<b>1<sup>st</sup></b>	FNAC from metastasis	Complete regression	FNAC
<b>2<sup>nd</sup></b>	FNAC and TACE	Complete regression	Angiography
<b>3<sup>rd</sup></b>	FNAC and blunt trauma with fracture rib	Incomplete regression	Blunt trauma with fracture rib
<b>4<sup>th</sup></b>	FNAC and RFA	Partial regression	RFA
<b>5<sup>th</sup></b>	FNAC	Complete regression	<ul style="list-style-type: none"> <li>• Infected HCC</li> <li>• Liver abscess</li> <li>• Fracture acetabulum</li> </ul>
<b>6<sup>th</sup></b>	FNAC	Incomplete regression	FNAC
<b>7<sup>th</sup></b>	FNAC	Incomplete regression	<ul style="list-style-type: none"> <li>• Infected HCC</li> <li>• Fracture neck femur with prosthetic hip replacement</li> </ul>

**Table 1: Spontaneous HCC regression with degree of response and inciting event in 7 patients**

Assessment of tumor regression depended on the use of modified RECIST criteria for the assessment of HCC response based on follow up triphasic CT according to European Association for the Study of the Liver, European Organisation for Research and Treatment of Cancer (EASL–EORTC) (2).

### Follow-up

1<sup>st</sup> patient followed after 6 month. 2<sup>nd</sup> patient followed 1 and 3 months after only one secession of transarterial chemo-lipiodol. 3<sup>rd</sup> patient followed after 5 months as he was exposed to blunt trauma with rib fissure fracture. This patient developed febrile illness with rigor after trauma. 4<sup>th</sup> patient followed 1 month after RFA. 5<sup>th</sup> patient followed after 3 months and he was exposed to fracture acetabulum. 6<sup>th</sup> patient followed after 6 months. 7<sup>th</sup> patient followed after 4 months and was exposed to fracture neck femur with prosthetic hip replacement.

## Results

### Initial CT scan

1<sup>st</sup> patient revealed segment V and VI HCC invading right posterior PV with vertebral metastasis. 2<sup>nd</sup> patient revealed segment IVa and VIII HCC. 3<sup>rd</sup> patient revealed segment VII and VIII HCC invading right hepatic vein and IVC with extension to right atrium. There was associated moderate ascites. 4<sup>th</sup> patient revealed two small HCCs in segment I and V. 5<sup>th</sup> patient revealed segment II and III HCC with left PV invasion. There was segment VI hepatic

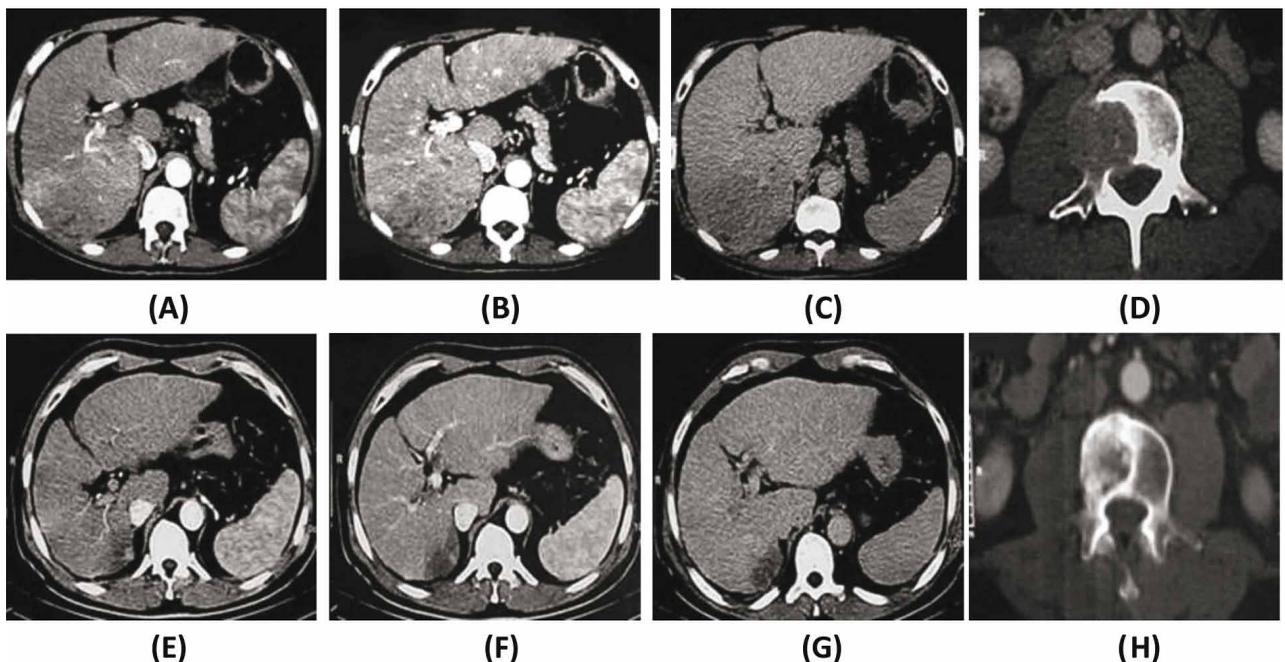
abscess. 6<sup>th</sup> patient revealed segment VIII HCC with PV invasion. 7<sup>th</sup> patient revealed segment II and III HCC with segment IV small HCC. There was associated moderate ascites.

### Follow-up CT scan

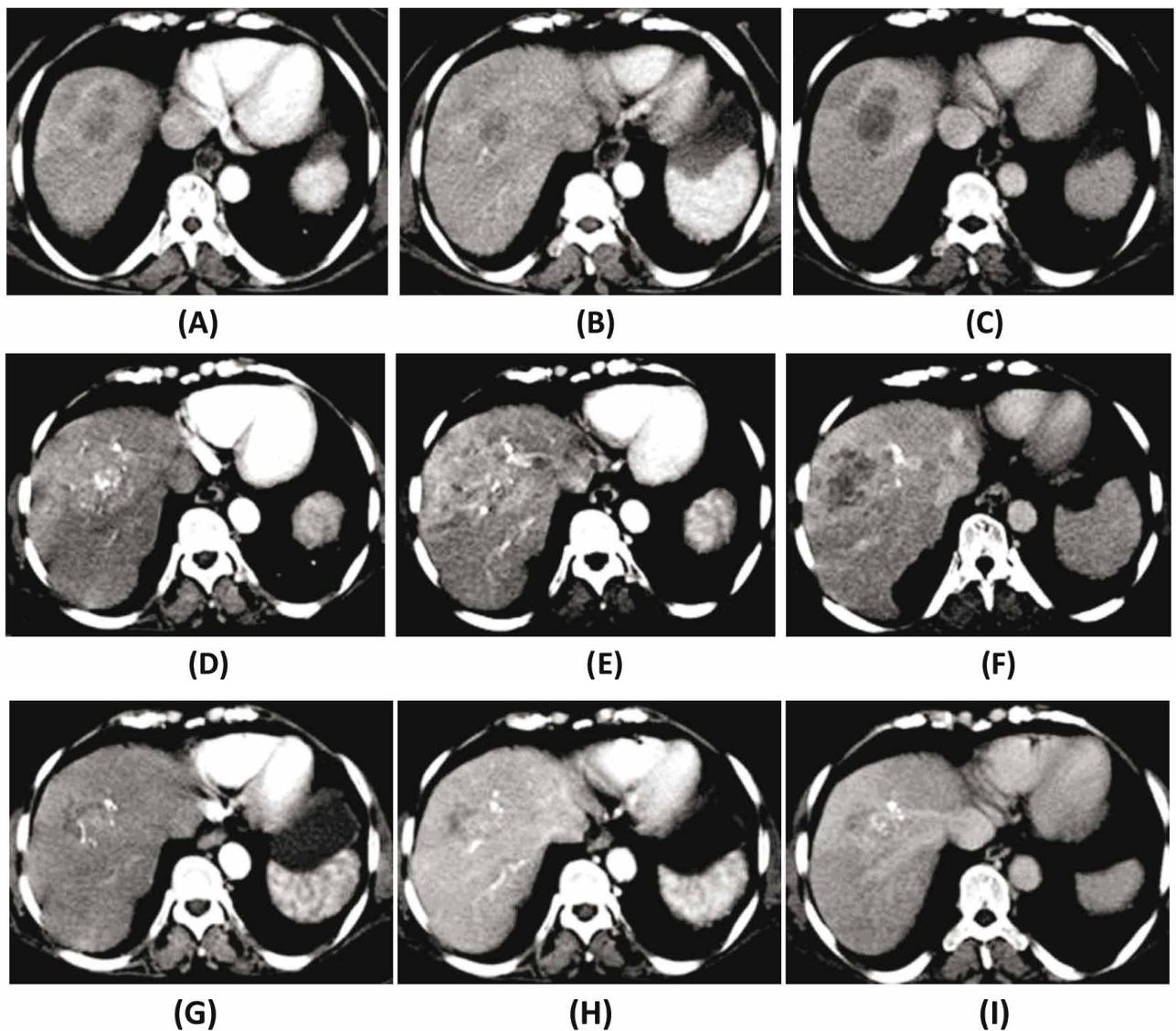
1<sup>st</sup> patient revealed residual smaller hypodense area with no detected enhancement after IV contrast injection denoting complete regression. Also, there was complete healed of vertebral metastases (Fig. 1). On the 2<sup>nd</sup> patient, there was residual enhanced tumor on follow up after 1 month. Follow up after two months without interference revealed totally regression of the tumor with no detected areas of viable tumor (Fig. 2). 3<sup>rd</sup> patient showed decrease in tumor size, disappearance of atrial thrombus, hepatic vein or IVC invasion denoting incomplete regression (Fig. 3). Partial regression of non-ablated lesion detected in the 4<sup>th</sup> patient (Fig. 4). Complete regression of HCC occurred on 5<sup>th</sup> patient (Fig. 5). Incomplete regression of HCC detected in 6<sup>th</sup> patient (Fig. 6). 7<sup>th</sup> patient revealed complete regression of segment II and III HCC with partial regression of segment IV HCC (Fig. 7) (Table 1).

## Discussion

Hepatocellular carcinoma is the third most common cause of cancer-related death worldwide, with an estimated 692,000 cases per year. Although patients with early disease have a relatively good prognosis with a 5-year survival rate of more than 70%, the majority of patients with hepatocellular carcinoma are diagnosed



**Figure 1: Initial triphasic CT scan: A–C** (arterial, portal & delayed phases) revealed right liver lobe HCC with vertebral metastasis **(D)**. **Follow up CT scan after 6 months: E–G** (arterial, portal and portal phases) revealed hypodense non-enhanced area denoting complete regression of HCC with healed metastasis **(H)**.



**Figure 2: Initial triphasic CT scan: A–C** (arterial, portal & delayed phases) revealed right liver lobe HCC. **Follow up CT scan after 1 month: D–F** (arterial, portal & portal phases) revealed residual enhanced HCC with evidence of mild lipidol uptake. **Follow up after 2 months: G–I** (arterial, portal & delayed phases) revealed hypodense non–enhanced area denoting complete regression with evidence of mild lipidol uptake.

with late–stage disease resulting in an overall 5–year survival rate of less than 16% <sup>(5)</sup>.

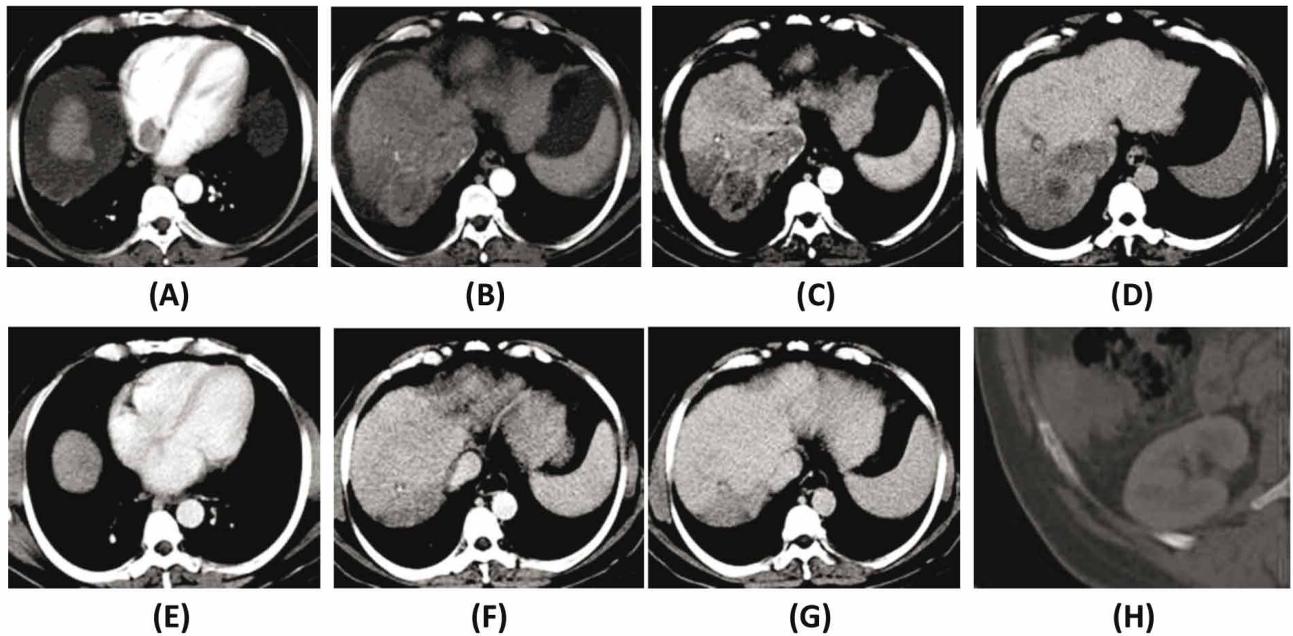
CT has long been a mainstay of liver and HCC imaging for both initial tumor characterization and post treatment follow–up for response assessment. Biphasic scanning in the hepatic arterial and portal venous phases is generally used for HCC detection <sup>(6)</sup>.

The EASL and European Organisation for Research and Treatment of Cancer (EORTC) <sup>(2)</sup> have recently endorsed the use of the modified RECIST criteria for the assessment of HCC response based on dynamic CT or MRI performed 1 month after locoregional therapy or systemic therapy. The modified RECIST criteria take into account size and vascularity (on arterial phase CT or MRI) of residual enhancing tumor and are appropriate for use in HCC

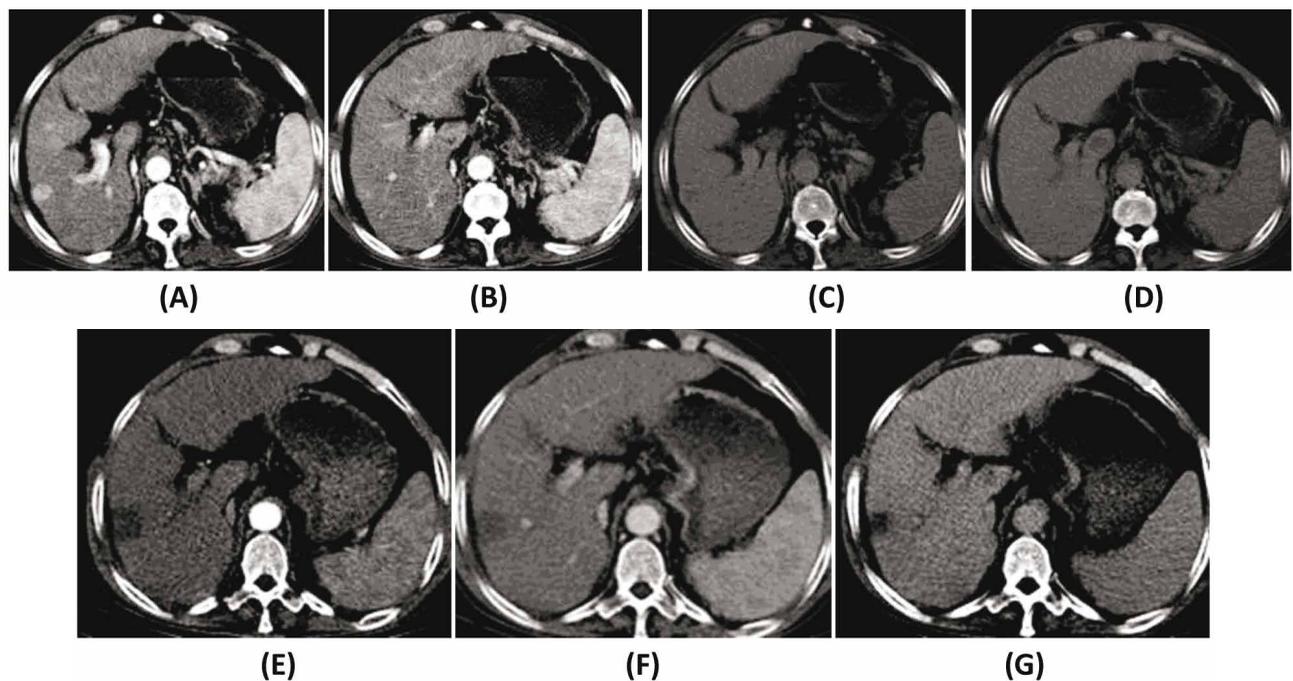
treated with locoregional therapy <sup>(2)</sup>. The evaluation of tumor response after systemic and locoregional therapies is essential in directing management for HCC. The evaluation of tumor response should include not only anatomic imaging biomarkers, such as reduction in tumor size, but also tumor enhancement and necrosis <sup>(7)</sup>.

Spontaneous regression is the partial or complete disappearance of a malignant tumor proven by microscopic examination in the absence of any substantial treatment <sup>(4,8)</sup>. Spontaneous immune responses, including T–cell responses as well as humoral responses to different tumor–associated antigens, have been described in hepatocellular carcinoma <sup>(9,10)</sup>.

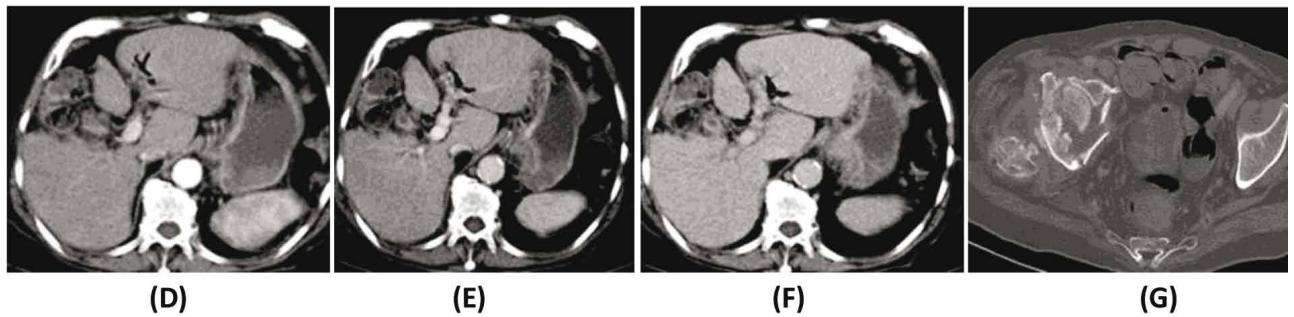
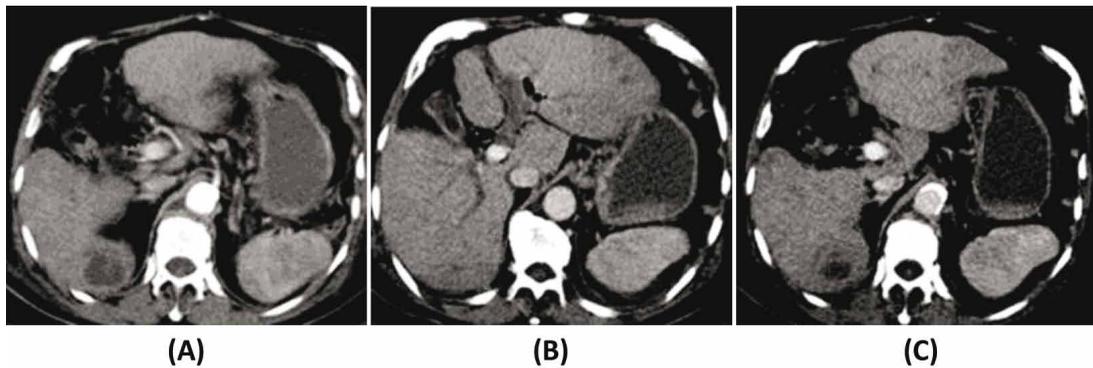
Given the presence of extensive necrotic phenomena, it has not been possible to ascertain whether an immune



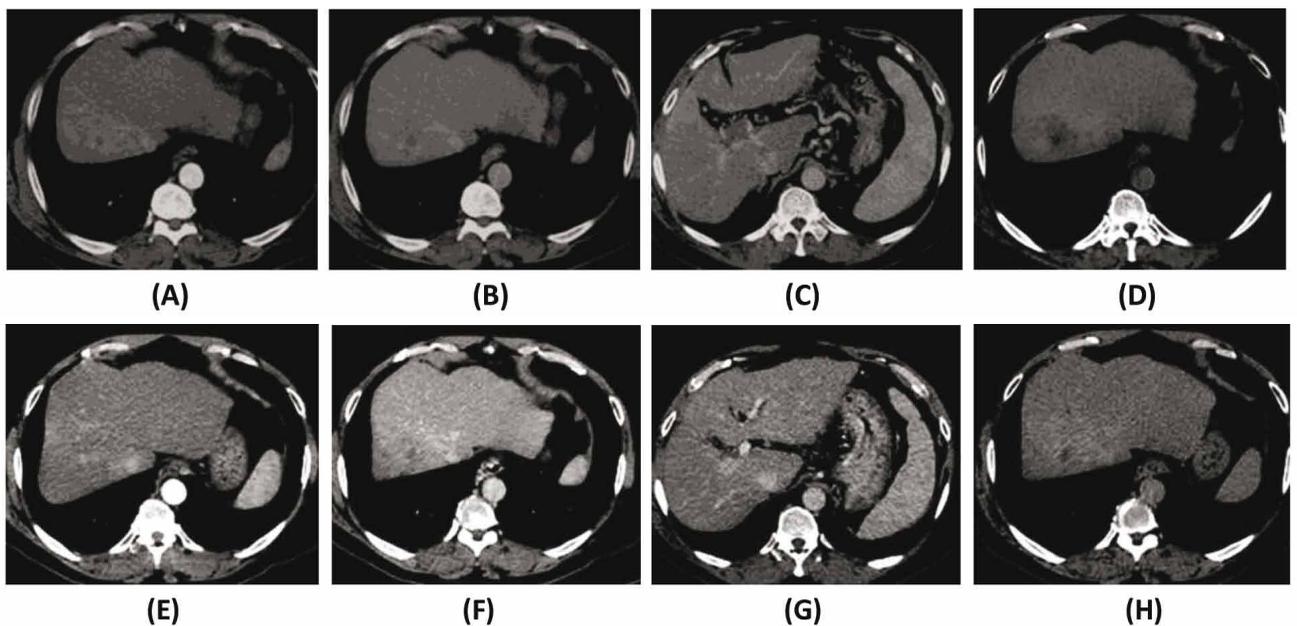
**Figure 3: Initial triphasic CT scan: A–D** (arterial, portal & delayed phases) revealed right liver lobe HCC invading RT. hepatic vein and IVC with right atrial thrombus. **Follow up CT scan after 5 month: E–H** (portal & delayed phases) revealed regression of atrial thrombus and patent IVC with residual small HCC. Evidence of fissure fracture of right rib **(H)**.



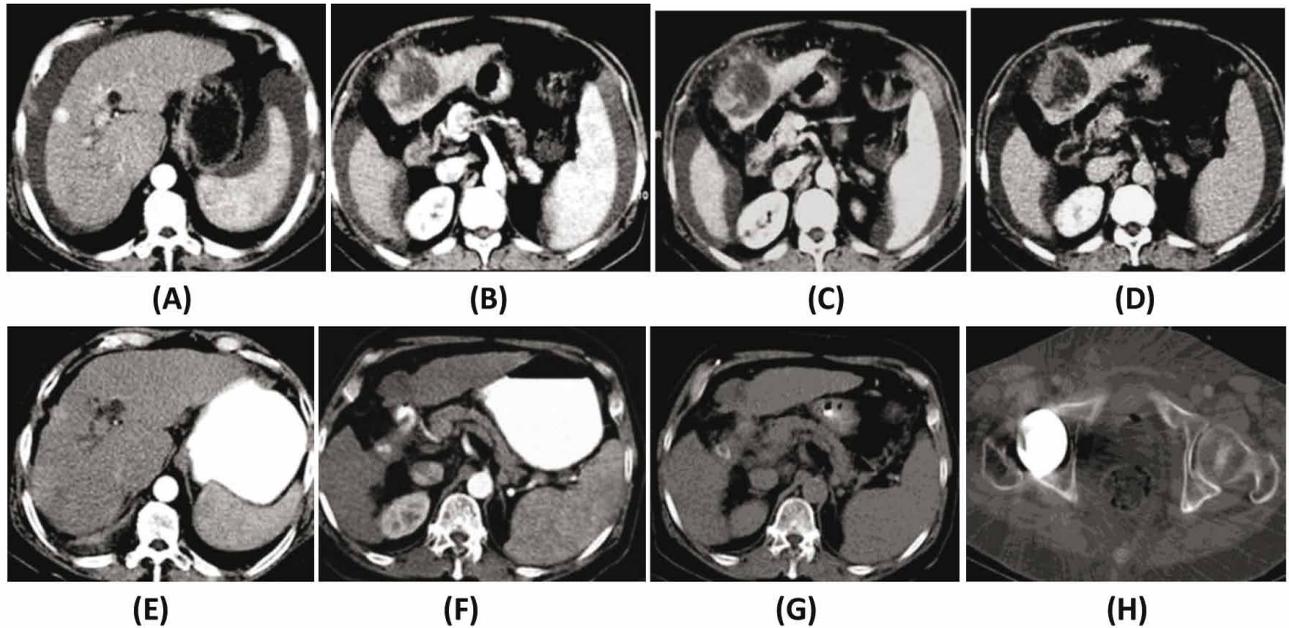
**Figure 4: Initial triphasic CT scan: A–D** (arterial, portal & delayed phases) revealed segment I & V two HCCs. Patient underwent RFA for segment V HCC. **Follow up CT scan after 1 months from ablation: E–G** (arterial, portal & delayed phases) revealed complete ablation of segment V HCC with mild decrease in size and decrease enhancement of segment I HCC denoting partial regression.



**Figure 5: Initial triphasic CT scan: A–C** (arterial and portal phases) revealed segment I & II HCC with left PV thrombus. Evidence of segment VI hepatic abscess. **Follow up CT scan after 3 months: D–F** (arterial, portal & delayed phases) revealed complete regression of HCC and abscess with recanalization of left PV. Evidence of fracture right acetabulum (**G**).



**Figure 6: Initial triphasic CT scan: A–D** (arterial, portal & delayed phases) revealed segment VIII with PV thrombus. **Follow up CT scan after 6 months: E–H** (arterial, portal & delayed phases) revealed incomplete regression of HCC with incomplete recanalization of PV.



**Figure 7: Initial triphasic CT scan: A–D** (arterial, portal & delayed phases) revealed two HCCs affecting segment II, III and IV. **Follow up CT scan after 4 months: E–G** (arterial and delayed phases) revealed complete regression of segment II & III HCC with partial regression of segment IV HCC. Evidence of prosthetic right hip **(H)**.

mechanism is responsible for an effective host response. Among the concomitant causes, pathologic alterations, such as arterial spasms, hemorrhage and inflammatory processes are sometimes indicated. No reports exist in the literature of patients with eventual second tumors who have presented spontaneous tumor regression<sup>(11)</sup>.

Mizokushi and colleagues evaluated T–cell responses in patients with hepatocellular carcinoma undergoing RFA. They observed immune responses to antigens for which no T–cell response was detected at baseline before RFA and the number of tumor–specific T cells after RFA correlated with the prevention of hepatocellular carcinoma recurrence in patients treated with curative intent<sup>(12)</sup>.

Activation and increased cytolytic activity of tumor–specific CD8+ T–cell responses after RFA have been demonstrated in patients with hepatocellular carcinoma and colorectal liver metastases<sup>(13)</sup>. This may explain partial regression of non–ablated lesion in 4th patient who underwent RFA for one lesion.

Pathological evidence of an inflammatory mechanism for regression was demonstrated in one patient where a biopsy of the previous tumour site revealed the presence of a chronic inflammatory infiltrate<sup>(14)</sup>. The evidence and observations of rapid tumor regression following infection sometimes within hours suggest that the innate rather than the adaptive immune response is a primary mediator

of tumor regression in such cases<sup>(15)</sup>. Infectious agents are present in nature that can cause cancer but we should also remember the dual role they play in preventing cancer. Acute infectious agents are a natural source of immunostimulants that challenge our immune system from time to time as well as pep it up to confront newer challenges evolution brings about like cancer<sup>(16,17)</sup>.

Wada et al., reported that patients with HCC whose resected tumors demonstrated a lymphocytic infiltration have a better prognosis than those without the infiltrate. These reports provide reasonable support to the theory that a systemic inflammatory response is associated with spontaneous regression<sup>(18)</sup>. This coincide with tumor regression occurred in 5<sup>th</sup> & 7<sup>th</sup> patients as pathology revealed infected hepatocellular carcinoma.

Complete regression occurred in 2<sup>nd</sup> patient who underwent trans–arterial chemolipiodol. This coincides with previous studies<sup>(19,20)</sup>. The patient presented with segment IVa and VIII HCC. He underwent one secession of transarterial chemo–lipiodol with evidence of mild lipiodol uptake. There was decrease in size on follow up after 1 month with residual enhanced tumor. Follow up after two months without interference revealed totally improvement of the tumor with no detected areas of viable tumor

Takeura et al. found regression after trauma with multiple bone fractures<sup>(21)</sup>. These coincide with regression of 3<sup>rd</sup>, 5<sup>th</sup> & 7<sup>th</sup> patients. 3<sup>rd</sup> patient developed regression after blunt trauma with fracture rib. 5<sup>th</sup> patient developed

regression after infection and fracture acetabulum. 7<sup>th</sup> patient developed regression after infection and fracture neck femur with prosthetic hip replacement.

Huz et al., found that tumour hypoxia and the inflammatory response are important components of spontaneous regression. But, the true mechanism of regression is certainly multifactorial and complex <sup>(14)</sup>. These coincide with our results. Inciting event detected in 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup> & 7<sup>th</sup> patients, but, unknown mechanism in the remaining 1<sup>st</sup> and 6<sup>th</sup> patients.

1<sup>st</sup> and 6<sup>th</sup> patients underwent FNAC from metastasis in 1<sup>st</sup> & from HCC in 6<sup>th</sup> patients. FNAC may be attributed mechanism of regression as 1<sup>st</sup> patient started to be decreased level of AFP after FNAC.

## Conclusion

In conclusion, spontaneous regression of HCC is an interesting phenomenon. It has been hypothesized that invasive techniques and trauma may be linked. Invasive techniques and trauma may initiate immunologic mechanisms that may be involved in the regression. Immunological evaluation of patient with hepatocellular carcinoma must be assessed before and after invasive technique, even after FNAC to detected immune-directed therapies. More reports and accumulation of such cases should help to clarify the mechanisms, contribute to a further understanding of this phenomenon and may lead to a new treatment strategy for HCC.

## Abbreviations used in this study:

MDCT: multi-detector computed tomography; HCC: hepatocellular carcinoma; EASL: European Association for the Study of the Liver; EORTC: European Organization for Research and Treatment of Cancer; mRECIST: modified Response Evaluation Criteria in Solid Tumor; TACE: trans-arterial chemoembolization; RFA: radiofrequency ablation; FNAC: Fine needle aspiration cytology; PV: portal vein

## References

- Lafaro KJ, Demirjian AN, and Pawlik TM. Epidemiology of hepatocellular carcinoma. *Surgical Oncology Clinics of North America* 2014; 24:1–17.
- European Association for the Study of the Liver, European Organisation for Research and Treatment of Cancer. EASL–EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 2012; 56:908–943.
- Hoption Cann SA, van Netten JP, van Netten C, et al. Spontaneous regression: a hidden treasure buried in time. *Med Hypotheses* 2002; 58(2):115–119.
- Everson TC and Cole WH. *Spontaneous Regression of Cancer*. Philadelphia: Saunders 1966; 6–7.
- Siegel R, Naishadham D, Jemal A. Cancer statistics. *CA Cancer J Clin* 2013; 63:11–30.
- Iannaccone R, Laghi A, Catalano C, et al. Hepatocellular carcinoma: role of unenhanced and delayed phase multi-detector row helical CT in patients with cirrhosis. *Radiology* 2005; 234:460–467.
- Yaghmai V, Besa C, Kim E et al. Imaging Assessment of Hepatocellular Carcinoma Response to Locoregional and Systemic Therapy. *American Journal of Roentgenology* AJR. 2013; 201: 80–96.
- Everson TC. Spontaneous regression of cancer. *Prog Clin Cancer* 1967; 3:79–95.
- Mizukoshi E, Nakamoto Y, Arai K, et al. Comparative analysis of various tumor-associated antigen-specific T-cell responses in patients with hepatocellular carcinoma. *Hepatology* 2011;53:1206–16.
- Koranyi F, Ormandy LA, Bleck JS, et al. Spontaneous tumor-specific humoral and cellular immune responses to NY-ESO-1 in hepatocellular carcinoma. *Clin Cancer Res* 2004; 10:4332–4341.
- Ricci SB and Cerchiari U. Spontaneous regression of malignant tumors: Importance of the immune system and other factors (Review). *Oncology Letters* 2010; 1:941–945.
- Mizukoshi E, Yamashita T, Arai K, et al. Enhancement of tumor-associated antigen-specific T cell responses by radiofrequency ablation of hepatocellular carcinoma. *Hepatology* 2013; 57:1448–1457.
- Hansler J, Wisniewski TT, Schuppan D, et al. Activation and dramatically increased cytolytic activity of tumor specific T lymphocytes after radio-frequency ablation in patients with hepatocellular carcinoma and colorectal liver metastases. *World J Gastroenterol* 2006; 12: 3716–3721.
- Huz JI, Mellis M, Sarpel U. Spontaneous regression of hepatocellular carcinoma is most often associated with tumour hypoxia or a systemic inflammatory response. *HPB* 2012; 14:500–505.
- Hoption Cann SA, van Netten JP, van Netten C. Dr William Coley and tumour regression: A place in history or in the future? *Postgraduate Med J* 2003; 79: 672–680.
- Kleef R, Jonas WB, Knogler W, et al. Review of fever, cancer incidence and spontaneous remissions. *Neuroimmunomodulation* 2001; 9:55–64.
- Abel U, Becker N, Angerer R et al. Common infections in the history of cancer patients and controls. *J Cancer Res Clin Oncol* 1991; 117:339–344.
- Wada Y, Nakashima O, Kutami R, et al. Clinicopathological study on hepatocellular carcinoma with lymphocytic infiltration. *Hepatology* 1998; 27:407–414.

19. Suzuki M, Okazaki N, Yoshino M, et al. Spontaneous regression of a hepatocellular carcinoma – a case report. *Hepatogastroenterology* 1989; 36:160–163.
20. Heianna J, Miyauchi T, Suzuki T, et al. Spontaneous regression of multiple lung metastases following regression of hepatocellular carcinoma after transcatheter arterial embolization. A case report. *Hepatogastroenterology* 2007; 54:1560–1562.
21. Takeura C, Tokoro T, Tanahashi Y, et al. Two cases of spontaneous regression of hepatocellular carcinoma with extrahepatic metastasis. Poster session at the 2012 American HepatoPancreatoBiliary Association Annual Meeting, Miami, FL. 2012