Management of bleeding liver tumors

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KEYWORDS
Liver tumors; Hepatocellular carcinoma; Hepatic adenoma; Bleeding; Surgery

Summary  Liver tumors bleed rarely; management has changed radically during the last 20 years, advancing from emergency surgery with poor results to multidisciplinary management. The first steps are the diagnosis and control of bleeding. Abdominopelvic CT scan should be performed as soon as patient hemodynamics allow. When active bleeding is visualized, arterial embolization, targeted as selectively as possible, is preferable to surgery, which should be reserved for severe hemodynamic instability or failure of interventional radiology. When surgery is unavoidable, abbreviated laparotomy (damage control) with periphepatic packing is recommended. The second step is determination of the etiology and treatment of the underlying tumor. Adenoma and hepatocellular carcinoma (HCC) are the two most frequently encountered tumors in this context. Liver MRI after control of the bleeding episode generally leads to the diagnosis although sometimes the analysis can be difficult because of the hematoma. Prompt resection is indicated for HCC, atypical adenoma or lesions at risk for degeneration to hepatocellular carcinoma. For adenoma with no suspicion of malignancy, it is best to wait for the hematoma to resorb completely before undertaking appropriate therapy.

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Introduction  Liver tumors bleed rarely (prevalence is 1% in Western countries [1]) but this can be a life threatening event. The two most frequent causes are hepatic adenoma and hepatocellular carcinoma (HCC). Before the turn of the century, emergency surgery was the standard therapy because of the poor prognosis of liver bleeding, as well as the presence of potentially malignant ruptured tumor [2]. Today, thanks to CT angiography and interventional radiology, less invasive management is recommended. Minimally invasive management is composed of two steps: the first is controlling the bleeding, the second is specific treatment of the underlying tumor, urgently if necessary, but usually at distance from the acute bleeding episode.

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Clinical presentation

Symptoms

Abdominal pain is almost constant (97% of cases [1]). Classically, there are three different clinical pictures:

• intra-hepatic hematoma due to intra-tumoral bleeding: this is the most frequent presentation. The patient is usually hemodynamically stable. In most cases, the hemorrhage goes unnoticed and the hematoma is discovered on imaging or on pathological examination of an operative specimen [3];
• intra-abdominal bleeding due to intraperitoneal rupture of a subcapsular tumor or secondary rupture of a subcapsular hematoma: the clinical picture includes abdominal pain, nausea and/or vomiting, abdominal distention due to hemoperitoneum and acute anemia, with the possibility of hypovolemic shock according to the quantity of bleeding. This presentation is rare but life threatening and constitutes an abdominal emergency;
• hemobilia by tumor ruptured into the biliary tract [4]: this can result in the triad of Quincke, i.e., jaundice, abdominal pain and melena. The presentation is exceptional and is proper to malignant tumors alone (HCC and cholangiocarcinoma).

Risk factors

Pre-existing liver tumors

The tumors most at risk of bleeding are large, hypervascular and subcapsular. Most cases are due to adenoma (44.2% of cases in the series of Battula et al. [1]), with tumors larger than 5 cm and telangiectatic [5,6], or to HCC in patients with viral hepatitis B or C (85.7% of cases in the series of Chen et al. [2]). It should be noted that in the immense majority of cases, bleeding is the initial symptom and leads to the discovery of the liver tumor.

Cirrhotic patient with coagulopathy

Cirrhosis is often associated with perturbed INR and thrombocytopenia. While this entity has never been correlated with the risk of spontaneous rupture of HCC, it increases the risk for failure of spontaneous arrest of the bleeding.

Anticoagulant and antiagregant therapy

According to the study by Battula et al. [1], anticoagulant or anti-agregant therapy do not seem to increase the risk of bleeding or poor prognosis: 9% of patients managed for bleeding from the liver (all causes taken together) were taking aspirin, 2% were taking anti-vitamin K therapy, and 3% were being treated with low-molecular weight heparin. These proportions do not differ from the overall population.

What to do urgently?

Resuscitation

Bleeding from a liver tumor is a serious event and sometimes lethal. Management should never be delayed. As soon as the patient arrives in the emergency room and bleeding is suspected, the patient should be assessed for signs of severity and resuscitated even before the diagnosis is known.

Signs of severity can be clinical or biological: hypovolemic shock [7–9], abdominal rigidity [2], clinical and laboratory signs of hepatocellular insufficiency [7,9–11]. If any of the above signs are present, the patient should be referred to the intensive care unit.

In all cases, the hemodynamic status of the patient should be closely monitored (blood pressure, O2 saturation, EKG, urinary output) and vascular volume repletion ensured (large bore venous catheters). The resuscitation regimen and the products infused should be adapted to the hemodynamic status and the degree of anemia. The patient should be typed and cross-matched, any coagul disorders corrected, and blood products administered as needed (packed RBCs, platelets, clotting factors).

Establish the diagnosis

Bleeding liver tumors represent a true abdominal emergency, both for diagnosis and therapy. Imaging investigations useful for diagnosis include:

• abdominal sonography: this investigation should always be performed, even in case of hemodynamic instability, included in the «FAST» protocol. Sonography can detect intraperitoneal fluid, suggest its hemorrhagic nature, and detect subcapsular or intra-hepatic hematoma arising from an intra-hepatic tumor. Historically, the classical diagnostic maneuvers of sonography and needle aspiration in a patient with pain and malaise led to the diagnosis of bleeding liver tumor in more than 70% of patients [2]. This strategy has been largely replaced by the widespread availability and use of CT scan in the emergency setting. Sonography and needle aspiration are still practiced in some Asian centers when a cirrhotic patient presents with non-traumatic hemoperitoneum [12];
• abdominal CT angiography: this is currently the critical investigation to perform in the emergency setting as soon as the patient becomes hemodynamically stable [1]. Arterial, portal or late phase images with or without intra-venous contrast allow confirmation of hemoperitoneum (Fig. 1) and liver hematoma (Fig. 2), evaluation of the volume of bleeding, and assessment of any subcapsular component of the hematoma (Fig. 3). Images in the arterial phase help to detect contrast extravasation, and will demonstrate visible active bleeding as long as the rate is approximately 1 mL/minute [13], helping to determine the etiology of bleeding and to characterize the tumor responsible for the bleeding episode, although this is often difficult because of intra-tumoral changes caused by the bleeding;
• abdominal magnetic resonance imaging (MRI): this high-performing investigation is rarely performed because of unavailability in most centers and the time required for its performance, which is usually incompatible with the potentially unstable hemodynamic status of the patient. However, MRI is often the key to determining the etiology of the underlying tumor and should be performed after stabilization from the acute episode to characterize the responsible liver tumor;
• angiography: it allows treatment by hepatic arterial embolization, usually based on findings of CT angiography. This investigation is rarely performed for initial diagnosis because CT angiography performs much better (88% vs 18% [11]), and allows visualization of the entire gastrointestinal arterial network at the same time;
• gastro-intestinal endoscopy: it can demonstrate hemobilia [14] when the patient presents with gastro-intestinal bleeding.

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Figure 1. Bleeding hepatocellular carcinoma in segment IV. A. CT scan with injection of contrast material: intra-lesional hematoma and hemoperitoneum. Selective intra-arterial chemo-embolization was performed. B. Control after chemo-embolization, revealing a relatively well-limited lesion but also suspicious satellite nodules.

Figure 2. Left lobe hepatocellular adenoma complicated with intra-tumor bleeding. Comparison between preoperative MRI (A) (injected T1 sequence, portal phase) and the operative specimen (B) with an intra-lesional dissecting hematoma.

Figure 3. Hepatocellular adenoma in segment VIII complicated by subcapsular hematoma. A. CT scan at 48h: huge subcapsular hematoma and anterior subcapsular lesion, difficult to characterize, with disclosure of associated lesions, suggestive of hepatocellular tumors (C). B. MRI at 2 months, (T1 after injection of gadolinium): residual hematoma located at the uppermost part of the liver, the lesion is still altered and difficult to characterize, but the associated lesion in the right liver is highly suggestive of telangiectatic adenoma. The nature of these lesions were confirmed after their resection.

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Hemodynamic instability

Sometimes the patient’s hemodynamic status remains unstable, in spite of all resuscitation undertaken. Emergency sonography can demonstrate hemoperitoneum and liver hematoma. Stopping the bleeding as rapidly as possible is the immediate goal. The patient should be taken to the operation room as soon as possible. The diagnosis of the bleeding tumor will be made during exploratory laparotomy. Resuscitation is pursued throughout the operation, which usually consists of abbreviated (damage control) laparotomy.

What are the therapeutic possibilities?

Conservative treatment

Correction of fluid and electrolye imbalances, anemia, coagulation parameters, blood volume, with ongoing close surgical surveillance, is necessary. This strategy alone should be applied to stable or stabilized patients, where imaging does not show any active bleeding [1,15–17].

Interventional arterial embolization

This is currently the treatment of reference for patients bleeding from a liver tumor, whether stable, stabilized by resuscitation [1], or persistently unstable [3]. Interventional angiography should always be preceded by CT angiography to determine the site of active bleeding [10,16,18] and to show any anatomic variations of the liver vascular tree. Although arterial embolization has less morbidity than surgery, it remains risky in cirrhotic patients and/or in case of portal vein thrombosis, because of the risk of decompensation of the underlying hepatic disease [19]. Selective or supra-selective arterial embolization helps to minimize this risk.

Arterial embolization is particularly effective for bleeding adenoma and HCC, both of which are highly arterialized tumors. Embolization is feasible in more than 90% of cases, although qualified as difficult because of anatomical variations or tortuous or small calibre arteries in 20% of cases [20]. The success rate is currently over 80% [7,8,21–24] (Table 1).

Whatever the technique chosen, the main goal is to obtain effective hemostasis, even if some prospective analyses have shown that embolization can also be associated with tumor regression in cases of HCC [9] or adenoma [21].

In the absence of controlled studies, there is currently no consensus as to material which to use for embolization:

- platinum or stainless steel microcoils: non-absorbable prothrombogenic material;
- PVA (polivinyl alcohol) or acrylic polymeric beads: non-absorbable particles;
- gelatin sponge (absorbable particles): these implants diffuse in the arterial microcirculation and are often used to complement other techniques;
- chemo-embolization combining an anti-mitotic agent with lipiodol (Fig. 1): this technique is used in the context of hemorrhagic HCC [21]. However, the recurrence rate is high (70% in the study of Zhu [25]), and this technique increases operative time and the complication rate, if resection is indicated [26].

Irrespective of the embolic agent used, the complications that can arise include:

- failure with re-bleeding, which may require emergency surgery;
- exacerbation of liver failure in the cirrhotic;
- post-embolization syndrome associated fever and hepatic cytolsis;
- subsequent operative difficulties if elective surgery is indicated.

These difficulties might be related to inflammation, itself secondary to the presence of intra-arterial foreign bodies, as has been reported in surgery for HCC after chemo-embolization [26]. Supra-selective embolization and/or use of absorbable implants could theoretically decrease this risk, even though, to the best of our knowledge, this has never been studied.

Emergency surgery

This was the standard treatment until the 1990s [2,7]. Since then, progress in interventional radiology and resuscitation have limited the current role of emergency surgery to rare cases of major hemodynamic instability or for patients when there are no other alternative [1].

Two types of operations can be considered: liver resection and local hemostatic procedures (Table 1).

Emergency liver resections

The outcome of this modality is mediocre, in terms of intra- and postoperative mortality and long-term survival, irrespective of the underlying tumor disease [1,2,6–8,27–30].

Some highly specialized teams are capable of performing such operations in very selected patients with superficial HCC and no liver insufficiency (one death, median survival 4 months in the series of Zhu et al. [25]). However, on one hand, no survival benefit has been shown in comparison to patients undergoing resection at a distance from the acute bleeding episode (0 deaths, median survival 60 months in the series of Yoshida et al. [31]), while, on the other hand, the results for “emergency” resections have been combined with those for early secondary resections. There is therefore no evidence to recommend this approach.

Emergency hemostatic procedures

In hemodynamically unstable patients, or if interventional radiology is unavailable, emergency surgery may be necessary. The goals are rapid and effective control of bleeding applying the principles of abbreviated damage control laparotomy. Once the hemoperitoneum has been evacuated and the origin of bleeding has been determined, the preferred technique of hemostasis is packing, after temporary clamping of the hepatic pedicle. A second look is planned 24 to 72h later to withdraw the pads used for packing and to verify local hemostasis.

The techniques of suture [32], intra-tumor injection of alcohol [33], and ligation of the proper hepatic artery [34,35] should no longer be performed because of reports of low efficacy and high morbidity.

Lastly, for HCC, some Asian authors have recommended:

- performing cholecystectomy or ligation of the gastro-duodenal artery to prevent complications related to future chemo-embolization [36];
# Management of bleeding liver tumors since 2000.

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• abundant peritoneal lavage with a cytotoxic solution (distilled water [37] or 5-fluorouracil [33]) with the intent of preventing peritoneal tumor implants.

Definitive surgery

The first argument in favor of observation for tumor-related bleeding is to be able to prepare the patient for surgery. Most postoperative deaths after emergency liver surgery are indeed due to liver or hemodynamic failure [16], which is not seen after elective surgery.

Moreover, delaying surgery gives time to perform an etiologic workup and evaluate the patient in order to select the best operation for the individual patient.

Other therapeutic alternatives

Other therapeutic options can be used in particular cases:
• endoscopic treatment: this can be useful in cases of hemobilia, in order to disobliterate the main bile duct after extraction of blood clots [13], and sometimes to place an endoprosthesis excluding the biliary branch from which bleeding is coming [38]. In any case, this does nothing to treat the underlying tumor;
• tumor radiofrequency ablation: this therapeutic policy was described in rare clinical cases or short series, and therefore has not been validated [21]. The theoretical advantage is to treat the underlying tumor if the size is compatible with current indications.

Secondary workup and therapy

Post-bleeding workup

Liver adenoma and hepatocellular carcinoma are the two most frequently encountered hepatocellular tumors that can bleed. However, emergency imaging is not always contributive because a large liver hematoma can cause perfusion anomalies and tumor or parenchymal changes. It is therefore recommended to repeat imaging studies well after the acute episode, preferably with MRI, the best way to distinguish hemorrhage from the underlying tumor tissues [39]. In difficult cases, a biopsy may be necessary.

### Table 1 (Continued)

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NA: non available.

a Studies about bleeding hepatic tumors from all etiologies.

b Studies about ruptured adenomas.

c Studies about ruptured HCC.

PATHOPHYSIOLOGIC MECHANISMS

Adenoma: the teleangiectatic type is at greatest risk of bleeding [6]: these tumors are relatively fragile and friable because of their characteristics (1) no capsule, (2) connective tissue is not dense, (3) hypervascularity, because of numerous telangiectasia and (4) sinusoid wall thickness.

HCC: the lesions most at risk for bleeding are subcapsular, exophytic HCC with invasion of the suprahepatic drainage system. Zhu et al. [70] have shown that the risk of bleeding can be explained by modifications in the feeding vessels of the tumor (overexpression of collagenase, decreased expression of collagen IV, absence of elastase, leucocyte infiltration of the vessel wall).

Case 1: diagnosis of adenoma

Bleeding from adenoma is seen in young, occidental women [6,7], usually taking contraceptive (estroprogestative) medications [39–41]. Abdominal trauma or post-partum time may also be a promoting factor. Initial CT scan showing other adenomas in the liver can lead to suspicion of the diagnosis. The hypervascular and sometimes steatotic character of these nodules can direct the diagnosis to a hepatocellular origin. CT imaging has been reported to fail, however, in 25% of cases [42]. At a distance from the initial bleeding episode, repeat liver imaging is useful, even if no doubt persists as to diagnosis, in order to define the exact size of the underlying adenoma, a critical criterion for deciding whether a resection should be considered or not.

Until now, classical indications have been to resect, irrespective of the size, all adenomas that have bled to:
• avoid recurrent bleeding;
• prevent malignant degeneration.

Recently, the bleeding event in itself and arterial embolization have been shown to lead to total regression of adenoma in 50% of cases [40,43]. In such cases, the recommendation is to simply follow patients if the size of the adenoma is less than 5 cm. No bleeding recurrence has been observed [3]. In certain cases, nonetheless, resection was performed because the adenoma increased in size [43].
Thus, it seems reasonable to simply follow patients who have bled from a typical liver adenoma whose size is stable and less than 5 cm. In the absence of controlled studies, it is important that this “non-operative” decision be taken with multidisciplinary concertation and that the follow-up be rigorously enforced.

Case 2: diagnosis of HCC

The prevalence of ruptured HCC has been studied only by the Japanese: 2.3% [44]. Bleeding from HCC occurs most often in males with cirrhosis (85% of cases in the series by Tan [8]). Asian patients are more prone to have cirrhosis due to viral hepatitis. In fact, HCC is the leading cause of bleeding liver tumors in Asia, and it is of interest to note that more than 50% of ruptured HCC in the Western world occur in patients of Asian origin [22].

In practical terms, the presence of clinical and laboratory findings associated with hepatocellular failure and/or portal hypertension, attesting to underlying cirrhosis, are suggestive of HCC. Discovery of cirrhosis on the initial CT scan also suggests the diagnosis of HCC. The vascular characteristics (arterial wash in, portal wash out) may persist during bleeding [18]. During the arterial phase, peripheral enhancement of the tumor may be interrupted at the level of rupture, which is called the enucleation sign [45].

The short-term prognosis of ruptured HCC is poor (mortality between 25 and 75% in the review by Lai et al. [16]); for this reason, these tumors are usually classed T4, irrespective of their size or number [46,47]. One recent Japanese national analysis [44] of more than 1000 ruptured HCC confirmed that prognosis is worsened by rupture. However, the prognosis for survival in patients with small resectable lesions is similar to that of non-ruptured HCC of one T stage higher, and not to T4 in all cases. This means that a curative approach can be maintained for these patients.

Up until the years 2000, the problem of peritoneal dissemination of HCC justified rapid surgical management. In fact, this risk is low (11 of 143 patients resected at distance from their bleeding episode vs 0 of 28 resected in the emergency setting, P = 0.2 [48]), and carcinomatosis can already be present at the time of bleeding because of the very aggressive character of HCC [19]. Therefore, this cannot be an argument in favor of emergency resection. After control of bleeding, workup including liver MRI, screening for distant metastasis, and thorough patient assessment (search for underlying liver disease, liver function tests and hepatic reserve, portal hypertension, co-morbidities) should be performed to best determine what therapy is most appropriate.

The therapeutic options after complete workup include:
- non-operative management for patients unfit for surgery, with liver failure, with advanced disease, metastasis;
- systemic chemotherapy with sorafenib for metastatic HCC if no contra-indication (notably liver failure) exists;
- chemo-embolization in case of non-resectable liver lesions (usually multifocal);
- radiofrequency or microwave destruction, reserved for fragile patients with small lesions, corresponding to the appropriate indication for such therapy;
- hepatic resection: the best curative option today, even though the outcome is inferior to results for surgery of non-ruptured HCC, stage for stage [44,48,49]. Because of the increased risk of postoperative liver failure in this subgroup of patients, it is essential to perform surgery at a distance from the bleeding episode, after correction of all the disorders brought on by the acute event;
- liver transplantation: theoretically not indicated for ruptured HCC. However, the question could arise for the patient already on the transplant waiting list. This eventuality is not described in the literature, probably because HCC rupture is so rare, and because the size of the HCC susceptible to rupture is most likely already a contra-indication to transplantation, even before the bleeding episode.

Case 3: doubt between adenoma and HCC

When the presentation of adenoma is atypical, potential malignant degeneration should be entertained and resection is indicated without delay (Fig. 4). Risk factors for malignant degeneration include [6]:
- adenoma in the male;
- presence of glycogen storage disease;
- androgen use;
- Fanconi type anemia;
- size > 5 cm or presence of atypical images on CT-scan.
These criteria must be discussed in presence of an hematoma next to or inside the tumor.

When a precise diagnosis cannot be made because of the difficulties in interpretation caused by altered morphology, as in the case of hematoma, management should not be
delayed until the hematoma is completely resorbed in order to avoid delay in treatment of a potential HCC.

In this setting, the options that should be discussed include:

- biopsy: this allows histologic proof of HCC; whenever biopsy is performed for adenoma, an immunochemical study will be useful for surgical decision-making since steatotic adenoma (LFABP negative) does not carry a risk of bleeding or malignant degeneration, in contrast to telangiectatic adenoma (CRP+ SAA+) or with mutated beta-catenin [50];
- first line resection.

Rare cases of other hemorrhagic tumors

Bleeding from the nearly all the other liver tumors susceptible of this complication is extremely rare. Among these, hemangioma and biliary cysts are the most frequently encountered. Because of the rarity of bleeding, no specific management plan has been codified. However, if is important to know the specificities of these lesions:

- hemorrhagic hemangioma (Fig. 5): in spite of the relatively high incidence of hemangioma, bleeding is extremely rare (fewer than 50 cases described [41]); the risk factors are female sex within the age of procreation, and corticosteroid use. The two major risks are progression to hemorrhagic shock in one third of cases and Kasabach–Meritt coagulopathy in the case of giant hemangioma. In the case of active bleeding, embolization seems to be effective with minimal morbidity [51];
- simple biliary cysts (Fig. 6): bleeding from biliary cysts is generally not very severe, sometimes asymptomatic (intra-cystic bleeding) and recurrent. Imaging can be misleading at a distance from a pauci-symptomatic bleeding episode, and lead to the suspicion of cystadenocarcinoma because the absorption of hematoma can create septa, nodules or wall-thickening [52];
- liver metastasis: bleeding from liver metastasis is most unusual. To the best of our knowledge, fewer than 50 cases have been described in the literature. All types of metastases can bleed: colorectal [1], choriocarcinoma [53,54], testicular [55], gastric [56], plasmocytoma [57] and melanoma [58]. Because of its rarity, the diagnosis of bleeding metastases is unlikely, and HCC or adenoma must be ruled out by biopsy in case of doubt;
- hemorrhagic focal nodular hyperplasia (FNH) [1,59] (Fig. 7): several cases of bleeding telangiectastic FNH described in the literature before 2000 would currently be assimilated to adenoma. Since the diagnosis of FNH is exceptionally rare, other etiologies must first first be eliminated whenever FNH is suspected, surveillance should be strict and, at the slightest doubt, the indication for resection should be raised;
- other extremely rare tumors include: angiosarcoma [60], serous or mucinous cystadenoma [61,62], histiocytosarcoma [63], angiomylipoma [64].

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Non-tumoral hemorrhage

Of note, non-traumatic liver bleeding can occur in a non-tumoral liver, in case of the HELLP syndrome, vasculitis, or peliosis hepatis [1].

Conclusion

Management of hemorrhage from a liver tumor is relatively well codified in 2014. CT angiography is the reference study to establish the diagnosis. All patients should undergo CT angiography as soon as their hemodynamic status allows, if necessary after resuscitation. The goal of CT angiography is to identify the location and activity of hepatic bleeding.

For therapy, resuscitation and interventional radiology are the cornerstones of treatment, irrespective of the underlying etiology. Surgery should be reserved for the most severe cases. During exploratory laparotomy, perihepatic packing is the initial gesture, allowing the patient to be transferred to the interventional radiology suite for arterial embolization. In all cases, delay in therapy and decompensated liver disease constitute pejorative prognostic factors.

If the diagnosis of adenoma is suspected with no risk factors for malignant degeneration and without ongoing bleeding, management can be decided after absorption of the hematoma, which can take several months. If there is reason to suspect malignancy, the theoretical risk of peritoneal dissemination and metastatic progression should lead more rapidly to surgery, even before complete absorption of the hematoma. If bleeding is due to HCC in a cirrhotic liver, the short-term prognosis is related to the severity of the underlying hepatic disease (Fig. 8).

Figure 7. Focal nodular hyperplasia with bleeding in the right liver. A. MRI (T2 sequence): highly altered lesion difficult to characterize. B. MRI (T1 sequence): intra-lesional location of T1 hypersignal corresponding to hemorrhagic changes. C. MRI (T1 sequence after injection): uncharacteristic inhomogeneous enhancement. D. Follow-up MRI at 6 months: typical aspect of FNH with central scar.

Figure 8. Decisional algorithm. According to Battula, Van Der Wint, Huurman, Lai, Hung [1,3,15–17].
Disclosure of interest
The authors declare that they have no conflicts of interest concerning this article.

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Management of bleeding liver tumors


Glossary

CT: Computed tomography
FAST: Focused assessment with sonography for trauma
FNH: Focal nodular hyperplasia
INR: International normalized ratio
HCC: Hepatocellular carcinoma

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