## **ORIGINAL ARTICLE**



# **Imaging Surveillance of Hypervascular Liver Lesions** in Non-Cirrhotic Patients

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Abstract A consensus surveillance protocol is lacking for non-cirrhotic patients with hypervascular liver lesions presumed to represent hepatocellular adenomas. Patients with hypervascular liver lesions <5 cm not meeting criteria for focal nodular hyperplasia or hepatocellular carcinoma underwent surveillance with contrast-enhanced magnetic resonance imaging (MRI) 6, 12, and 24 months after baseline imaging. If lesions remained stable or decreased in size, then surveillance imaging was discontinued. Between 2011 and 2014, 116 patients with hypervascular liver lesions were evaluated. Seventy-nine patients were eligible for the surveillance protocol. Median follow-up was 24 months (range, 1–144 months). One patient (1 %) continued oral contraceptive pill (OCP) use and presented with hemorrhage requiring embolization 5 months after initial diagnosis. Ten patients (13 %) underwent elective embolization or surgical resection for size  $\geq$ 5 cm. The remaining 68 patients (86 %) continued surveillance without hemorrhage or malignant transformation. Risk factors for requiring intervention during the surveillance period included younger age, larger lesion size, and estrogen use (all p<0.05). Patients with hepatocellular adenomas <5 cm can safely be observed after discontinuing OCP with serial imaging 6, 12, and 24 months after diagnosis. If lesions remain stable or decrease in size, then longer-term surveillance is unlikely to identify patients at risk for complications.

**Keywords** Liver cell adenoma · Hepatocellular carcinoma · Focal nodular hyperplasia

## Introduction

Hepatocellular adenomas are rare monoclonal neoplasms occurring most commonly in women using oral contraceptive

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pills (OCP). In a case-control study published in 1979, the estimated incidence of hepatocellular adenomas was 3 per 1, 000,000 per year and increased to 3-4 per 100,000 with longterm OCP use.2 More recent studies have shown a rising incidence of hepatocellular adenomas in association with a growing population of patients with obesity and the metabolic syndrome. 3, 4 Adenomas are associated with a significant risk of complications, including hemorrhage, rupture, and malignant transformation. The prevalence of hepatocellular adenomas is 10-fold lower in men, in whom the risk of malignant transformation is reportedly 47 %.5 Therefore, surgical resection is recommended for all men with suspected adenomas. In women, the risk of complications is associated with larger adenoma size. In a surgical series of 122 patients, the incidence of macroscopic hemorrhage and malignant transformation in adenomas <5 cm was 5 and 2 %, respectively, compared to 25 and 9 % in adenomas  $\geq$ 5 cm.

Given the association between larger size and complications, surgical resection is recommended in women with adenomas 5 cm or larger in greatest diameter.<sup>1-7</sup> For smaller adenomas, there is no consensus on interval and duration of



radiologic surveillance. Some authors advocate lifelong follow-up, which entails risks of cumulative radiation exposure and potentially unnecessary costs. 8 In this study, we evaluated an imaging surveillance protocol for non-cirrhotic patients with hypervascular liver lesions <5 cm that did not meet criteria for focal nodular hyperplasia (FNH) or hepatocellular carcinoma. All patients were asked to discontinue OCP use and were followed with contrast-enhanced magnetic resonance imaging (MRI) 6, 12, and 24 months after initial diagnosis. If lesions remained stable or decreased in size, then imaging was discontinued. Among 79 patients eligible for the surveillance protocol, 1 patient who continued OCP use presented with hemorrhage requiring emergent embolization. Ten patients underwent elective embolization or surgical resection for adenoma size  $\geq 5$  cm despite cessation of OCP. The remaining 68 patients did not experience complications after median clinical follow-up of 24 months.

## **Materials and Methods**

An institutional review board-approved retrospective review was performed of all non-cirrhotic patients with hypervascular liver lesions presented at our multidisciplinary liver conference between June 2011 and May 2014. Dates of initial diagnosis ranged between June 2005 and April 2014.

Demographic and outcome data were collected from electronic medical records, including clinical, perioperative, and pathologic data. Patients diagnosed with hemangiomas at initial imaging were excluded. Adenomatosis was defined as the presence of 10 or more adenomas. Patients were classified as having the metabolic syndrome if they had obesity (body mass index  $\geq$ 30) with associated diabetes, hypertension, or hyperlipidemia.

## Radiographic Surveillance Protocol

Our imaging protocol is shown in Fig. 1. Patients with lesions <5 cm that met classic imaging findings of FNH were not recommended to undergo further imaging. Patients with indeterminate or suspected adenomas <5 cm were asked to discontinue OCP and followed with repeat contrast-enhanced MRI 6, 12, and 24 months after baseline imaging. If lesions remained stable or decreased in size, then surveillance imaging was discontinued. Selected patients with suspected adenomas ≥5 cm were also entered into the surveillance protocol at the discretion of the treating provider.

### **Statistical Analysis**

Categorical variables were compared using the chi-square test and continuous variables using the Mann–Whitney test. Two-tailed p values <0.05 were considered significant. Analyses

were performed using SPSS 12.0 statistical software (SPSS Inc., Chicago, IL).

#### Results

## **Patient Demographics**

Between 2011 and 2014, 116 non-cirrhotic patients with hypervascular liver lesions were evaluated in a multidisciplinary liver conference. Among these 116 patients, 37 patients underwent surgical resection, selective hepatic arterial embolization, or percutaneous biopsy showing focal nodular hyperplasia. The remaining 79 patients were entered into the surveillance protocol. Five patients had a prior history of cancer, including breast cancer (n=3), ovarian cancer (n=1), and non-Hodgkin's lymphoma (n=1). Thirty-five patients (44 %) were taking OCPs at time of diagnosis. Other potential risk factors included hormone replacement therapy (n=1) and topical estrogen use (n=2). All patients were asked to discontinue estrogen use after diagnosis. Features of the metabolic syndrome including obesity, diabetes, and/or hyperlipidemia were present in 20 patients (25 %). The clinical course of the 79 patients is shown in Fig. 2. Median duration of clinical follow-up was 24 months (range 1-144 months). Median duration of radiologic surveillance was 19 months (range 1–144 months).

# **Factors Associated with Need for Intervention**

Among the 79 patients undergoing surveillance, 11 patients (14 %) underwent embolization and/or surgery a median of 24 months (range 5–72 months) after initial diagnosis (Table 1). In 10 patients, the indication for surgery was adenoma size ≥5 cm despite cessation of oral contraceptives. One patient with suspected FNH measuring 8.5 cm continued OCP use and presented 5 months after initial diagnosis with hemorrhage requiring emergent embolization.

The need for embolization or surgery was significantly associated with younger age at diagnosis (p=0.018), estrogen use at diagnosis (p=0.002), and larger lesion size (p=0.002). Male gender was not associated with the need for intervention. Five men undergoing radiologic surveillance had lesions <3 cm that demonstrated features of atypical hemangiomas or FNH on follow-up imaging.

Seventeen patients undergoing surveillance had lesions  $\geq$ 5 cm at diagnosis, including 8 patients who underwent biopsy or subsequent imaging consistent with FNH. Four of the 17 patients underwent intervention for persistent adenoma size  $\geq$ 5 cm (n=3) and hemorrhage (n=1). The remaining 5 patients with suspected adenomas  $\geq$ 5 cm discontinued OCPs and did not suffer complications during the surveillance period.

Among the 68 patients who did not require intervention, 64 patients (94 %) had lesions that remained stable or decreased



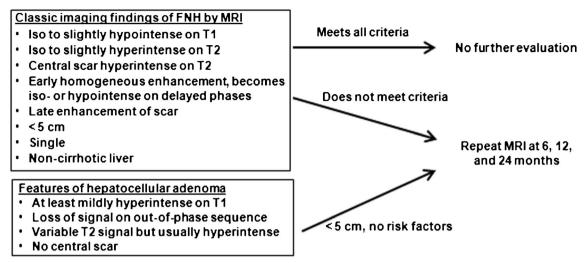


Fig. 1 Radiologic surveillance protocol for non-cirrhotic patients with hypervascular liver lesions. FNH focal nodular hyperplasia, MRI magnetic resonance imaging

in size. Four patients with enlarging lesions underwent biopsy or demonstrated features characteristic of FNH on subsequent imaging. None of the adenomas undergoing surveillance developed malignant transformation during the follow-up period.

## **Discussion**

The most common hypervascular liver lesions in non-cirrhotic patients include hemangioma, FNH, and hepatocellular adenoma. While hemangiomas and FNHs rarely cause complications, adenomas are at risk for hemorrhage, rupture, and malignant transformation. The risk for complications is directly correlated with larger adenoma size. Therefore, surgical resection has been recommended for larger adenomas in women, with proposed size cutoffs ranging between 3 and 5 cm. Hepatocellular adenomas are rare in men, with a female-to-male ratio of 10:1. In men, the risk of malignant transformation is reportedly as high as 47 %, and surgical resection is recommended in all men with suspected adenomas, regardless of size. For women with adenomas less than 5 cm, the optimal duration and interval of radiologic

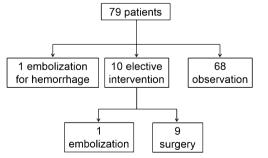


Fig. 2 Flow diagram of 79 non-cirrhotic patients undergoing surveillance of hypervascular liver lesions

surveillance are unknown. Some authors recommend lifelong surveillance, which entails significant cost and cumulative radiation exposure.<sup>8</sup>

In this study, we sought to validate a radiologic surveillance algorithm for women with suspected or known adenomas less than 5 cm. Patients were asked to discontinue estrogen use and followed with contrast-enhanced MRI 6, 12, and 24 months after initial diagnosis. If lesions remained stable or decreased in size, then imaging was discontinued. Among the 79 patients undergoing radiologic surveillance, 10 underwent elective surgical resection or embolization for adenoma size 5 cm or greater, despite cessation of OCPs. One patient who continued OCP use presented with hemorrhage requiring emergent embolization 5 months after initial diagnosis. The remaining 68 patients were followed under the surveillance protocol without complications. These results lend support to the strategy practiced in the Netherlands of initial observation off OCP and intervention for persistent size 5 cm or greater after 6 months of follow-up.9

Factors associated with the need for intervention during the surveillance period were younger age diagnosis, estrogen use, and larger lesion size. These data support results from a multicenter surgical series, which demonstrated that size greater than 7 cm and hormone use within 6 months were risk factors for adenoma rupture. In the current study, among 68 patients who did not require intervention during the surveillance period, most had lesions that remained stable or decreased in size, and surveillance imaging was discontinued. Based on these results, we do not recommend lifelong surveillance for women with suspected adenomas less than 5 cm, provided they avoid OCPs and any other hormonal therapy.

One patient with a centrally located adenoma that did not decrease in size after discontinuation of OCPs underwent elective embolization, avoiding a potentially morbid central hepatectomy. In a study from Memorial Sloan-Kettering Cancer



**Table 1** Seventy-nine patients entered into radiologic surveillance protocol, *n* (%)

Factor	Patients requiring surgery or embolization, $n=11$	No intervention required, $n=68$	p value
Median age at diagnosis, years (range)	30 (25–44)	38 (19–77)	0.018
Gender			0.353
Male	0	5 (7)	
Female	11 (100)	63 (93)	
Estrogen use at time of diagnosis	10 (91)	28 (41)	0.002
Metabolic syndrome	5 (45)	15 (22)	0.098
Multiple lesions	5 (45)	29 (43)	0.861
Adenomatosis	3 (27)	7 (10)	0.116
Median size at diagnosis, cm (range)	5.0 (3.0–11.0)	3.3 (0.6–9.2)	0.002

Center, 13 patients underwent embolization of 37 adenomas for hemorrhage or suspicion of cancer. Among the 37 embolized adenomas, 27 (73 %) disappeared or decreased in size after one embolization. Embolization and ablation should be avoided in men, given their high risk of malignancy.

A significant limitation of this study is the short median duration of follow-up of 24 months. According to our surveillance protocol, imaging is discontinued if suspected adenomas <5 cm remain stable or decrease in size after 2 years, provided patients do not have other risk factors, such as OCP use, anticoagulation, or male gender. However, given our short median follow-up, longer-term surveillance may be required, depending upon adenoma size and the clinical scenario. Other limitations include the variable quality of MRIs performed at multiple imaging centers, with differences in technique, equipment, and contrast agents. In addition, the treatment of patients with suspected adenomas 5 cm or larger was subject to clinician discretion. While most patients underwent surgical resection, selected patients were managed conservatively.

## Conclusion

In conclusion, the results of this study demonstrate that women with suspected adenomas smaller than 5 cm who discontinue estrogen use can safely be observed with contrastenhanced MRI 6, 12, and 24 months after baseline imaging. If lesions remain stable or decrease in size, discontinuation of surveillance imaging may be considered, particularly for lesions that demonstrate significant shrinkage after cessation of OCPs. Further imaging is unlikely to identify patients at risk for complications.

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