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A multicentre retrospective analysis on growth of residual hepatocellular adenoma after resection

Anne J. Klompenhouwer[1] | Belle V. van Rosmalen[2] | Martijn P. D. Haring[3] | Maarten G. J. Thomeer[4] | Michail Doukas[5] | Joanne Verheij[6] | Vincent E. de Meijer[3] | Thomas M. van Gulik[2] | Robert B. Takkenberg[7] | Geert Kazemier[8] | Frederik Nevens[9] | Robert A. de Man[10] | Jan N. M. Ijzermans[1]

[1]Department of Surgery, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands

[2]Department of Surgery, Amsterdam University Medical Centers, University of Amsterdam (Location Academic Medical Center), Amsterdam, The Netherlands

[3]Division of Hepatopancreatobiliary Surgery and Liver Transplantation, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

[4]Department of Radiology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands

[5]Department of Pathology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands

[6]Department of Pathology, Amsterdam University Medical Centers, University of Amsterdam (Location Academic Medical Center), Amsterdam, The Netherlands

[7]Department of Gastroenterology and Hepatology, Amsterdam University Medical Centers, University of Amsterdam (Location Academic Medical Center), Amsterdam, The Netherlands

[8]Department of Surgery, Amsterdam University Medical Centers, University of Amsterdam (Location VU Medical Center), Amsterdam, The Netherlands

[9]Department of Gastroenterology and Hepatology, University Hospital KU Leuven, Leuven, Belgium

[10]Departmnt of Gastroenterology and Hepatology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands

Correspondence
Dr. A.J. Klompenhouwer, Erasmus MC, University Medical Center Rotterdam, Department of Surgery, Dr. Molewaterplein 40, 3015 GD Rotterdam, The Netherlands.
Email: a.klompenhouwer@erasmusmc.nl

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Abstract

Background & Aims: Hepatocellular adenoma (HCA) is a benign liver tumour that may require resection in select cases. The aim of this study was to the assess growth of residual HCA in the remnant liver and to advise on an evidence-based management strategy.

Method: This multicentre retrospective cohort study included all patients with HCA who underwent surgery of HCA and had residual HCA in the remnant liver. Growth was defined as an increase of >20% in transverse diameter (RECIST criteria). Data on patient and HCA characteristics, diagnostic work-up, treatment and follow-up were documented and analysed.

Results: A total of 134 patients were included, one male. At diagnosis, median age was 38yrs (IQR 30.0-44.0) and median BMI was 29.9 kg/m^2 (IQR 24.6-33.3). After resection, median number of residual sites of HCA was 3 (IQR 2-6). Follow-up of residual HCA showed regression in 24.6%, stable HCA in 61.9% and growth of at least one lesion in 11.2%. Three patients (2.2%) developed new HCA that were not visible

The authors Klompenhouwer and van Rosmalen are shared first authorship.

on imaging prior to surgery. Four patients (3%, one male) underwent an intervention as growth was progressive. No statistically significant differences in clinical characteristics were found between patients with growing residual or new HCA versus those with stable or regressing residual HCA.

Conclusion: In patients with multiple HCA who undergo resection, growth of residual HCA is not uncommon but interventions are rarely needed as most lesions stabilize and do not show progressive growth. Surveillance is indicated when residual HCA show growth after resection, enabling intervention in case of progressive growth.

KEYWORDS

adenoma liver cell, follow-up studies, surgical procedure

1 | INTRODUCTION

Hepatocellular adenoma (HCA) is a benign tumour of the liver which predominantly occurs in females. It is associated with the use of oral contraceptives (OC) or androgens, obesity and metabolic disorders such as glycogen storage disease (GSD) or hepatocyte nuclear factor 1a maturity-onset diabetes of the young (HNF1A-MODY).[1-3] Regression often occurs after cessation of OC and weight reduction.[4-6] Several molecular HCA subtypes have been described: HNF-1α inactivated (H-HCA), inflammatory (I-HCA), β-catenin-activated (β-HCA), β-catenin-activated inflammatory (β-IHCA) and recently sonic hedgehog (sh-HCA) adenomas.[7,8] When no specific mutations are found, the HCA are termed as unclassified (U-HCA).

After HCA diagnosis, lifestyle adaption with cessation of OC and weight reduction is indicated, irrespective of HCA diameter.[9] In case of growth or when the HCA fails to regress to less than 5cm, resection may be indicated.[9,10] Other indications for resection are HCA in men, patients with β-HCA or β-IHCA.

Up to half of all patients with HCA present with multinodular disease which appears to be associated with a higher BMI.[11,12] The risk of complications does not differ from those with solitary HCA; therefore it has been recommended to base management decisions in patients with multiple HCA on the size of the largest tumour.[9] In patients with unilobular disease, a hemihepatectomy or segmental resection can be performed to resect all HCA. However, in patients with widespread HCA, residual HCA may remain in situ after resection. It is unclear whether these HCA may grow as a result of post-resectional liver regeneration, as studies regarding the follow-up of residual HCA have been lacking from published literature. The aim of this study was to assess whether growth of residual HCA in the remnant liver occurs and to advise on an evidence-based management strategy.

KEY POINTS

- In this study we looked at patients who underwent a resection of hepatocellular adenoma (HCA, a benign liver tumour) and had residual HCA in the remnant liver.
- We investigated whether growth of these residual HCA occurred and found that growth is not uncommon, but interventions are rarely needed as most lesions stabilize during follow-up.
- In case these lesions do grow, follow-up is advised enabling an intervention when progressive growth occurs.

2 | METHODS

This study was a multicentre retrospective cohort study performed in five major hepatobiliary centres in the Netherlands and Belgium [Erasmus MC University Medical Center Rotterdam, Amsterdam University Medical Centers, Location Academic Medical Center and Location VU Medical Center, University Medical Center Groningen and University Hospital KU Leuven]. All Dutch centres take part in the Dutch Benign Liver Tumor Group (DBLTG). Identification of eligible patients was done by the two first authors (AJK and BVR) performing a search in the electronic patient records in each participating centre, using the search terms benign liver tumor, hepatocellular adenoma or common synonyms. Additionally, all centres taking part in the DBLTG are required to have an updated database of the patients diagnosed with benign liver tumours. These databases were searched as well for patients with HCA. Eligible patients were those diagnosed with multiple (>1) HCA, based on either contrast-enhanced MRI, histological examination or both. Patients were included if they had undergone resection of one or more HCA and had residual sites of HCA in situ after resection. The minimum follow-up time after resection was 6 months.

The study protocol was reviewed by the accredited institutional review board; informed consent was waived.

2.1 | Data collection

Electronic medical records were reviewed for baseline patient characteristics: sex, age at diagnosis, BMI, comorbidity and use of hormonal medication were documented. Lesion characteristics documented were size of the largest HCA at diagnosis, number of

lesions and size of the residual HCA before and after resection. Histopathological assessment of resection specimen was performed at each participating centre. HCA subtypes were determined based on histology of the resection specimen or of a liver biopsy. When no material for pathology was present, subtype differentiation was based on contrast-enhanced MRI. Subtypes included were H-HCA, I-HCA, β-HCA, β-IHCA and U-HCA; sh-HCA were not included as immunohistochemical staining and molecular diagnosis was not yet implemented at the time of diagnosis of most patients. Indication for resection, type of resection (hemihepatectomy [at least three segments] or segmental resection [two segments or less]) and the number of resected HCA were documented. Complications after surgery were documented and graded according to the Clavien-Dindo Classification, with grade I and II complications classified as minor complications and grade III or higher as major complications. Follow-up of the residual HCA was based on imaging (MRI or CT), two dimensional measurements were performed and the largest transversal diameter was documented. Tumour growth was defined as an increase of >20% and HCA regression as a decrease of >30% as per RECIST criteria for response evaluation in solid tumours.[13] The three largest residual tumours were assessed as index lesions for growth or regression. If at least one HCA showed an increase of >20% this was scored as growth [regardless the behaviour of the other two], if at least two HCAs showed a decrease of >30% and the other remained stable, this was scored as regression.

2.2 | Statistical analysis

For the statistical analysis, patients were divided into two subgroups: patients whose residual HCA showed growth or who developed new lesions (showing undesirable behaviour) versus those whose residual HCA were stable or showed regression. Continuous variables were summarized as median and interquartile range (IQR), categorical variables as frequencies (n) and percentages. Differences between groups were analysed using Mann-Whitney *U* test for continuous variables and chi-squared test for categorical variables. All statistical analyses were performed with SPSS software version 24.0 (IBM).

3 | RESULTS

3.1 | Clinical characteristics

A total of 134 patients were included: 48 from Erasmus MC University Medical Center Rotterdam, 30 from Amsterdam University Medical Centers, Location Academic Medical Center and six from Location VU Medical Center, 35 from University Medical Center Groningen and 15 from University Hospital KU Leuven. Patients were diagnosed between 1992 and 2018 [1989-1999: n = 5, 2000-2004: n = 15, 2005-2009: n = 42, 2010-2014: n = 51, 2015-2018: n = 21]. Baseline characteristics are summarized in Table 1.

TABLE 1 Baseline characteristics

	N (%) or median (IQR)
Sex	
Female	133 (99.3)
Male	1 (0.7)
Age at diagnosis (yr)	38 (30.0-44.0)
BMI (kg/m^2)	29.9 (24.6-33.3)
HCA-related comorbidity	
Diabetes mellitus	17 (12.7)
Glycogen storage disease	3 (2.2)
Maturity-onset diabetes of the young	2 (1.5)
Hormone usage	
Oral contraceptives	116 (86.6)
None	6 (4.5)
Steroids or other hormonal medication	2 (1.5)
Unknown	10 (7.5)
Diameter of largest HCA at diagnosis (mm)	89 (69.5-110.0)
Number of HCA at diagnosis	
2-5	53 (39.6)
6-10	48 (35.8)
>10	33 (24.6)
Months between resection and first follow-up	6 (4-9)
Diagnostic work-up	
Contrast-enhanced MRI	123 (91.8)
Biopsy	48 (35.8)
HCA subtype	
H-HCA	18 (13.5)
I-HCA	69 (51.5)
B-HCA	2 (1.5)
B-IHCA	3 (2.2)
U-HCA	10 (7.5)
H-HCA + I-HCA	2 (1.5)
Undetermined	30 (22.4)

3.2 | Surgical resection

All patients underwent surgical resection of HCA, median time between diagnosis and surgery was 5 months (IQR 2.0-12.0). The most common indication for resection was size of the HCA >50 mm (46.3%), followed by atypical imaging characteristics or suspected hepatocellular carcinoma (HCC) (20.1%), haemorrhage (11.9%) and symptoms (10.4%). Other indications were growth of HCA (6.7%) after cessation of OC, an active pregnancy wish (3.0%), confirmed β-HCA on biopsy (0.7%) and male sex (0.7%). The majority was treated with a segmental resection (61.2%) or hemihepatectomy (32.8%), median hospital stay after resection was 9 days (IQR 7.0-10.0). All resections were complete resections. No major post-operative complications occurred, 18.7% of the patients suffered minor post-operative complications.

3.3 | Follow-up

Median total follow-up time was 49 months (IQR 27.0-78.0) and the median number of residual HCA was 3 (IQR 2-6). Median time between surgical resection and first follow-up scan was 6 months (IQR 4-9), follow-up of residual HCA showed regression in 24.6%, stable lesions in 61.9%, growth in 11.2% and in 2.2% new lesions were observed that were not visible on imaging prior to resection. No haemorrhage occurred in the residual HCA during follow-up.

No statistically significant differences between patients whose residual HCA showed growth or who developed new lesions versus those whose residual HCA were stable or showed regression were found for BMI, age at diagnosis, number of residual HCA, HCA-related comorbidity, HCA subtype and resection type (Table 2).

Among the 18 patients with growing or new lesions, 14 were treated conservatively. In these patients, growth was diagnosed at the first follow-up imaging after resection, all lesions remained <50 mm and the majority stabilized within 2 years of follow-up. Four patients (3%, three females and one male) underwent intervention for growing residual HCA. Of the females, the first patient underwent transarterial embolization (TAE), the second underwent two re-resections and the third patient underwent both re-resection as well as TAE for growing residual HCA (Figure 1). None of these patients had HCA-related comorbidity and no dysplasia or transformation to HCC was found in these patients. The only male patient included in this study, known with non-cirrhotic portal hypertension and diagnosed with β-IHCA, underwent radiofrequency ablation (RFA) for a new HCA and is currently on the waiting list for liver transplantation because of multiple new and progressively growing HCA as depicted by contrast-enhanced MRI. Histopathological examination of the resection specimen confirmed HCA in all four patients. In one patient with a residual HCA of 15 mm, follow-up after resection showed complete regression after resection as depicted by contrast-enhanced MRI. She then restarted her OC and the residual HCA grew to 60mm. After cessation of OC, the residual HCA regressed completely again (Figure 2).

4 | DISCUSSION

HCA may require resection in selected cases. In patients with many and widespread HCA, residual sites of HCA may remain in situ after resection. It is unclear whether these lesions may grow as a result of liver regeneration after resection. This retrospective cohort study including 134 patients evaluated whether in patients with multiple HCA, growth of residual HCA in the remnant liver occurs and to advise on an evidence-based management strategy.

In this study, growth or new HCA was a reason for intervention in 3.0% of patients. Reasons for intervention in cases with growing

TABLE 2 Growing or new lesions vs stable or regressing lesions

	Growing/new lesions n = 18 N (%) or median (IQR)	Stable/regressing lesions n = 116 N (%) or median (IQR)	*P*-value
BMI (kg/m^2)	26.4 (23.7-30.5)	30.1 (24.8-33.6)	.169
Age at diagnosis (yr)	41 (33.3-44.3)	38 (29.3-44.0)	.579
Number of residual HCA	2 (1.5-5)	3 (2-6)	.339
HCA-related comorbidity			
Diabetes mellitus	0 (0)	17 (14.7)	.136
GSD	0 (0)	3 (2.6)	
MODY-3	0 (0)	2 (1.7)	
HCA subtype			
H-HCA	2 (10.5)	16 (14.0)	.291
I-HCA	10 (55.6)	59 (50.9)	
B-HCA	0 (0)	2 (1.7)	
B-IHCA	2 (10.5)	1 (0.9)	
U-HCA	0 (0)	10 (8.6)	
H-HCA + I-HCA	0 (0)	2 (1.7)	
Undetermined	4 (22.2)	26 (22.4)	
Primary resection type			
Segment resection	8 (44.4)	74 (63.8)	.098
Hemihepatectomy	10 (55.6)	34 (29.3)	
Enucleation	0	8 (6.9)	

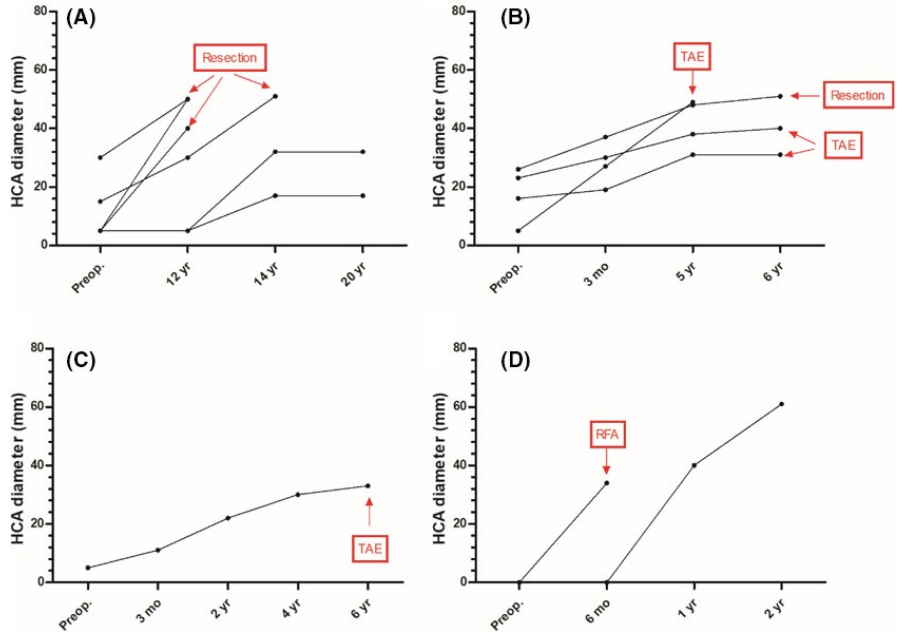

FIGURE 1 Cases with growing residual HCA requiring intervention. HCA, hepatocellular adenoma; Preop, pre-operative; Yr, number of years post-operative; Mo, number of months post-operative; OC, oral contraceptive; TAE, transarterial embolization. (A) Female patient with multiple residual HCA who underwent a re-resection 12 and 14 years after the first resection because of progressively growing residual HCA. (B) Female patient with multiple residual HCA who underwent transarterial embolization and re-resection 5 and 6 years after the first resection because of progressively growing residual HCA. (C) Female patient with single residual HCA who underwent transarterial embolization 5 years after resection because of progressively growing HCA. (D) Male patient with β-catenin-mutated HCA, who underwent radiofrequency ablation 6 months after resection because of one new HCA. Patient still has multiple new growing lesions and is currently on the waiting list for liver transplantation

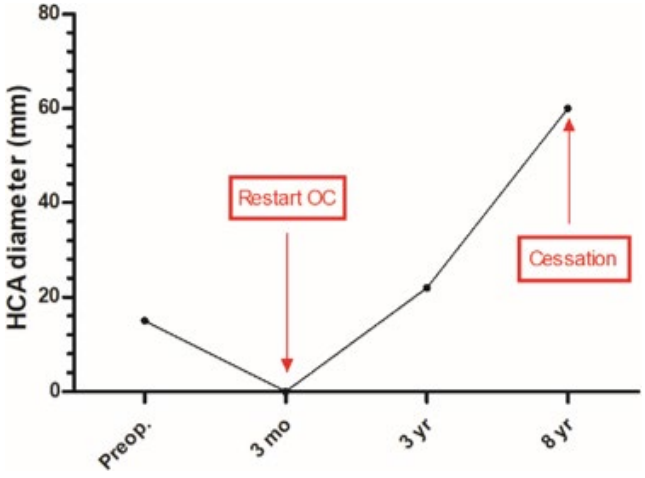

FIGURE 2 Case demonstrating the effect of oral contraceptive on HCA. Female patient with single residual HCA that showed complete regression after resection. When OC was restarted, the lesion showed progressive growth. It regressed again after cessation of OC

residual lesions were either an increase to >50 mm or progressive growth without stabilization of the lesion. One of these patients was a male with growing and new HCA who is still under surveillance because of progressive growth. Although this patient was diagnosed with HCA based on histopathological examination, the new and progressively growing lesions suggest that the diagnosis might also be well-differentiated HCC. It may be very difficult to distinguish HCA from well-differentiated HCC, even for expert pathologists.[14-16]

In one patient with a residual HCA, follow-up after resection showed complete regression after resection as depicted by contrast-enhanced MRI. After she restarted her OC, the residual HCA showed growth. Complete regression occurred again after cessation of OC. This suggests that patients with HCA might have a lifelong contraindication for the use of OC, even if no residual HCA is present after resection or complete regression of residual HCA has occurred.

Regression of residual HCA could either still be a result of cessation of OC or a result of weight loss or menopause, but might also be explained by the altered tumour regulation of the tissue environment in the liver with resection of the largest lesion(s). It has been established that this tumour regulation of the tissue environment plays a role in tumour formation and tumour growth in HCC in cirrhotic livers.[17] Unfortunately, the latter is still unexplored territory in the field of HCA. An interesting group to study regarding tumour environment of HCA would be patients with multiple tumours, who have undergone TAE or RFA for the largest tumour, since liver regeneration caused by increased portal flow plays no role in these patients.

Although the authors realize that a minimum follow-up time of 6 months might seem short, we have chosen this follow-up period consciously. After resection, liver regeneration occurs within the first weeks as a result of an increased flow to the remnant liver causing an

increase in growth factors.[18] Therefore, growth of residual HCA can be expected in the first period after resection. The flow and levels of growth factors stabilize after the first period and any growth of residual HCA is more likely attributed to the natural course of the disease and not a result of liver regeneration after resection.

In this cohort, factors predictive of growth of residual HCA could not be identified. BMI, age at diagnosis, resection type, number of residual HCA, HCA-related comorbidity and HCA subtype were considered to be clinically relevant, but no statistically significant differences were found between patients whose residual HCA showed growth or who developed new lesions versus those whose residual HCA were stable or showed regression. Ideally, change in BMI would have been added as a potential predictive variable, as weight loss seems to be related to regression of HCA and therefore weight gain may induce growth.[19] Unfortunately, in the participating centres, change in BMI was underreported. No difference in growth rate was demonstrated between patients who underwent hemihepatectomy versus those who underwent segmental resection or enucleation. As liver regeneration increases with a larger resected hepatic volume, a difference might have been expected. Additionally, no differences were found for HCA subtype while there has been a difference found for HCA regression in different subtypes.[20] The lack of statistically significant differences may well be attributed to the relatively small sample size.

In this study, almost a quarter of patients had >10 HCA and could be defined as liver adenomatosis. Recently, a study was published describing the long-term follow-up of 40 patients with liver adenomatosis.[21] In their cohort, 93% of the patients underwent surgery and 23% of the patients harboured a new lesion or showed growth of residual HCA. This lead to a surgical resection in 10%. In our study these percentages are lower, which might be attributed to the larger study group. Additionally, these authors described that the heterogeneous nature of liver adenomatosis justifies close and specific management, although complications (haemorrhage and malignant transformation) did not seem to occur more often than in patients with <10 HCA.[21] The heterogeneous nature underlines the prevailing thought that management of HCA should be based on HCA subtype and less on the number of HCA.[9]

The current study is the first to report on the management of residual HCA after hepatic resection in a large, multicentre cohort with long follow-up. The multicentre design offers advantages of an increase in statistical power and generalizability of the results. Inevitably, it is also subject to some limitations. First of all, the study may be subject to selection bias as we only included patients from expertise centres. Patients showing growth of residual HCA after resection might be referred to an expertise centre more often than patients with stable or regression lesions. Therefore the percentage of patients with growing residual HCA may be lower than seen in this study. Secondly, patients were included during a long period with five patients diagnosed even before 2000. All of these patients were diagnosed at an early age and followed for at least 20 years. Additionally, all HCA were proven on histopathological examination. A third limitation might lie in the fact that transversal measurements were used to assess tumour growth or regression as per RECIST criteria, and that the exact regeneration volume of the remnant liver was not measured. However, the authors believe that using transversal measurements reflects clinical practice. Finally, one might be that only one male patient was included. However, in the participating centres, males usually undergo treatment for all HCA given the higher risk of malignant transformation and therefore do not have any residual HCA after resection.

In conclusion, this study shows that growth of residual HCA is not uncommon and interventions are rarely needed as most lesions stabilize and do not show progressive growth. Follow-up of residual HCA should be performed after surgery. When residual HCA show growth after resection, patients should be kept under surveillance for at least 2 years, after that the majority stabilizes. It would be advisable to schedule the first follow-up scan 3-6 months after surgical resection and repeat imaging every 6-12 months until regression or stabilization occurs. An intervention such as TAE or RFA for small HCA or re-resection in large or atypical residual HCA may be considered in case of progressive growth and if lifestyle advices (cessation of OC and weight loss) fail to cause stabilization or regression.

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CONFLICT OF INTEREST

The authors do not have any disclosures to report.

ORCID

Anne J. Klompenhouwer https://orcid.org/0000-0002-6740-3862
Martijn P. D. Haring https://orcid.org/0000-0003-4789-3910
Jan N. M. Ijzermans https://orcid.org/0000-0003-3558-1039

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