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REVIEW ARTICLE

Malignant transformation of hepatocellular adenomas into hepatocellular carcinomas: a systematic review including more than 1600 adenoma cases

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Abstract

Background: Malignant transformation of hepatocellular adenomas (HCAs) into hepatocellular carcinomas (HCCs) has been reported repeatedly and is considered to be one of the main reasons for surgical treatment. However, its actual risk is currently unknown.

Objective: To provide an estimation of the frequency of malignant transformation of HCAs and to discuss its clinical implications.

Methods: A systematic literature search was conducted using the following databases: The Cochrane Hepatobiliary Group Controlled Trials Register, The Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, MEDLINE and EMBASE.

Results: One hundred and fifty-seven relevant series and 17 case reports (a total of 1635 HCAs) were retrieved, reporting an overall frequency of malignant transformation of 4.2%. Only three cases (4.4%) of malignant alteration were reported in a tumour smaller than 5 cm in diameter.

Discussion: Malignant transformation of HCAs into HCCs remains a rare phenomenon with a reported frequency of 4.2%. A better selection of exactly those patients presenting with an HCA with an amplified risk of malignant degeneration is advocated in order to reduce the number of liver resections and thus reducing the operative risk for these predominantly young patients. The Bordeaux adenoma tumour markers are a promising method of identifying these high-risk adenomas.

Keywords

hepatocellular adenoma, liver adenoma, malignant transformation, hepatic adenoma, frequency, hepatocellular carcinomas

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Introduction

Hepatocellular adenomas (HCAs) are uncommon and essentially benign tumours in the liver that occur predominantly, but not exclusively, in young women taking oral contraceptives (OCs).[1,2] HCAs are caused by benign proliferation of hepatocytes with high glycogen and fat content but lack normal hepatic architecture. They usually present as a solitary nodule that may reach up to 30 cm in diameter.

Clinical manifestations range from asymptomatic presentation or abdominal pain localized to the epigastric region or right upper quadrant to a palpable liver mass or even life-threatening haemorrhage in the case of rupture.[3,4] However, these tumours are most often encountered as an incidental finding during imaging for unrelated pathology.

Although the exact pathogenetic mechanism of the development of HCAs remains unknown, an association between

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formation of HCAs and the use of OCs or androgen-containing anabolic steroids is assumed.[5–7] Studies from the past century suggest that long-term use of OCs increases the annual incidence of HCAs from 1 per million to 3 to 4 per 100 000.[1,8] In addition, OCs and androgen-containing steroid anabolics have also been suggested to increase the number and size of these adenomas. Conversely, HCAs may shown signs of regression on discontinuance of OC use.[9,10] HCAs are further reported to be associated with type I and type III glycogen storage disease (GSD) and, furthermore, are more likely to be multifocal or to become malignant in these patients.[11]

The most important complications of HCAs are haemorrhage and malignant transformation into hepatocellular carcinomas (HCCs). Thus, these are the two main reasons for surgical treatment. However, little is known about the true incidence, associated risk factors and the aetiology of malignant alteration of HCAs. The aim of the current systematic review is to provide an estimation of the frequency of this phenomenon by means of a systematic literature search and, moreover, to discuss the clinical implications.

Methods

Search strategy

A search of all literature up to February 2010 was performed independently by two investigators (J.H.M.B.S. and R.J.S.C.) employing all relevant databases including the MEDLINE, PubMed and EMBASE databases, The Cochrane Hepatobiliary Group Controlled Trials Register and The Cochrane Central Register of Controlled Trials (CENTRAL). Keywords were 'hepatocellular adenoma', 'benign liver tumours', 'malignant transformation' and 'liver resection'. The search was limited to studies restricted to humans and articles published from 1970 onwards. This time period was chosen as the number of reports on hepatocellular adenomas began rising in the 1970s. All titles and abstracts were screened and relevant articles were selected.

Study selection criteria

Studies were included if they described a series of patients with HCAs undergoing surgery, embolization or other (conservative) treatment. Case reports and imaging studies of these benign lesions were also included. Only those studies containing a definite histological diagnosis of the tumours were included. Studies concerning HCAs in patients with GSD were excluded as these patients carry a higher risk of developing these lesions and, moreover, are thought to have an increased risk of malignant degeneration. Furthermore, patients with adenomatosis (more than 10 HCAs) were excluded, as this is considered as a different entity.[12,13] No further formal quality assessment or selection criteria were employed.

Data extraction

The reference lists of retrieved articles were reviewed for potentially relevant studies and case reports were also reviewed. When the full text of an article was not available, an Inter Library Loan account was used to retrieve these articles from national libraries. All data of selected articles were screened for duplicate adenoma cases that had already been reported in prior studies. In the case of an overlapping series, only the most recent or complete publication was included. The corresponding author of relevant studies identified from the initial search, together with experts in the field, were contacted for any information on unpublished articles and in case of need for clarification.

Outcome measures and statistical analysis

The main outcome measure was the rate of malignant transformation. In addition, the numbers of (resected) HCAs, the number of females, mean age at presentation, mean diameter of the lesion, OC use and presence of haemorrhage were all assessed. All reported adenoma cases were listed in a table. All data were presented as mean or median values and percentages.

Results

A total of 3935 articles were identified through the electronic searches of PubMed (n = 120), The Cochrane Hepatobiliary Group Controlled Trials Register and CENTRAL in the Cochrane Library (n = 12) and a combined Ovid MEDLINE and EMBASE search (n = 3803). Through reading titles and abstracts 1196 duplicates as well as 2658 noticeably irrelevant articles and eight articles on GSD or adenomatosis were excluded. Furthermore, four articles were excluded as they contained a series of adenomas that had been previously reported. Altogether, 69 articles were selected for more detailed evaluation. From this analysis, a further 108 studies were included through cross-referencing and three studies were excluded because of a previously reported series of adenomas. In total, 174 articles (157 series and 17 case reports) on liver surgery and imaging, including case series of HCA, were retrieved (Fig. 1).

Hepatocellular adenoma series in the literature

The 157 series contained a total of 1617 HCAs worldwide, of which 1445 HCAs (89%) were resected (Table 1). Thirty-six patients with adenomatosis and 14 patients with GSD were excluded from a total of eight studies. There were 51 series that contained only a single patient with HCA. Most of these reports were published in the 1970s when individual cases of HCA in women using OCs were regularly reported. The three largest series contained 91,[14] 124[15] and 128[16] HCAs, respectively (patients having adenomatosis or GSD not included).

Case reports on malignant transformation of hepatocellular adenomas

The literature search identified 17 case reports concerning malignant transformation (a total of 19 cases), which are presented in Table 2. The mean age of these patients at the time of surgery was 41 years (range, 19 to 70). Five of these patients (26%) were men,

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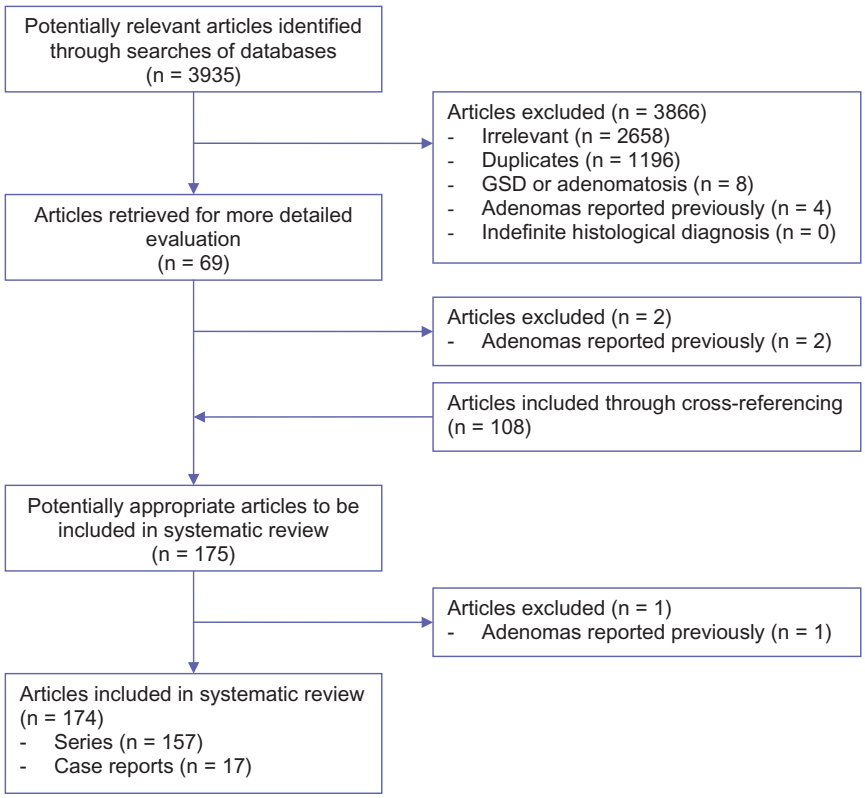

Figure 1 Flowchart literature search. GSD, glycogen storage disease

of whom one had a history of oral prednisolone use and another had a history of anabolic steroid use.[17,18] Twelve of the 14 women reported to have malignant alteration of an HCA presented with a history of OC usage. The mean time elapsed between commencement of OC therapy and diagnosis of HCA was 14 years. Most cases of malignant transformation of HCAs were seen at the time of the diagnosis of HCA. Furthermore, only three cases (16%) among these 19 cases of malignant degeneration presented with multiple HCAs[19–21] and six cases (32%) were complicated by haemorrhage.[21–26]

Although some authors noted that HCAs may regress on discontinuation of oral contraceptive use,[9,10,22] three case reports suggested that even after discontinuation of OC use, HCC can still develop irrespective of the occurrence of regression of the HCA.[20,22,26] Moreover, the reports by Chuang *et al.*[17] and Colovic *et al.*[27] showed that malignant transformation of HCAs can occur in patients without a history of OC use.

Frequency of malignant transformation of hepatocellular adenomas in the literature

Out of the 1617 HCAs listed in Table 1, 50 tumours (3.1%) underwent malignant transformation into HCC. By combining these data with the case reports aforementioned (Table 2), an estimation of the exact frequency of malignant alteration of HCAs could be made, as the data showed that 68 of a total of 1635 (4.2%) HCAs underwent malignant transformation. Moreover, of all resected HCAs (1462 in total), 4.5% contained focal malignancy. Although not the main scope of the current review, haemorrhage was found in 406 out of 1635 (25%) tumours, in keeping with literature data.[13,14,28]

Association between size of HCA and risk of malignant transformation

The size of HCA has, by current consensus, remained the main decision criterion in determining whether or not resection is indicated, based upon the observation that intratumoral bleeding only seldom takes place in lesions smaller than 5 cm.[2,15,29] Concordant to this observation, most of the resected adenomas identified in the current search were resected after they reached a minimal size of 5 cm.[4,30] However, limited data was hitherto reported concerning the possibility of an association between the size of HCAs and the risk of malignant transformation. Particularly, no specific studies on this subject have been conducted and, moreover, most series in the literature did not report precise measurements of the tumours. Nonetheless, some case reports and series of HCAs with particular diameters were reported. Deneve *et al.*[15] analysed 124 patients with an HCA, of which five cases contained signs of malignant alteration. The mean size of these five tumours was

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Table 1 Overview of series of hepatocellular adenomas with or without malignant transformation into hepatocellular carcinomas

Study	Year	HCA (*n*)	Resected (*n*)	HCC (*n*)	Female (*n*)	Mean age (y)	Mean diameter (cm)	OC use (*n*)	Haemorrhage (*n*)	Embolization (*n*)	Smallest diameter (cm)[a]
Malt *et al*.[59]	1970	4	3	0	3	–	15.8	–	1	0	
Kay and Schatzki[60]	1971	1	0	0	1	26	10	–	0	0	
Horvath *et al*.[61]	1972	1	1	0	1	28	15	1	0	0	
Motsay and Gamble[62]	1972	5	5	0	5	30.2	9.6	–	1	0	
Baum *et al*.[63]	1973	7	7	0	7	–	–	7	2	0	
Contostavlos[64]	1973	1	0	0	1	37	15	1	1	0	
Davis *et al*.[65]	1973	3	3	0	3	25	–	–	3	0	
Hermann and David[66]	1973	1	1	0	1	20	12	–	1	0	
Albritton *et al*.[67]	1974	4	4	0	4	32.8	–	–	0	0	
Berg *et al*.[68]	1974	4	1	0	4	26.5	–	3	3	0	
Kelso[69]	1974	1	1	0	1	36	–	1	1	0	
Knapp and Ruebner[70]	1974	1	1	0	1	33	17	1	1	0	
Tountas *et al*.[71]	1974	1	1	0	1	30	–	1	1	0	
Ameriks *et al*.[72]	1975	8	8	0	8	34	15	8	3	0	
Antoniades *et al*.[73]	1975	1	1	0	1	32	10.8	1	1	0	
Antoniades and Brooks[74]	1975	1	1	0	1	30	6.5	1	1	0	
Galloway *et al*.[75]	1975	4	1	0	4	41.5	–	1	2	0	
Model *et al*.[76]	1975	1	1	0	1	31	2.5	1	1	0	
Nissen and Kent[77]	1975	1	1	0	1	27	–	1	1	0	
Stenwig and Solgaard[78]	1975	1	1	0	1	1	31	10	1	1	
Ammentorp and Carson[79]	1976	4	4	0	4	28.8	–	4	0	0	
Andersen and Packer[80]	1976	1	1	0	1	24	4.5	1	1	0	
Baek *et al*.[81]	1976	1	1	0	1	31	18	1	1	0	
Brander *et al*.[82]	1976	1	0	0	1	24	–	1	1	0	
Edmondson *et al*.[5]	1976	42	41	0	42	–	–	34	29	0	
Lansing *et al*.[83]	1976	3	3	0	2	33.7	8.7	1	1	0	
Sears *et al*.[84]	1976	1	1	0	1	26	10	1	1	0	
Chan and Detmer[85]	1977	4	4	0	4	35.3	11.3	4	2	0	
Fechner[86]	1977	6	5	0	6	30.2	–	5	3	0	
Fortner *et al*.[87]	1978	1	1	0	–	–	–	–	–	0	
Gold *et al*.[88]	1978	12	7	0	7	30	6,8	6	1	0	
Ramseur and Cooper[89]	1978	1	1	0	1	26	8	1	0	0	
Bird *et al*.[90]	1979	1	1	0	1	39	15	1	1	0	
Cady *et al*.[91]	1979	1	1	0	–	–	–	–	–	0	
Catalano *et al*.[92]	1979	4	4	0	4	29	–	4	0	0	
Mariani *et al*.[41]	1979	1	1	0	1	27	8.5	1	1	0	
Wheeler *et al*.[93]	1979	1	0	0	1	–	–	1	0	1	
Weil *et al*.[94]	1979	8	8	0	7	24	–	4	4	0	
Kelly[95]	1980	2	1	0	2	30	–	2	1	0	
Neuberger *et al*.[96]	1980	3	2	1	3	35	–	3	0	0	–
Herczeg *et al*.[97]	1981	1	1	0	1	36	–	1	1	0	
Isman *et al*.[98]	1981	2	2	0	0	41	–	–	2	0	
Thompson and Little[99]	1981	1	1	0	1	30	9	1	0	0	
Bühler *et al*.[9]	1982	3	0	0	3	30.3	6.7	3	1	0	
Kerlin *et al*.[100]	1983	23	17	2	21	34	9	17	16	0	–
Meensook and Sirisabya[101]	1983	1	1	0	1	25	16	1	1	0	
Thompson *et al*.[102]	1983	5	5	0	5	32	–	2	2	0	
Cassinelli[103]	1985	1	1	0	1	38	–	1	0	0	
Gonzalez and Marks[104]	1985	12	12	0	–	–	–	–	2	0	
Welch *et al*.[105]	1985	13	12	0	12	31	11	9	11	0	
Mathieu *et al*.[106]	1986	27	27	0	27	34	7.5	26	5	0	
Creagh *et al*.[107]	1988	1	1	0	0	27	4	1	1	0	

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Table 1 *Continued*

Study	Year	HCA (*n*)	Resected (*n*)	HCC (*n*)	Female (*n*)	Mean age (y)	Mean diameter (cm)	OC use (*n*)	Haemorrhage (*n*)	Embolization (*n*)	Smallest diameter (cm)[a]
Leese *et al*.[2]	1988	18	17	0	15	33	13	11	9	4	
Marks *et al*.[42]	1988	3	3	0	3	35.7	–	3	1	0	
Ringe *et al*.[108]	1989	5	4	0	4	34	10	–	1	0	
Flowers *et al*.[109]	1990	6	6	0	5	28.8	7.3	5	6	0	–
Iwatsuki *et al*.[110]	1990	25	25	0	20	31	12	12	4	0	
Leborgne *et al*.[111]	1990	2	0	0	2	28	14	2	2	1	
Tao[47]	1991	9	7	0	9	33.5	–	9	0	0	–
Belghiti *et al*.[112]	1993	12	12	1	12	33	9.2	11	6	0	–
Arrivé *et al*.[113]	1994	29	21	3	27	37.4	5.4	24	15	0	–
Eckhauser *et al*.[114]	1994	8	8	0	8	31.5	9.5	7	0	0	
Foster and Berman[19]	1994	13	–	1	12	–	–	–	1	0	12
Golli *et al*.[115]	1994	8	8	0	7	30	6.8	6	1	0	
Paineau *et al*.[116]	1994	1	1	0	0	–	–	0	0	0	
Paulson *et al*.[117]	1994	9	6	0	8	–	–	6	–	0	
Pertschy *et al*.[118]	1994	30	29	0	–	–	–	–	0	0	
Cherqui[119]	1995	6	6	0	6	32	7.8	5	3	0	
Chung *et al*.[110]	1995	16	15	0	14	34.6	5.4	5	12	0	
Cuesta *et al*.[120]	1995	1	1	0	1	56	6	–	0	0	
Ferzli *et al*.[121]	1995	1	1	0	1	43	9	–	–	0	
Nagorney[122]	1995	24	19	1	22	35	9	9	4	0	–
Ault *et al*.[29]	1996	11	4	3	10	37.6	–	9	4	4	5.5
Azagra *et al*.[123]	1996	1	1	0	1	42	6	–	0	0	
Cheng *et al*.[124]	1996	1	1	0	1	39	6.4	1	1	0	
Kelly *et al*.[125]	1996	9	9	0	–	–	–	–	0	0	
Vogl *et al*.[126]	1996	1	0	0	1	27	–	–	0	0	
De Carlis *et al*.[127]	1997	19	19	2	19	31.8	7.9	17	5	0	–
Krug *et al*.[128]	1997	8	8	0	–	–	–	–	–	0	
Weimann *et al*.[129]	1997	41	36	2	–	–	–	–	–	0	–
Croes *et al*.[130]	1998	8	8	0	8	30	–	6	8	0	
Lezoche *et al*.[131]	1998	1	0	0	1	–	3	–	–	0	
Meissner[132]	1998	1	1	0	1	41	4.5	1	1	0	
Ott and Hohenberger[133]	1998	23	23	0	–	–	–	–	4	0	
Katkhouda *et al*.[134]	1999	9	9	0	–	–	–	5	0	0	
Closset *et al*.[135]	2000	16	16	1	16	35	8.1	10	7	0	15
Herman *et al*.[136]	2000	10	10	0	10	29.2	–	9	0	0	
Ichikawa *et al*.[137]	2000	24	13	2	20	–	–	12	10	0	–
Mouiel *et al*.[138]	2000	1	1	0	–	–	–	–	0	0	
Ji *et al*.[139]	2000	4	4	0	1	37	–	0	–	0	
Aseni *et al*.[39]	2001	1	0	0	1	25	5.5	1	0	0	
Charny *et al*.[54]	2001	12	8	1	10	34	8.6	–	0	0	–
Heeringa and Sardi[140]	2001	1	1	0	1	27	5.5	1	1	0	
Hung *et al*.[141]	2001	12	12	0	6	46.8	5.9	2	4	0	
Kammula *et al*.[142]	2001	8	8	0	–	–	–	–	–	–	
Mamada *et al*.[143]	2001	1	1	0	0	26	4.5	0	0	0	
Reddy *et al*.[144]	2001	25	25	1	25	33	5.9	21	3	0	25
Terkivatan *et al*.[30]	2001	33	19	0	29	36	–	27	12	0	
Wilkens *et al*.[145]	2001	10	10	0	8	38.9	7.4	–	–	0	
Antonetti *et al*.[146]	2002	1	1	0	–	–	–	–	–	0	
Farges *et al*.[147]	2002	2	2	0	–	–	–	–	–	0	
Marini *et al*.[148]	2002	7	7	1	7	37.4	13.5	0	7	3	–
Croce *et al*.[149]	2003	2	2	0	–	–	–	–	–	0	
Descottes *et al*.[150]	2003	17	17	0	–	–	–	–	0	0	
Ho *et al*.[151]	2003	1	1	0	–	–	3.2	–	–	0	
Morino *et al*.[152]	2003	5	5	0	–	–	–	–	–	0	

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Table 1 *Continued*

Study	Year	HCA (*n*)	Resected (*n*)	HCC (*n*)	Female (*n*)	Mean age (y)	Mean diameter (cm)	OC use (*n*)	Haemorrhage (*n*)	Embolization (*n*)	Smallest diameter (cm)[a]
Clarke *et al*.[153]	2004	8	8	0	–	–	–	–	–	0	
Kim *et al*.[154]	2004	11	11	2	–	–	–	–	0	0	–
Liu *et al*.[155]	2004	2	2	0	–	–	–	–	–	0	
Ronald *et al*.[156]	2004	3	3	0	0	36	8.3	0	0	0	
Atwell *et al*.[57]	2005	3	0	0	3	37	3.5	3	2	0	
Dulucq *et al*.[157]	2005	3	3	0	–	–	–	–	0	0	
Geller *et al*.[158]	2005	5	5	0	–	–	–	–	–	0	
Giusti *et al*.[159]	2005	1	1	0	0	45	18	0	0	0	
Psatha *et al*.[160]	2005	4	1	0	0	34.5	7	2	1	0	
Socas *et al*.[161]	2005	2	0	0	0	29	–	2	1	0	
Toso *et al*.[162]	2005	23	23	2	–	–	–	–	10	2	6.4
Erdogan *et al*.[58]	2006	22	16	0	22	35.8	7.2	17	22	1	
Learn *et al*.[163]	2006	1	1	0	–	–	–	–	–	0	
Schemmer *et al*.[164]	2006	7	7	0	–	–	–	–	–	0	
Tang *et al*.[165]	2006	1	1	0	–	–	–	–	–	0	
Vibert *et al*.[166]	2006	3	3	0	–	–	–	–	–	0	
Van der Windt *et al*.[167]	2006	48	16	0	48	36	–	45	13	3	
Ardito *et al*.[168]	2007	7	7	0	–	–	–	–	0	0	
Chaib *et al*.[169]	2007	28	28	0	24	36.3	8.0	22	3	0	
Dagher *et al*.[170]	2007	6	6	0	–	–	–	–	–	0	
Hompes *et al*.[171]	2007	2	2	0	–	–	–	–	–	0	
Ibrahim *et al*.[172]	2007	5	5	0	1	37.2	8.1	–	0	0	
Koffron *et al*.[173]	2007	47	47	0	–	–	–	–	–	0	
Nissen *et al*.[174]	2007	2	2	0	2	46.5	5.3	–	0	0	
Poultsides *et al*.[175]	2007	1	1	0	1	33	7	–	0	0	
Reddy *et al*.[176]	2007	25[b]	25	0	24	38	8.5	15	–	0	
Stoot *et al*.[3]	2007	11	2	0	10	34	7	9	11	11	
Teeuwen *et al*.[177]	2007	2	2	0	2	29.5	–	2	0	0	
Balaa *et al*.[178]	2008	1	1	0	–	–	–	–	–	0	
Buell *et al*.[179]	2008	25	25	0	–	–	–	–	–	0	
Cho *et al*.[28]	2008	41	41	2	38	36	–	22	12	0	5.7
Feng *et al*.[180]	2008	17	17	0	–	–	–	–	–	0	
Machado *et al*.[181]	2008	3	3	0	–	–	–	–	–	0	
Micchelli *et al*.[31]	2008	17	17	3	–	–	–	[c]	–	0	4
Petri *et al*.[182]	2008	22	22	0	20	38.3	7.7	–	–	0	
Popescu *et al*.[183]	2008	1	1	0	1	38	7.5	–	–	0	
Pulitano *et al*.[184]	2008	7	7	0	–	–	–	–	–	0	
Spencer *et al*.[185]	2008	1	1	0	–	–	–	–	–	0	
Troisi *et al*.[186]	2008	11	11	0	–	–	–	–	–	0	
Abu Hilal *et al*.[187]	2009	8	8	0	–	–	–	–	–	0	
Al Awad-Jibara *et al*.[188]	2009	1	1	0	1	40	5.8	0	0	0	
Bioulac-Sage *et al*.[16]	2009	128	128	5	116	41	7	106	23	0	–
Bryant *et al*.[189]	2009	23	23	0	–	–	–	–	–	0	
Deneve *et al*.[15]	2009	124	119	5	116	39	–	68	31	5	–
Dokmak *et al*.[14]	2009	91	91	9	79	–	–	70	22	–	2–5
Ito *et al*.[190]	2009	5	5	0	–	–	–	–	–	0	
Machado *et al*.[191]	2009	3	3	0	3	–	11.6	–	–	0	
Skalicky *et al*.[192]	2009	9	9	0	–	–	–	–	–	0	
Tomus *et al*.[193]	2009	3	3	0	–	–	–	–	–	0	
Watkins *et al*.[194]	2009	1	1	0	0	45	2.1	0	0	0	
Total		**1617**	**1445**	**50**	**1075**			**787**	**400**	**35**	

[a]Smallest size of HCAs showing malignant transformation.
[b]This study contained 2 groups, 25 patients without and 7 with glycogen storage disease (GSD) type Ia, of which the latter was excluded.
[c]All cases with malignant transformation included OC use.
HCA, hepatocellular adenoma; HCC, hepatocellular carcinoma; Ocs, oral contraceptives; –, no data available or not reported.

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Table 2 Overview of reported single cases of malignant transformation of hepatocellular adenomas into hepatocellular carcinomas

Reference	Year	Age/ gener	Use and duration of OCs or steroids (years)	Number of HCAs and size at time of diagnosis of HCC	Time to HCA diagnosis (years)[a]	Interval between diagnosis of HCA and HCC (years)	Haemorrhage	Resected	Outcome
Tesluk and Lawrie[26]	1981	34/F	Yes, 5	Solitary, 16 cm	5	3	Yes	Yes	Postoperative death after one month
Gordon *et al.*[22]	1986	36/F	Yes, 14	Solitary, 13 cm	14	3	Yes	Yes	Disease free
Gyorffy *et al.*[20]	1989	53/F	Yes, 19	Multiple (3), 12 cm	19	2	No	No	Tumour-related death after 7 months
Korula *et al.*[195]	1991	40/F	Yes, 15	Solitary, 6.5 cm	21	None	No	Yes	Disease free
Ferrell[196]	1993	29/F	Yes, 0.5	Solitary, 18 cm	5	None	No	Yes	Disease free
Foster and Berman[b19]	1994	56/F	Yes, 10	Multiple (3–4)	10	5	No	No	Tumour-related death after 5 months
Herman *et al.*[197]	1994	30/F	Yes, 15	–	15	None	No	Yes	n/a
Herman *et al.*[197]	1994	37/F	Yes, 20	–	20	None	No	Yes	n/a
Perret *et al.*[198]	1996	24/F	Yes, 3	Solitary, 14 cm	3	None	No	Yes	Disease free
Scott *et al.*[199]	1996	22/M	No	Solitary, 6 cm	–	None	No	Yes	Disease free
Ye *et al.*[21]	1999	42/F	Yes, 25	Multiple (2), 9 cm	25	None	Yes	Yes	Disease free
Larson *et al.*[25]	2002	52/M	No	Solitary, 12 cm	–	11	Yes	Yes	Recurrence after 6 years
Chuang *et al.*[17]	2002	19/M	Yes, 15[c]	–	15	None	No	Yes	n/a
Chuang *et al.*[17]	2002	46/F	No	Solitary, 10 cm	–	None	No	Yes	n/a
Ito *et al.*[23]	2003	57/F	Yes, 1 month	Solitary, 10 cm	30	None	Yes	Yes	Disease free
Burri *et al.*[200]	2006	40/F	Yes, 4.5	Solitary, 6 cm	16	None	No	Yes	Disease free
Colovic *et al.*[27]	2007	70/F	No	Solitary, 11.5 cm	–	None	No	Yes	Disease free
Gorayski *et al.*[18]	2008	35/M	Yes, 2	Solitary, 9 cm	10	None	No	Yes	Disease free
Kim *et al.*[24]	2009	53/M	No	Solitary, 4.5 cm	–	None	Yes	Yes	Disease free

[a]Time to HCA diagnosis since start of oral contraceptive therapy (which may has been discontinued before diagnosis).
[b]This case is also enlisted in Table 1.
[c]Oral prednisolone.
HCA, hepatocellular adenoma; HCC, hepatocellular carcinoma; Ocs, oral contraceptives; –, no data available or not reported.

11.6 cm in largest diameter. No tumour smaller than 8 cm showed malignant transformation in this study. As shown in Table 2, the mean size of solitary HCAs with features of malignant alteration reported in the retrieved case reports was 10.5 cm (range 4.5 to 18 cm). Overall, the smallest size at which malignant transformation was reported in the literature was 4 cm. This malignant alteration occurred in a solitary tumour of a 23-year-old woman who had taken OCs for 8 years.[31] In the series of 91 patients of Dokmak *et al.*,[14] malignant alteration of either solitary or multifocal HCAs was seen in nine cases. In this study, only one case of malignant transformation was observed in an adenoma measuring less than 5 cm in diameter (2–5 cm, exact size not presented), concerning a male individual with a history of steroid intake. Overall, the current literature search showed that a total of three cases of malignant alteration (4.4% of all HCAs showing this phenomenon) occurred in a tumour measuring less than 5 cm in diameter.[14,24,31]

Discussion

This systematic review has focussed on the risk of malignant transformation of HCAs into HCCs. The present study shows that malignant alteration is a rare complication of these uncommon benign tumours. By performing a systematic search of studies reporting cases of this benign liver disease over the past 40 years and combining the data on these HCAs, a total of 1568 reported HCAs were found. The overall frequency of malignant transformation reported was 4.2% among all adenoma cases and 4.5% among all resected HCAs.

Although earlier series of HCAs had already shown one or two cases, Foster and Berman[19] were the first to report an estimated risk of malignant transformation, as they found a frequency of 13%. Barthelmes and Tait,[13] Cho *et al.*[28] and Micchelli *et al.*[31] used a similar approach for determining the incidence of malignant degeneration employed in the current study. However, these three studies identified a remarkably smaller number of case series than included in the current review, and, moreover, the latter study did not include cases of HCAs in which no malignant alteration was found.[31] Additionally, most case series used in the frequency estimation comprised a limited sample size and reported only on resected adenomas. This could have led to an overestimation of the true risk, apart from the selection bias of reported studies and cases in general. The series of Dokmak *et al.*,[14] Deneve *et al.*[15] and Bioulac-Sage *et al.*[16] seem more robust for estimating the frequency of malignant alteration, as these authors analysed a larger population containing 91, 124 and 128 patients, respectively (cases with adenomatosis or GSD not included). Hepatic adenomatosis is regarded as a different entity by many authors concerning presentation and size and number of the adenomas, as well as the different therapeutic options.[12,13] Equally, several

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groups have recently reported germ line mutations of hepatocyte nuclear factor 1α inactivation in adenomatosis, and this has been suggested to be associated with maturity-onset diabetes of the young type 3.[32–34] Also, these mutations may have implications on the risk of malignant degeneration. Therefore, and also to limit heterogeneity, liver adenomatosis was excluded in the present review. As previously mentioned, patients with known GSDs are at a higher risk of developing HCAs[11,35] and were therefore not included in the current review.

Risk factors of malignant transformation of hepatocellular adenomas

Although the risk of malignant transformation seems small (4.2%), this is a serious complication which cannot be neglected. As HCAs are difficult to discriminate from HCCs, because of similar imaging characteristics and histopathological features, it is important to identify factors that increase the risk of malignant transformation. Unfortunately, in the current study a true risk analysis based on tumour size was difficult to perform as many studies only reported the mean size of the adenomas included. However, as three cases have been reported in which malignant transformation occurred in a tumour measuring less than 5 cm in diameter, the recommendation to only treat HCAs larger than 5 cm in diameter in order to prevent malignant transformation is open for debate.[14,24,31]

Upon reviewing the literature, several groups of patients were identified as having an increased risk of malignant alteration of these benign liver tumours. High-risk groups reported were those patients with a history of androgen or anabolic steroid intake,[18] patients of male gender[14,36] and, as previously stated, patients with GSD.[11,37,38] Furthermore, as has been reported since the late 1970s, intake of OCs could potentially play a role in the enlargement of existing HCAs. To date, discontinuation of OC usage is still the advice given to patients that are diagnosed with an HCA,[13] as several reports showed regression in size of the HCAs after cessation of OC intake.[9,39,40] However, some case reports suggested that discontinuation of OCs will not abort the risk of malignant transformation.[41,42] Therefore, even after discontinuation of OC use, long-term follow-up of patients with unresected HCAs remains necessary. Another proposed risk factor for malignant alteration is the presence of dysplasia in HCAs. This characteristic harbours a risk of progression to HCC.[43–47]

Several studies have identified mutations of the β-catenin gene in HCAs and reported that activated β-catenin mutations deregulate the β-catenin pathway. This pathway is part of the more complex Wnt signalling pathway which plays a major role in the proliferation of liver cells.[36,48–50] These mutations may thus lead to hyperproliferation of liver cells and, consequently, malignancy. The Bordeaux group has performed genotype–phenotype analyses in HCAs and identified four different tumour subtypes with specific characteristics: (i) hepatocyte nuclear factor 1α (HNF1α) mutated (30%–50%), (ii) β-catenin-activated (10–15%), (iii) inflammatory (35%) and (iv) unclassified tumours (5%–10%).[36,51,52] Hepatocellular carcinoma associated with adenoma was found in 46% of β-catenin-mutated tumours, whereas this has never been observed in inflammatory lesions and rarely found in HNF1α-mutated tumours. This suggests that HCAs with β-catenin activation carry a higher risk of malignant transformation. Furthermore, the Bordeaux group identified four immunohistochemical markers that characterize each of the four HCA subtypes with high specificity and sensitivity: liver-fatty acid binding protein (L-FABP), glutamine synthetase (GS), nuclear β-catenin and serum amyloid A (SAA).[53] They found absence of L-FABP expression to indicate HNF1α mutation, whereas combined GS overexpression and nuclear β-catenin staining suggested β-catenin-activating mutations. Finally, the Bordeaux group noted that SAA staining and overexpression of C-reactive protein (CRP) predicted inflammatory HCA. These markers have proven to be a promising method to identify adenoma patients at risk of developing HCC. Table 3 provides an overview of HCA subtypes and their immunohistochemical markers.

Table 3 Types of HCAs and their immunohistochemical markers

HCA type	Frequency (%)	Malignant transformation	Markers
β-catenin activated	10–15	Yes	β-catenin+/GS+
HNF1α inactivated	30–50	Rarely	LFABP–
Inflammatory	35	No	SAA+/CRP+
Unclassified	5–10	No	None

CRP, C-reactive protein; GS, glutamine synthetase; HCA, hepatocellular adenoma; HNF1α, hepatocyte nuclear factor 1α; LFABP, liver-fatty acid binding protein; SAA, serum amyloid A; +, positive; –, negative.

Future treatment perspectives

As for future treatment perspectives, more research is needed to investigate the mechanism of malignant degeneration. Only then can this group of predominantly young patients be withheld a potentially unnecessary liver resection, while this surgical treatment has still a reported morbidity and mortality of up to 27% and 3%, respectively.[30,54–56] At present, for all patients presenting with one or more HCAs larger than 5 cm, resection is the treatment option of choice in accordance with the current guidelines. Only 4.2% of HCAs will have actual foci of HCC, and therefore a considerable number of resections will be performed in vain. However, this rate should preferably be seen as an upper limit of the true frequency as publication bias might have occurred. After all, men who have an anabolic steroid-induced adenoma containing foci of malignancy are more likely to be reported in the literature than those adenoma patients without malignant transformation. Nevertheless, over 95% of all patients presenting with HCAs measuring over 5 cm, will unnecessarily be exposed to a potentially hazardous surgical procedure. By identifying those patients who will derive most benefit from surgery as their HCA harbours an increased risk for malignant alteration, fewer patients will have to undergo this unnecessary surgery. The Bordeaux HCA markers are

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a promising risk prediction tool. However, biopsy could lead to haemorrhage, sample errors or tumour seeding, but these potential complications are rare in experienced centres. Also, the value of β-catenin staining needs to be studied more intensively. Recently, interest has turned towards less invasive procedures to treat patients that present with HCAs larger than 5 cm. There is preliminary evidence to suggest that developments in minimally invasive techniques such as (percutaneous) radiofrequency ablation (RFA) or microwave ablation may alter the treatment of HCA. The limited data so far available suggest that these techniques can be performed with low morbidity and zero mortality, but additional research is required to explore their exact role in adenoma treatment.[57]

Recently, two groups have reported the therapeutic effects of selective arterial embolization to stop haemorrhaging from ruptured adenomas.[3,58] They also showed that embolizing ruptured adenomas prevented growth of these lesions. Subsequently, selective arterial embolization was utilized in a number of non-haemorrhaging adenomas.[3] During follow-up, none of these adenomas grew and the majority even regressed in size. On examining the haemorrhaging and non-haemorrhaging adenomas separately, a statistically significant decrease in size was noted in both groups. It is this tumour regression, and its probable subsequent reduction of the risk of severe haemorrhaging and malignant transformation, that might propose selective arterial embolization as a novel treatment for large unruptured HCAs. As no significant complications from this treatment were reported arterial embolization of HCAs might be the direction for further future research.[3,58] To the best of our knowledge, no studies have been performed to specifically investigate this treatment.

In conclusion, the current review shows that malignant transformation of HCAs into HCCs is a rare complication of these uncommon benign tumours. By pooling data of series and case reports, comprising more than 1600 reported HCAs, we found an overall frequency of malignant transformation of 4.2% for all adenomas and of 4.5% for all resected adenomas. A multicentre study with a large registry of HCAs is paramount for estimating the actual risk of malignant transformation. Further research should focus on the underlying mechanisms of malignant transformation of HCAs into HCCs, associated risk factors and the use of new tumour markers. By means of a better selection of precisely which patients with an HCA present with an increased risk of malignant degeneration – and who could therefore derive the greatest benefit from treatment – a reduction in unnecessary liver resections can be achieved. This would reduce the risks associated with surgery in these predominantly young patients.

Conflicts of interest

None declared.

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