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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,