

ORIGINAL ARTICLE

Hepatic incidentaloma: the rule of tens

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Abstract

Objectives: Hepatic incidentalomas (HI) are asymptomatic lesions detected incidentally during investigations for other pathologies. This prospective series outlines the management and outcomes of 121 HI managed over 7 years.

Methods: Data were recorded prospectively on 121 patients referred between 2003 and 2010 for assessment of HI out of 1081 patients referred for a hepatic resection. Patients were reviewed in multidisciplinary meetings and investigated with tumour markers and radiological investigations. HI were classified as hypo- or hypervascular depending on arterial phase CT scan findings. Univariate and multivariate analysis was performed to define predictive factors for malignancy.

Results: Forty HI were hypovascular, 35 were benign (18 cysts, 12 focal fatty sparing, 1 fetal lobulation and 4 solitary necrotic nodules) and 5 cholangiocarcinomas (all resected). Eighty-one HI were hypervascular, 72 were benign [40 focal nodular hyperplasia (FNH), 8 adenoma and 24 hemangiomas] and 9 cancers (5 HCC, 4 metastases: 7 resected). Male gender [relative risk (RR) 2.70, confidence interval (CI) 1.69–3.51], age >45 years (RR 3.15, CI 2.71–3.89), tumour diameter >4 cm (RR 3.35, CI 3.13–4.01) and late (8 min) enhancement on magnetic resonance imaging (MRI) (RR 4.15, CI 3.01–4.79) were predictive of malignancy.

Conclusions: HI constitute 10% of practice volume. 10% of hyper and hypovascular incidental lesions are malignant. Most can be treated aggressively after diagnosis.

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Introduction

Incidentaloma is a term attached to asymptomatic lesions detected incidentally during investigations for other pathologies. Most commonly incidentalomas are detected during radiological investigations although they may also be observed during surgical procedures such as a laparotomy or laparoscopy. Hepatic incidentalomas (HI) were first described by Miles Little¹ in 1990 and his paper is the first to use the term 'incidentaloma'. Hepatic incidentalomas are often detected during ultrasound

investigations for pelvic symptoms or upper abdominal pain. They are recognized as a modern condition and their investigation and clinical work up represent a significant work load for hepatobiliary specialists as hepatic lesions may represent malignant or premalignant lesions. Detection of these lesions at an early asymptomatic stage may therefore provide an opportunity to aggressively treat life-threatening conditions while they are localized, with anticipated improvements in outcome, and with the potential for intervention with minimally invasive therapies. However, many HI are benign non-threatening lesions which do not require intervention, and in which the risks of surgical resection outweigh the biological risks associated with the lesion. Consequently, all HI require careful, accurate investigation and assessment with the aim of establishing a precise diagnosis without resection.

While a biopsy is a potential tool to establish tissue diagnosis in HI, the risks of a biopsy in disseminating localized tumours make

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its routine application unsafe and consequently imaging and serum tumour marker determinations now form the core of the approach to investigating these lesions.

This investigation describes an approach to the investigation and management of incidentally detected hepatic lesions presenting to a single surgeon between 2003 and 2010.

Methods

The clinical details of patients referred for assessment with incidentally detected solitary liver lesions were recorded prospectively in a computerized database. Patients referred with a diagnosis of HI were reviewed with a full history and physical examination with particular emphasis on detection of any signs of chronic liver disease or malignancy. Blood tests were taken in all patients including a full blood count, plasma creatinine, urea, electrolytes and liver function tests. Tumour markers were routinely checked and included carcinoembryonic antigen (CEA), Ca 19-9 and α -fetoprotein (AFP). Des gamma carboxy prothrombin or other novel markers of hepatocellular malignancy were not routinely available and were not utilized in these patients.

All available radiological investigations were reviewed in a multidisciplinary meeting. In general, most patients were referred with an abdominal ultrasound examination and many had an accompanying computed tomographic (CT) scan at the time of referral. In the early part of this series, CT scans were generally ordered if they were not available. However, with the finding on ultrasound of a solid liver lesions, magnetic resonance imaging (MRI) became increasingly used as a definitive imaging modality. Similarly for small hepatic lesions where a cyst was suspected but could not be confirmed MRI was utilized. After multidisciplinary review of patients where all available imaging was reviewed along with available clinical examination findings, tumour marker and liver function tests, suspected cystic lesions were further investigated with MRI scans while solid lesions were recommended to undergo either a CT scan or a dedicated MRI scan. A number of patients were assessed with both imaging techniques. A percutaneous biopsy was used, only after extensive discussion, in patients with suspected disseminated malignant disease to prove the presence and histotype of malignancy and assist in defining optimal systemic therapies. The other indication for a biopsy was to prove the presence of benign disease when this was strongly suspected after review of all radiological and clinical findings. A biopsy in this setting was undertaken to definitively prove benign pathology, reduce patient anxiety and to prevent the requirement for ongoing radiological imaging. Many patients were reviewed at several multidisciplinary meetings as their diagnostic work up progressed.

Cox's regression analysis was performed to determine the respective influence of patient and lesion characteristics on a final malignant diagnosis. A *P*-value of ≤ 0.05 was considered significant.

Results

Between 2003 and 2010, 121 patients were referred for assessment, investigation and treatment of incidentally detected liver lesions. In this period, a total of 1081 patients were referred for hepatic resection. Of these, 74 (61%) were female and had a median age of 42 years (range 17–74). Of 121 patients, 118 (97.5%) had initially undergone an abdominal ultrasound examination to investigate abdominal pain. Three patients presented with incidental liver lesions initially detected on abdominal CT scans. Two of these were undertaken in the assessment of a trauma patient after a motor vehicle accident and another for the assessment of a possible pelvic mass. The liver lesions were initially investigated with a CT scan and then classified as hyper- or hypovascular lesions depending on their arterial phase perfusion. Particular note was also made of any radiological signs of cirrhosis (ascites, small and irregular hepatic outline and associated varices).

Overall, patients underwent a median of 3 imaging investigations (range 1–4), were discussed at 3 multidisciplinary meetings and work up took between 8 and 47 days (median 22 days).

Hypovascular lesions

Forty patients (33%) presented with hypovascular lesions. The median age was 54 years (range 43 to 74), 25 were male and 15 female. Nineteen patients had a past history of cancer (14 non-melanotic skin cancer, thyroid cancer 2, uterine carcinoma 1, cervical carcinoma 1 and laryngeal cancer 1). No patient had radiological signs of cirrhosis. Thirty-eight patients presented after ultrasound examination. All 40 patients underwent a triple phase CT scan and 17 were investigated with MRI.

The final diagnosis of the 40 hypovascular lesions is shown in Table 1. Twelve patients were found to have areas of focal fatty sparing in steatotic livers and two of these patients had type 2 diabetes.

Hypervascular lesions

Eighty-one patients (67%, median age 34 years, range 17 to 56) presented with hypervascular lesions and 58 were female. No patient had a history of prior cancer but four patients had radiological signs of cirrhosis. All 81 patients presented after an abdominal ultrasound. The final diagnosis of the 81 hypervascular lesions is presented in Table 2. On the basis of MRI scanning, 40 were found to be focal nodular hyperplasia with hypervascularity

Table 1 Final diagnosis in 40 patients presenting with hypovascular incidentalomas

Diagnosis	Number	Number resected
Total	40	9
Fetal lobulations	1	1 (diagnosis only)
Focal fatty sparing	12	0
Solitary necrotic nodule	4	4
Cholangiocarcinoma	5	4
Cysts	18	0

Table 2 Final diagnosis in 81 patients presenting with hypervascular incidentalomas

Diagnosis	Number	Biopsied	Resected	Follow-up
Total	81	18	16	16
FNH	40	5	1	26 (6–36 months)
Adenoma	8	8	8	
HCC	5	5	5	
Haemangioma	24	0	2	0
Neuroendocrine	4	0	3	

FNH, focal nodular hyperplasia; HCC, hepatocellular carcinoma.

persisting in the hepatobiliary phase after Kupffer cell-specific contrast (gadobenate dimeglumine, Multihance; Bracco Imaging, High Wycombe, UK). Five patients were found to have hepatocellular carcinomas (HCC). In all patients there were clinical risk factors for HCC (heavy alcohol intake in three and one patient with chronic hepatitis B), although no patients had elevated serum AFP. These lesions are difficult to differentiate from adenomas but generally brisk enhancement on arterial phase CT scans with complete washout on venous phase scans was seen. Four patients were found to have solitary neuroendocrine metastases. These lesions were hypervascular but all were found to have identifiable primary tumours in the terminal ileum.

Risk factors for malignancy

Of those lesions found to be malignant, 5 of 40 (12%) were hypovascular and 9 of 81 (11%) were hypervascular. Male gender [relative risk (RR) 2.70, confidence interval (CI) 1.69–3.51], age >45 years (RR 3.15, CI 2.71–3.89), late (8 min) enhancement on MRI (RR 4.15, CI 3.01–4.79) and tumour diameter >4 cm (RR 3.35, CI 3.13–4.01) were predictive of malignancy (Table 3).

Discussion

This investigation was undertaken to summarize a single surgeon's experience with the investigation and management of incidentally detected lesions of the liver. Incidentalomas are a significant part of modern hepatobiliary practice with the 121 patients reported in this series presenting over a 7-year period. This reflects the increasing use and widespread availability of cross-sectional imaging to investigate abdominal symptoms and the availability of surgical and ablative techniques to treat hepatic lesions. Historically many of these lesions probably were present in the general population but were not detected because of the lack of available imaging and, when they were, few if any treatment options were available and patients were managed expectantly. However, patients with hepatic lesions now require accurate investigation and diagnosis. Many with incidentally detected lesions arrive for assessment with high rates of anxiety regarding possible cancer diagnoses, often primed by referring practitioners, and many arrive for assessment requesting a hepatic resection or biopsy. Consequently the 'test of time' approach utilized in older

publications on the topic is now unacceptable to most patients.² It is possible that this finding may be under-estimated as focal nodular hyperplasia (FNH) were referred more frequently than haemangioma raising the possibility that many 'incidental' haemangiomas were worked up and diagnosed without specialist hepatobiliary referral.

Routine biopsy of incidental hepatic lesions is a tempting prospect. However, this investigative technique has a number of pitfalls. The primary concern with fine needle or core biopsy of hepatic tumours is a 10–20% risk of needle tract metastases and tumour dissemination in malignant lesions.^{3,4} These data are based on follow-up of patients with colorectal liver metastases undergoing a biopsy. However, there is reason to suspect that similar figures would apply to other metastatic adenocarcinomas and peripheral cholangiocarcinomas. The risk of seeding is less for hepatocellular carcinoma (HCC) at around 3%.⁵ A sampling error and the presence of necrotic material may also compromise the accuracy of a needle biopsy and false-negative rates of 7–10% have been recorded.⁶ Earlier series have concluded that a biopsy is not helpful in at least 50% of patients, even when it is performed intra-operatively.² In comparison, at least in the case of colorectal liver metastases, cross-sectional imaging has a 99% specificity.^{3,6} Collectively, these observations have determined that a routine needle biopsy should not be undertaken in the investigation of HI. Instead it is utilized in patients with disseminated malignancy, who are not surgical candidates, to provide a tissue diagnosis and guide the application of palliative chemotherapy or radiotherapy. Alternatively it has been used in patients in whom the evidence points to a benign lesion but in whom a definitive tissue diagnosis is required or in those patients with truly indeterminate lesions where cross-sectional imaging has not been able to arrive at a definitive diagnosis and in whom resectional surgery is high risk or contraindicated. Typically this is utilized in patients with small hypervascular lesions where HCC is suspected and serum alpha-fetoprotein is normal. With a confirmed malignant diagnosis, these patients may be eligible for listing for a hepatic transplantation, ablative therapy or resection.

A routine hepatic resection has also been undertaken in the management of HI. The last 10 years of hepatic surgery have been characterized by numerous reports confirming the safety of HR and mortality rates of less than 1% are now the norm for most hepatobiliary units in patients with normal hepatic parenchyma.^{7,8} However, deaths after a resection for benign lesions have been reported.⁹ Shimizu *et al*² reported on a series of 32 patients with an incidentally detected presumed malignant tumours undergoing resection. All patients were found to have a benign tissue diagnosis. Fifteen patients had a benign tissue diagnosis and could have been safely observed whereas 17 patients were considered to have benefited from resection simply because of significant concerns over a potential malignant diagnosis. Belghiti¹⁰ has also described a series of 51 female patients undergoing resection for presumed benign lesions. A resection was carried out in all patients with no serious morbidity and no mortality. Three

Table 3 The influence of patient and lesion characteristics on a final malignant diagnosis

Variable	Number/number cancers/ total	Univariate	Multivariate	P-value
Male	9 / 14 / 121	RR 2.67, CI 1.60–3.79	RR 2.70, CI 1.69–3.51	0.046
Female	5 / 14 / 121	RR 1.03, CI 0.96–1.19	RR 1.05, CI 0.96–1.11	NS
Age > 45 years	11 / 14 / 121	RR 3.07, CI 2.63–3.79	RR 3.15, CI 2.71–3.89	< 0.01
Radiological signs of cirrhosis	4 / 14 / 121	RR 0.87, CI 0.56–0.93	RR 0.93, CI 0.57–0.99	NS
Tumour diameter > 4 cm	12 / 14 / 121	RR 3.21, CI 2.77–3.89	RR 3.35, CI 3.13–4.01	< 0.009
Hypovascular	5 / 40 / 121	RR 0.31, CI 0.26–0.73	RR 0.37, CI 0.29–0.86	NS
Hypervascular	9 / 81 / 121	RR 0.44, CI 0.34–0.69	RR 0.47, CI 0.35–0.71	NS
Elevated CEA	0 / 14 / 121	RR 0	RR 0	NS
Late enhancement on MRI	5 / 14 / 121	RR 3.50, CI 2.93–4.40	RR 4.15, CI 3.01–4.79	<0.043
Elevated Ca19-9	2 / 14 / 121	RR 0.39, CI 0.19–0.64	RR 0.44, CI 0.22–0.68	NS
Elevated AFP	2 / 14 / 121	RR 0.37, CI 0.18–0.66	RR 0.39, CI 0.20–0.59	NS

CEA, carcinoembryonic antigen; MRI, magnetic resonance imaging; AFP, α -fetoprotein; RR, relative risk; CI, 95% confidence interval; NS, not statistically significant.

patients (6%) had an unexpected final malignant diagnosis (all small HCC) after presenting with small hypervascular lesions. Consequently, while routine resection of hepatic incidentalomas can now be undertaken safely, the majority are benign and a resection is not indicated and the clinical effort must be directed at achieving a secure and accurate diagnosis.

Two earlier investigations, both from areas with a high incidence and prevalence of HCC, have attempted to define risk factors associated with hepatic incidentalomas that make a malignant diagnosis more likely. In Italy, Belli *et al*¹¹ reported 35 incidentally detected hepatic lesions. Twenty-two proved to be benign and 13 were HCC. The presence of a risk factor for HCC increased the chance the hepatic lesion was malignant and patients with cancers were older than those with benign lesions (65 versus 45 years). Liu *et al*¹² reported 107 incidentally detected hepatic lesions from Hong Kong. Of these, 62 were malignant after resection and were made up of 48 HCC, 8 cholangiocarcinoma, 2 lymphoma, 2 cystadenocarcinoma, 1 carcinoid tumour and 1 malignant histiocytoma. On multivariate analysis, male gender, age greater than 50 years and tumour size greater than 4 cm were independent predictive factors for malignancy. These investigators also found low operative mortality and morbidity in patients undergoing a hepatic resection and found that, of 48 patients with incidentally detected HCC, survival was significantly better than patients presenting with symptomatic lesions.

New Zealand does have a high incidence of HCC¹³ although the majority of tumours in this series were peripheral cholangiocarcinomas or metastatic neuroendocrine tumours. Five HCCs were also detected. The risk factors for malignancy were similar to those of Liu *et al*¹² and Belli.¹¹ Older age, larger lesions and male gender were significant risk factors along with late contrast enhancement of lesions on MRI. While the majority of HI in this series, as in others, were young (age ≤ 35), female and hypervascular, only one of these proved to be an HCC. Of the remaining tumours, all were

male apart from three patients with neuroendocrine metastases. Eleven patients were aged 45 years or older with the youngest patient being a male aged 39 years with an HCC. Four of the five patients with HCC had radiological signs of cirrhosis whereas no patient with a benign HI had evidence of cirrhosis. Finally, 12 of the 14 patients with a malignant diagnosis had tumours ≥ 4 cm in diameter whereas the remaining 2 patients had lesions 3.4 and 3.8 cm in diameter confirming that larger lesions are more likely to be malignant.

The current investigation has shown that at least 10% of hypervascular lesions and hypovascular lesions presenting incidentally are malignant indicating that the vascularity per se is not a risk factor for malignancy. The distinction in vascularity was based on arterial phase imaging during a CT scan. This proved to be a useful screening method in defining potential malignant diagnoses and directing subsequent investigations. This meant that all patients underwent a CT scan but in practice this proved to be the case. Of the hypovascular lesions, 18 were found to be simple cysts using a combination of ultrasound and CT/MRI for small cysts or cysts in patients with body habitus or position that made imaging with ultrasound difficult. Twelve patients were proven to have focal fatty sparing on fat suppressed MRI. While a tissue diagnosis was not obtained in any of these patients, they have remained well for at least 2 years after diagnosis making an underlying malignancy unlikely. Four patients with solitary necrotic nodules were resected. While this is a benign lesion, we have previously written about the difficulty in making the diagnosis pre-operatively and the issues in differentiating these lesions from necrotic tumours.^{14,15} Interestingly, Shimizue *et al*² reported three patients in their series who were resected because of 'encapsulated necrosis' which probably represent solitary necrotic nodules. In the current series, five patients were found to have peripheral cholangiocarcinomas on the basis of imaging showing an infiltrative, hypovascular tumour and raised plasma Ca19-9 in two patients. One

patient thought to have a small cholangiocarcinoma was found to have a small amount of fat in a persistent fetal lobulation at laparotomy.

The hypervascular lesions proved to be a more difficult group of diagnoses. In particular, the differentiation between an adenoma, well-differentiated HCC and focal nodular hyperplasia is difficult, particularly for small lesions.¹⁰ Five patients with small hypervascular lesions with complete washout on the portal venous phase were biopsied on suspicion of being HCC and this diagnosis was confirmed in all five patients. Two of these patients had mildly raised, but not diagnostic, alpha fetoprotein levels and four patients had radiological evidence of cirrhosis. Twenty-four patients were diagnosed with haemangiomas on CT and MRI scanning. In two patients the enhancement was atypical and surgery or a biopsy was recommended. In both patients, a resection was undertaken confirming the presence of a haemangioma. Eight patients were thought to have adenomas or well-differentiated HCC. A biopsy confirmed adenomas and all were resected. Forty patients with hypervascular lesions were diagnosed with FNH after a dedicated MRI scan. Of these, five were biopsied, confirming FNH, because of slightly atypical imaging findings. One was resected because of the presence of a hypervascular nodule adjacent and a possible associated HCC. The pathology confirmed FNH only. Of the 35 FNH and 22 haemangiomas that were not resected and not biopsied, all have remained well at a minimum of 2 years of follow-up making an underlying malignant diagnosis unlikely.

This investigation was undertaken to describe one methodology developed to manage patients presenting with incidentally detected liver lesions. This is an increasingly common clinical problem for hepatobiliary surgeons and reflects the increasing use and accuracy of cross-sectional imaging techniques and a more aggressive contemporary stance taken in investigating and treating hepatic tumours. Overall, HI can constitute 10% of a practice load and often require multiple radiological investigations and multi-disciplinary review. However at least 10% of hypovascular and hypervascular lesions were malignant and can be aggressively treated.

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Conflicts of interest

None declared.

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