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ORIGINAL SCIENTIFIC REPORT

Indeterminate Pulmonary Nodules in Resected Liver Metastases from Colorectal Cancer: A Comparison of Patient Outcomes

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Abstract

Aims Hepatic metastasectomy remains the only potentially curative treatment for colorectal liver metastases (CRLM). Some of these patients develop indeterminate pulmonary nodules (IPNs). This study aimed to compare outcomes of patients with and without IPN undergoing resection of CRLM to ascertain whether their presence is clinically significant.

Methods Cases and controls were identified from a prospectively maintained database of CRLM resections. Patients with staging radiology demonstrating IPNs were included as cases. Controls were matched to the cases by four primary factors: age, type of resection (primary or redo), clinical risk score (CRS) and chemotherapy.

Results The median disease-free survival (DFS) and overall survival (OS) for the cases were 7.0 months (95% CI 4.8–9.2) and 28.6 months (95% CI 21.2–36.0), respectively, and 12.0 months (95% CI 10.7–13.2) and 30.5 months (95% CI 19.4–41.6) for the controls. The 1-, 3- and 5-year survival rates were 92.7, 39.7 and 0.0% for the IPN group, and 92.4, 32.9 and 21.9% for those without. In total, 60.7% of IPN patients progressed to lung metastases, of which 39.3% underwent pulmonary resections. DFS was significantly shorter in the IPN group ($p = 0.022$), but OS was not significantly different ($p = 0.421$). The presence of IPN was independently associated with a shortened DFS ($p = 0.027$), as was a CRS of 3 or greater ($p = 0.007$).

Conclusion This study suggests that IPN does not significantly affect OS, but may predict earlier disease recurrence. IPN presence alone should not preclude radical resection but could be used to prompt more careful post-operative surveillance to detect lung metastases at a potentially operable stage.

Introduction

Colorectal cancer is the third most common cancer in the UK and the second most common cause of cancer death [1, 2]. The liver is the most common site of metastatic spread, and 20–25% of patients will have synchronous liver metastases at the time of presentation, with a further 20% going on to develop metachronous disease following colonic resection [3], usually within three years. Hepatic metastasectomy remains the only accepted potentially curative treatment for these tumours and has been key to improving long-term survival [4–6], with reported 5-year survival rates approaching 60% in some cases [5–7], but unfortunately only approximately 15% of patients are deemed surgically resectable [8]. There are a number of reasons for this including size, number, unfavourable anatomical location of the metastases and medical comorbidity prohibiting major surgery. In addition, the presence of unresectable extra-hepatic disease remains a contraindication [8] and is more commonly detected with

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the advent of positron emission tomography (PET) scanning.

It is not uncommon for preoperative staging computed tomography (CT) of the chest to reveal lung lesions, which cannot be characterised as benign or malignant, described as indeterminate pulmonary nodules (IPN). Indeed, some sources suggest that IPN may be present in as many as one-third of colorectal cancer patients [9, 10]. The majority of IPN will eventually prove to be benign [10], but inevitably a smaller number will turn out to be metastatic deposits. The presence of IPN poses a clinical challenge because a clear management algorithm does not exist and remains the topic of ongoing debate. Imaging tools for further characterisation such as PET-CT are frequently used, but are rarely able to clarify the nature of an indeterminate lesion principally due to their small size [11]. Currently, no consensus exists on the best management of patients with IPN in the setting of potentially resectable colorectal liver metastases (CRLM).

In patients with one or more IPN and in the absence of any other contraindications to hepatic resection, most institutions will adopt an aggressive approach, assuming that the IPN(s) will ultimately prove benign, or that close post-operative surveillance will detect progression in a timely manner and allow for further surgical intervention [11]. However, it is not clear whether a more conservative approach involving repeated imaging prior to reconsidering the suitability of surgery would be a more appropriate strategy, or indeed eliminating the surgical option altogether when resection cannot ultimately be curative. The aim of this study was to examine and compare the outcomes of patients with and without IPN undergoing radical resection of their CRLM to ascertain whether their presence is clinically significant and should therefore influence planning of their treatment.

Methods

Patient selection and IPN classification

Patients were identified from a prospectively maintained database that included all primary and redo hepatic resections for CRLM between 2000 and 2012. The data were retrospectively analysed, with additional information obtained from review of case notes and computerised medical records. Only patients with staging radiology (confirmed by dual reporting) demonstrating IPNs were included. The Fleischner Society's glossary of terms for thoracic imaging describes a pulmonary nodule as a rounded opacity, well or poorly defined, measuring up to 3 cm in diameter [12]. We used this definition in our study in addition to including all sub-centimetre lung lesions (regardless of morphology), which according to the RECIST criteria (response evaluation criteria in solid tumours) indicates a lesion is non-measureable and therefore equivocal [13]. Patients whose preoperative imaging suggested their lung lesion(s) were unequivocally metastatic (rather than indeterminate) were excluded. All other IPNs that fitted the above criteria were included and were assumed not to represent metastatic disease and hence their attempt at curative hepatic resection. Patients unexpectedly found to be inoperable at the time of surgery were also excluded. All images were subject to independent double reporting by specialist hepato-pancreatico-biliary (HPB) radiologists and had been discussed at the HPB multidisciplinary team meeting (MDT) where they were subject to systematic and robust peer-review.

Case-matched controls were then identified from within the same database for the purposes of comparison with the IPN group. Controls were selected on the basis of being matched to the cases by four primary factors: age, type of resection (primary or redo), clinical risk score (CRS) and chemotherapy, which we further sub-matched according to the specific clinical context(s) in which it was prescribed (neo-adjuvant for primary, adjuvant for primary, down-staging for metastatic disease or adjuvant for metastatic disease).

Data collection

All patients underwent intentionally curative hepatic resection at the same HPB surgical unit. The extent of resection was classified as minor (1–3 Couinaud segments) or major (>3). Patients were routinely followed up in outpatients and underwent surveillance CT imaging at a minimum of 6-month intervals for the first two years, and annually thereafter. Data were collected on the following parameters: patient demographics; primary tumour stage; CRS (see Table 1 for individual components) [14]; the administration of chemotherapy and their specific regimens; the date and extent of liver resection; histopathological information on resection margins; the date and site of disease recurrence; and dates of death if applicable. Overall survival (OS) and disease-free survival (DFS) were our two co-primary outcomes for the study and were, respectively, recorded as the number of days from date of hepatic resection to date of death or date last known alive, and from date of hepatic resection to date recurrent disease was first detected or date of last known disease-free follow-up.

Statistical analysis

Statistical analyses were performed using Statistical Package for the Social Sciences version 20.0® (SPSS,

Table 1 Hazard ratios by clinical variable

Variable	Disease-free survival HR (*p* value) [95% CI]	Overall survival HR (*p* value) [95% CI]
IPN present	2.010 (0.027) [1.081–3.739]	1.315 (0.423) [0.673–2.572]
Age >65 years	0.597 (0.122) [0.311–1.148]	0.662 (0.256) [0.325–1.349]
Chemotherapy		
Adjuvant for primary	0.738 (0.344) [0.393–1.386]	0.562 (0.168) [0.248–1.274]
Neo-adjuvant for metastases	1.252 (0.136) [0.931–1.683]	1.032 (0.888) [0.668–1.594]
Adjuvant for metastases	0.908 (0.747) [0.5041.635]	0.978 (0.948) [0.502–1.906]
CRS		
Node-positive primary	1.096 (0.768) [0.595–2.019]	0.748 (0.417) [0.371–1.509]
Disease-free interval <12 months	1.536 (0.192) [0.806–2.927]	1.875 (0.140) [0.814–4.316]
Largest met >50 mm	2.077 (0.066) [0.954–4.523]	2.096 (0.135) [0.794–5.538]
>1 met present	0.752 (0.594) [0.264–2.143]	3.403 (0.005) [1.438–8.053]
CEA >200	1.302 (0.795) [0.177–9.579]	1.390 (0.747) [0.187–10.329]
Total CRS ≥3	2.272 (0.007) [1.249–4.131]	2.491 (0.012) [1.218–5.094]
Major resection	1.339 (0.330) [0.745–2.447]	1.640 (0.149) [0.838–3.210]
Histologically clear margins (R0)	1.341 (0.339) [0.735–2.447]	1.290 (0.469) [0.648–2.566]

Chicago, Illinois, USA). The Chi-squared and Fisher's exact tests were applied to determine the presence of significant associations and differences between the two cohorts. Univariate Cox regression and Kaplan–Meier analyses were used to calculate the prognostic significance of clinical variables. All variables demonstrating a *p* value of less than 0.10 on univariate analysis were then entered into a multivariate analysis using Cox proportional hazard regression in a stepwise backward method. Statistical significance was defined as $p < 0.05$.

Results

The database from which the study population was recruited included 460 hepatic resections involving 366 individual patients. Twenty-eight patients undergoing either primary or redo hepatic resection for CRLM were identified with IPN on their preoperative imaging giving a prevalence rate of IPN of 7.7%. Twenty-eight corresponding matches without evidence of IPN were selected. The median age at surgery within the study population was 64 years, and the majority of the patients were male (66.1%). Statistical comparison of all clinical and pathological variables between the two cohorts demonstrated no significant differences, confirming that the groups were well matched (Table 2).

Table 2 Clinical variables by group

Variable	IPN group ($n = 28$)	No IPN group ($n = 28$)	*p* value
Male gender	20 (71.4%)	17 (60.7%)	0.397
Age >65 years	13 (46.4%)	13 (46.4%)	1.000
Chemotherapy			
Adjuvant for primary	9 (32.1%)	10 (35.7%)	0.778
Neo-adjuvant for metastases	11 (39.3%)	10 (35.7%)	0.783
Adjuvant for metastases	8 (28.6%)	14 (50.0%)	0.101
CRS			
Node-positive primary	17 (60.7%)	20 (71.4%)	0.397
Disease-free interval <12 months	16 (57.1%)	22 (78.6%)	0.086
Largest met >50 mm	6 (21.4%)	3 (10.7%)	0.469
>1 met present	18 (64.3%)	16 (57.1%)	0.584
CEA >200	0 (0.0%)	1 (3.6%)	1.000
Total CRS ≥3	12 (42.9%)	13 (46.4%)	0.788
Major resection	14 (50.0%)	11 (39.3%)	0.420
Histologically clear margins (R0)	9 (32.1%)	10 (35.7%)	0.778

Within the IPN group, a total of 25 (89%) patients developed disease recurrence. Seventeen (60.7%) patients demonstrated progression of their IPN as lung metastases. Within this subgroup, 12 (42.9%) patients had their recurrent disease confined to the lung, and 5 (17.9%) had synchronous liver and lung disease. Of these, seven underwent isolated pulmonary resections, four underwent consecutive redo liver and lung resections and six were treated with palliative chemotherapy. All the pulmonary metastasectomies were histologically proven to be metastatic colorectal cancer. Of the remaining 11 patients, 7 (25.0%) developed isolated liver recurrence (2 of whom underwent redo surgery), 1 (3.6%) developed brain metastases and 3 (10.7%) remained disease-free at the time of their last follow-up (Fig. 1).

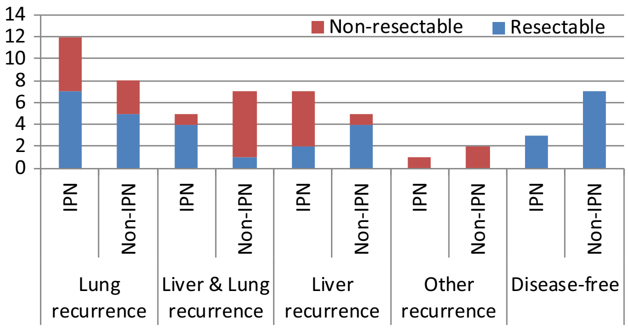

Fig. 1 Pattern of disease progression among the two cohorts

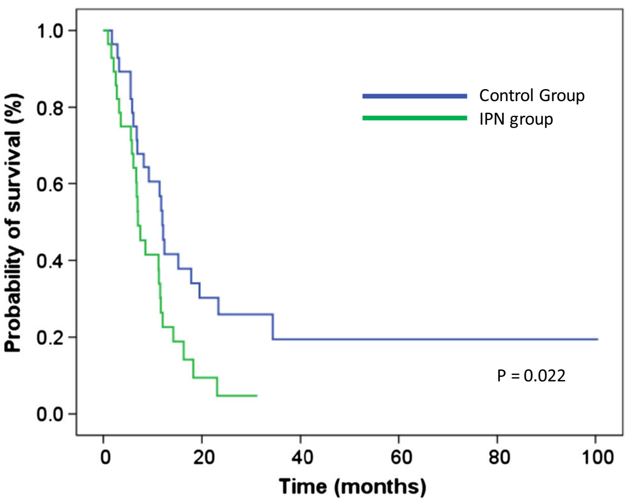

Fig. 2 Disease-free survival

Within the non-IPN group, 21 patients (75%) developed disease recurrence. Of these, 8 (28.6%) were pulmonary, 5 (17.9%) were hepatic, 6 (21.4%) were both pulmonary and hepatic and 2 (7.1%) were nodal. Of the solid organ metastases, there were five lung resections, four liver resections and one consecutive liver followed by lung. Seven patients (25%) remained clear of metastatic disease (Fig. 1).

The study population as a whole had a median DFS of 11.2 months (95% CI 7.1–15.3) and OS of 30.3 months (95% CI 22.9–37.7), with the overall 1-, 3- and 5-year survival rates calculated at 92.5, 34.7 and 13.0%, respectively. The median DFS and OS for the IPN cohort were 7.0 months (95% CI 4.8–9.2) and 28.6 months (95% CI 21.2–36.0), respectively. For the non-IPN cohort, the corresponding figures were 12.0 months (95% CI 10.7–13.2) and 30.5 months (95% CI 19.4–41.6). The 1-, 3- and 5-year survival rates for the individual cohorts were 92.7, 39.7 and 0.0% for the IPN group, and 92.4, 32.9 and 21.9% for those without. Log-rank analysis revealed DFS to be significantly

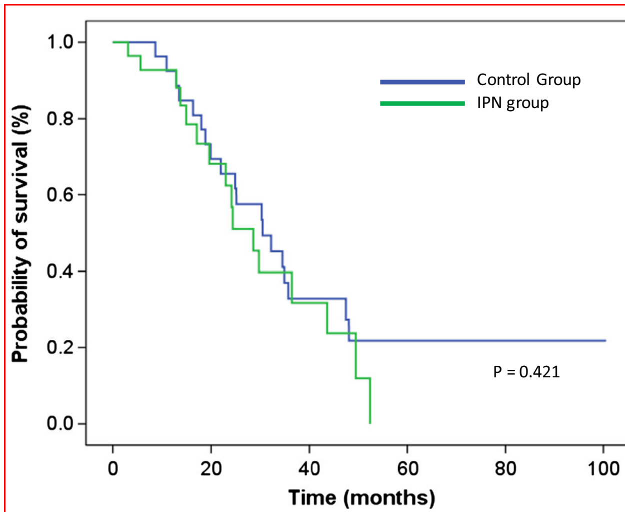

Fig. 3 Overall survival

worse in the IPN group ($p = 0.022$), but OS was not significantly different ($p = 0.421$) (Figs. 2, 3).

Cox regression univariate and multivariate analyses demonstrated the presence of IPN to be independently associated with a shortened DFS ($p = 0.027$). Additionally, a CRS of 3 or greater was also found to be an independently significant risk factor for both a shorter disease-free ($p = 0.007$) and overall ($p = 0.012$) survival (Table 1).

Discussion

The MDT approach to all cancers in the UK is well established and has been shown to both standardise and improve the quality of care for patients, especially for tumours requiring specialised input only available at regional tertiary centres [15]. Gold-standard practice demands that CRLM patients will have decisions about their most appropriate treatment modality, including determination of surgical suitability, made within this environment [15]. While current treatment strategies for CRLM would usually include a combination of surgery and chemotherapy, it is recognised that the only potentially curative option remains hepatic resection [5, 6]. Furthermore, surgical resection of colorectal pulmonary metastases has also been shown in selected cases to be successful and to confer a significant survival advantage [16]. A key part of the diagnostic and staging process is the MDT review of relevant images, allowing for the examination for possible extra-hepatic disease that may be amenable to radical resection itself, or conversely may preclude hepatic resection altogether and instead dictate a palliative approach.

The dilemma that the discovery of IPN on preoperative staging imaging produces is better recognised and has been the focus of a number of studies. The reported prevalence varies from 4 to 43%. Quyn and colleagues found IPN to be present in just 4% of their population and reported that 21% of these progressed to lung metastases within 2 years [17]. A similar prevalence rate (4.09%) but a higher rate of progression (30.9%) was found by Varol et al. [18]. Both of these studies found that an increased number of IPN was significantly predictive of progression, which was also supported by Griffiths' study [19], and Nordholm-Carstensen's systematic review which included almost 6000 patients of whom 9% had IPN and 10% of which developed metastatic disease [10]. With such a low risk (1%) for the overall population, they concluded that the presence of IPN should not trigger alteration of the routine preoperative workup or post-operative follow-up. Other studies have reported higher IPN prevalence rates of 10.3% [20], 16.3% [11], 26.3% [21], 27.2% [22] and as high as 43% by Maithel et al. [23].

In the present study, the prevalence rate of IPN was 7.7%, which is slightly lower than the largest study mentioned above [10]. However, this may be an underestimation of the true value for a number of reasons. Firstly, the population did not include all patients with CRLM, but just those deemed suitable for potentially curative resection. Secondly, patients with IPN who were found to be unresectable intra-operatively were excluded, regardless of the reason for inoperability. Thirdly, patients were also excluded in whom IPN were initially identified, but then had subsequent imaging prior to surgery which demonstrated more convincing characteristics of either a benign or malignant, rather than an indeterminate nature.

Previous studies on this subject comparing survival rates between patients with and without IPN have done so simply by examining the cohort of patients where IPN was identified. While the overall number of participants included in the present study is smaller, to our knowledge it is the first study that has attempted to identify a group of specifically matched controls without IPN for comparison. The importance of this is that it eliminates the potential confounding factors that would be present if the presence of IPN itself was indicative of more aggressive disease. This supposition is supported by the high recurrence rate observed among both cohorts and also the significantly worse DFS for the IPN cohort. The IPN were predominantly found among high-risk patients in our study, as evidenced by the fact that the case-matched patients without IPN had a higher than expected disease recurrence rate of 75%. Given the statistical similarity of the two groups, in addition to the significantly shorter DFS among the IPN group, this would suggest that the presence of IPN alone is a negative prognostic indicator. This is further substantiated by multivariate analysis revealing IPN to be independently associated with a shorter DFS.

Several of the studies discussed above looked at patients with colorectal cancer alone (without liver metastases) and focussed on analysing subsets of either the IPN or the primary tumour as predictive of malignant potential. Variables common to several studies found to be significantly associated with IPN progressing to metastatic disease were the presence of multiple nodules [10, 19–21] and regional lymph node metastases of the primary tumour [10, 21–24]. The patients included in the current study were recruited from a population who had all progressed to liver metastases, and therefore, the IPN may not necessarily have been present at the time of initial colorectal cancer staging. However, two-thirds of the population in the current study demonstrated regional lymph node positivity in the histology of their primary resection, which by the conclusions of these previous studies would automatically make them more likely to progress to metastatic disease. On the whole, a preoperative workup and post-operative surveillance other than routine are not advocated by these studies.

The lack of a significant difference in OS between patients undergoing hepatic resection with and without IPN demonstrated in the present study supports the findings of previous similar research looking specifically at patients with CRLM and IPN [11, 25]. However, neither of these studies found a significantly shorter DFS, which was in contrast to our results. Their common conclusion that hepatic resection should not be precluded by the presence of IPN logically follows, and the results of the present series would also support this. The use of the colorectal CRS as a prognostic indicator in patients with CRLM has long been established [14], and the significant association found by this study between a colorectal CRS of 3 or greater and both shorter DFS and OS is supportive of this. However, even these high-risk patients should not be deemed unresectable because of IPN alone. Gomez and colleagues advocate a more intensive post-operative surveillance regimen in all resected patients with IPN, the cornerstone of which is a PET scan at three months [11]. The shorter DFS that was present in our IPN patients suggests that a closer follow-up strategy of this nature may be worthwhile as it may enable earlier detection of potentially resectable lung metastases.

Conclusion

IPN are common in patients with CRLM, and currently no specific guidelines exist on their management, especially in patients with resectable hepatic disease. This study suggests that IPN do not significantly affect OS, but may be a predictor of earlier disease recurrence. IPN presence alone should not preclude radical resection but could be used to prompt more careful post-operative surveillance to detect lung metastases at a potentially operable stage. Further studies are warranted to investigate this.

Compliance with ethical standards

Conflict of interest None declared.

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