Research Article

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Hepatocellular cancer: The impact of obesity, type 2 diabetes and a multidisciplinary team

Jessica Dyson[1,†], Bryan Jaques[2,†], Dipankar Chattopadyhay[2,3], Rajiv Lochan[2], Janine Graham[4], Debasish Das[1], Tahira Aslam[5], Imran Patanwala[1], Sameer Gaggar[1], Michael Cole[3], Kate Sumpter[2,4], Stephen Stewart[1,6], John Rose[5], Mark Hudson[1], Derek Manas[2], Helen L. Reeves[1,2,3,*]

[1]*The Liver Group, Department of Medicine, Freeman Hospital, Newcastle-upon-Tyne Hospitals NHS Foundation Trust, UK;* [2]*Hepatopancreatobiliary Team, Freeman Hospital, Newcastle-upon-Tyne Hospitals NHS Foundation Trust, UK;* [3]*Northern Institute for Cancer Research, Newcastle University, Newcastle-upon-Tyne, UK;* [4]*Northern Centre for Cancer Care, Freeman Hospital, Newcastle-upon-Tyne Hospitals NHS Foundation Trust, UK;* [5]*Department of Radiology, Freeman Hospital, Newcastle-upon-Tyne Hospitals NHS Foundation Trust, UK;* [6]*Centre for Liver Disease, Mater Miscericordiae University Hospital, Dublin, Ireland*

See Focus, pages 1–2

Background & Aims: Hepatocellular cancer (HCC) commonly complicates chronic liver disease and increases in incidence have been reported despite falling prevalences of viral hepatitis.

Methods: Following the introduction of centralised specialist teams to manage patients with cancer in England, we characterised the demographics of patients with HCC referred to the Newcastle-upon-Tyne Hospitals NHS Foundation Trust between 2000 and 2010. Regional HCC mortality data was from Public Health England.

Results: HCC related mortality in the region rose 1.8 fold in 10 years, from 2.0 to 3.7 per 100,000. 632 cases were reviewed centrally, with 2–3 fold increases in referrals of patients with associated hepatitis C, alcoholic liver disease or no chronic liver disease and a >10 fold increase in HCC associated with non-alcoholic fatty liver disease (NAFLD). By 2010 NAFLD accounted for 41/118 (34.8%) cases. Irrespective of associated etiologies, metabolic risk factors were present in 78/118 (66.1%) cases in 2010, associated with regional increases in obesity and diabetes. Median overall survival was just 10.7 months. Although patients with NAFLD associated HCC were older (71.3 yr *vs.* 67.1 yr; p <0.001) and their cancers less often detected by surveillance, their survival was similar to other etiologies. This was attributed to significantly higher incidental presentation (38.2%) and lower prevalence of cirrhosis (77.2%).

Conclusions: HCC related mortality is increasing, with typical patients being elderly with metabolic risk factors. The prognosis for most of the cases is poor, but older patients with co-morbidities can do well, managed, within a specialist multidisciplinary team if their cancer is detected pre-symptomatically.

Cancer

Introduction

Historically, hepatocellular cancer (HCC) has accounted for less than 1% of cancer cases in the UK, although worldwide, HCC is the 4th commonest cause of cancer related death [1]. Geographical variations in incidence and mortality have largely reflected the prevalence of hepatitis B and C (HBV; HCV) viral infections associated with chronic liver disease (CLD). In regions of low viral prevalence, alcoholic liver disease (ALD) has been the predominant risk factor, although the increasing contribution of obesity related liver disease, namely non-alcoholic fatty liver disease (NAFLD), is suspected. Irrespective of etiology, HCC incidence and annual mortality data are remarkably similar owing to the lack of effective therapies for the vast majority. Over the last two decades, several life prolonging advances have been introduced for the management of patients with early and intermediate stage HCC, highlighting the need not only for earlier detection, but also accurate staging. Surgical resection or liver transplantation provides the opportunity for cure, while embolic and ablative therapies can extend survival [2]. The tyrosine kinase inhibitor sorafenib can prolong survival for patients with advanced HCC and well preserved liver function [3,4]. In the face of evolving treatment opportunities requiring careful application in the presence of co-existing liver disease, patient assessment and management increasingly require specialist multidisciplinary input.

Keywords: Non-alcoholic fatty liver disease; Hepatocellular cancer; Obesity; Type 2 diabetes; Multidisciplinary team.

Received 5 March 2013; received in revised form 29 July 2013; accepted 12 August 2013; available online 23 August 2013

☆ DOI of original article: http://dx.doi.org/10.1016/j.jhep.2013.10.003.

* Corresponding author. Address: Northern Institute for Cancer Research, Paul 'O Gorman Building, The Medical School, Framlington Place, Newcastle University, Newcastle-upon-Tyne NE2 4HH, UK. Tel.: +44 0191 2464423 (Work)/2137210 (Clinical Secretary).

E-mail address: H.L.Reeves@ncl.ac.uk (H.L. Reeves).

† These authors contributed equally to this work.

Abbreviations: NAFLD, non-alcoholic fatty liver disease; HCC, hepatocellular cancer; CLD, chronic liver disease; BCLC, Barcelona Clinic for Liver Cancer; ALD, alcoholic liver disease; HCV, hepatitis C; HBV, hepatitis B; PBC, primary biliary cirrhosis; AIH, autoimmune hepatitis; HPB, hepatopancreatobiliary; MDM, multidisciplinary meeting; OLTx, orthotopic liver transplant; BSC, best supportive care.

With the aims of improving cancer care across the nation and addressing regional variations in the quality of services delivered, the 'NHS Cancer Plan' was introduced in England by the Department of Health in July 2000 [5]. As a consequence, all patients with cancer should be referred to a regional specialist multidisciplinary meeting (MDM). In this study, we have explored HCC related mortality across the decade following the Cancer Plan 2000, characterising the cohort of patients with HCC referred to the regional hepatopancreatobiliary (HPB) MDM in Newcastle-upon-Tyne. In 2000 less than 10% of regional patients were referred to specialist services, increasing to over 85% by 2010. Regional mortality increased nearly 2 fold in this time frame and cohort analysis confirmed a relatively late stage of detection for the majority of patients. We also report the remarkable increase in the prevalence of the metabolic syndrome and type 2 diabetes mellitus (T2DM) in the cohort as a whole, with over a third of patients developing HCC on a background of non-alcoholic fatty liver disease (NAFLD).

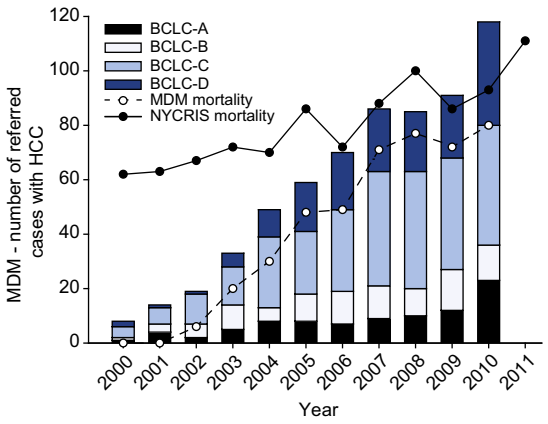

Fig. 1. Increasing HCC mortality and referrals to the regional multidisciplinary team between 2000 and 2010. Regional mortality increased 1.8 fold. By the end of the decade, referrals to the specialist MDM had markedly increased, with 86% concordance between regional and MDM reported mortality.

Patients and methods

Consecutive patients referred to the Newcastle-upon-Tyne Hospitals NHS Foundation Trust HPB MDM between the years 2000 and 2010 have been included. This HPB team served a stable population of approximately three million individuals in the North East of England, Cumbria and North Yorkshire and its weekly meeting was supported by an intranet secure clinical database on which data was prospectively collected. The presence of associated liver disease was determined on history, examination, liver screen and imaging. Patients classed as having NAFLD were men or women with evidence of a fatty liver on biopsy or imaging, with an otherwise negative liver screen, drinking <21 or <14 units of alcohol per week respectively for at least 5 years prior to their first presentation with liver disease. Patients were staged and managed according to the Barcelona Clinic for Liver Cancer (BCLC) model [2,6]. TNM, Child-Pugh, OKUDA, CLIP, and BCLC stages were documented, as were demographic and clinical parameters, mode of detection/presentation, ECOG performance status, treatments offered and survival. Data were interpreted alongside regional HCC mortality data, provided by Northern and Yorkshire Cancer Registry and Information Service (NYCRIS) (http://www.nycris.nhs.uk). The study was registered with the hospital trust audit department and cases were followed until 30/06/2013, defining a minimum period of 2.5 years post diagnosis.

Statistical analyses

All statistical analyses were done with SPSS for Windows, version 14 (SPSS Inc. Chicago Illinois, USA), licensed to Newcastle University. Associations were explored by linear regression, with differences between groups of continuous variables assessed by *t*-test (parametric data) or Kruskal Wallis (non-parametric data) tests. Differences between categorical variables were assessed by Pearson Chi square, or Fisher's exact tests approximated using a Monte Carlo approach where cells within a contingency table of greater than 2×2 contained low numbers (<5). A p value of <0.05 was considered significant. Survival was recorded as months from diagnosis to 30/06/2013. Differences in cumulative survival were determined using the Kaplan-Meier method and a Log-Rank test. The Cox proportional hazards-regression model was used to identify parameters associated with survival. Factors initially considered by univariate analysis included age, mode of presentation, gender, body mass index (BMI), number of tumours, size of largest tumour, serum alpha-fetoprotein (AFP), serum albumin, serum bilirubin, clotting (INR), serum sodium, serum creatinine, performance status, primary treatment, associated etiology, as well as the presence of T2DM, metabolic risk factors, cirrhosis, extrahepatic disease, portal vein thrombosis (PVT), ascites, encephalopathy, or constitutional symptoms. A cut-off of p <0.01 was used to select variables entered into the multivariate model.

Results

The increasing regional burden of HCC

In the last decade, 632 patients with a diagnosis of HCC confirmed either radiologically in the presence of cirrhosis, or by liver biopsy, were managed by the Newcastle MDM. The numbers of cases referred per year increased steadily in that time frame, from just 8 patients in 2000 to 118 patients in 2010 (Fig. 1). To estimate the relative contributions of rising incidence and the success of Cancer Plan 2000 initiated change in referral practice, we compared mortality data within the regional catchment area provided by NYCRIS to that within the MDM cohort. These data (Fig. 1) support both contributing factors, with a 1.8 fold increase in regional mortality (rising from 2.0 to 3.7 per 100,000) and >10 fold increase in patients referred. The initially low mortality within the MDM cohort raised the possibility of referral bias, thus age and stage at presentation were explored. The average age of the patients referred rose from a median of 57.0 years in 2000, to 69.9 years in 2010 (Pearson correlation 0.183; p <0.001), although the proportions of the patients with early, intermediate or advanced disease did not change significantly, as demonstrated by the breakdown according to BCLC stage (Fig. 1) (Pearson Chi square $p = 0.478$). Thus, there was an increase in referral of patients with all BCLC stages of disease, including those considered curative (Stage A; 89 cases, 14.1%), those considered fit but with more advanced disease (Stage B; 95 cases, 15.0%), as well as those with symptomatic disease (Stage C; 284 cases, 44.9%) and very symptomatic or advanced disease suitable only for best palliative supportive care (Stage D; 164 cases, 26.0%). Despite the lack of change in BCLC stage, treatments offered have changed in 10 years, as summarised in Table 1.

The choice of first line therapy in an aging population with HCC

In the year 2000, of the 8 patients referred, 6 received an orthotopic liver transplant (OLTx). While the actual numbers transplanted per year remained constant, proportionately this represented 75% in 2000 *vs.* just 5.9% in 2010. Although the increase in age and associated co-morbidity likely limited the role of transplantation for patients referred in later years, supporting early referral bias, what increased markedly, rather than the numbers of patients transplanted, was the median time spent on the transplant waiting list, rising from 150 days in the year 2000 to 350 days in 2010. Consequently, the numbers of patients removed from the waiting list because of HCC progression or deteriorating fitness also increased. While patients transplanted