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ORIGINAL ARTICLE

Increasing survival of hepatocellular carcinoma patients in Scotland: a review of national cancer registry data

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Abstract

Objectives: This study describes changes in the survival of patients with hepatocellular carcinoma (HCC) registered with the Scottish Cancer Registry between 1985 and 2008.

Methods: Data on patients diagnosed with HCC were extracted from the Scottish Cancer Registry, along with linked data on treatment and risk factors for liver disease. One-, 3- and 5-year relative survival rates were calculated for each time period and a Cox regression model was used to assess the impact of prior admissions on survival.

Results: The incidence of HCC increased between 1985 and 2008. The proportion of patients with prior alcohol-related admissions rose over the time period studied from 16.0% to 27.1%. Five-year relative survival increased in women between 1985–1989 and 2005–2007 from 0.5% [95% confidence interval (CI) 0.0–3.7] to 10.6% (95% CI 5.2–18.1). In men, 5-year relative survival increased from 0.4% (95% CI 0.2–2.2) to 4.4% (95% CI 1.5–9.9). Regression analysis showed that older age, history of alcohol-related admissions and deprivation were associated with lower survival, and hospitalization for viral hepatitis was associated with higher survival.

Conclusions: Against the background of an increasing incidence of HCC in Scotland, survival times have increased substantially.

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Introduction

The annual incidence of and mortality associated with primary hepatic malignancy in the UK has increased over the past two decades.[1,2] This is thought to have resulted largely from increasing hepatitis C infections and rising rates of harmful alcohol consumption, both of which exist in the context of an increasing obesity problem.[3] Certainly, primary hepatic malignancy is an increasingly important public health problem and has become one of the 20 most frequent cancers in the UK and the 10th most common cause of death by cancer in men in Scotland.[1,2] Rising trends in primary liver cancer are not exclusive to the UK. In the USA, liver and bile duct cancer rose from 14th place in 1990 to ninth in 2005 in terms of its contribution to annual cancer-related deaths.[4]

Prior analyses have shown that survival in primary liver cancer is low; 1-year survival in Scotland was 10% between 1985 and 1990.[5] Two major changes in clinical practice may have affected survival in primary liver cancer over the past two decades: an increasing range of treatments for unresectable disease, and increased surveillance for early-stage disease.[6] Advances in chemoembolization, ablation and surgical resection techniques have been shown to improve the prospects of surviving this disease considerably.[7,8] Although curative rates for these treatments are still low, these procedures have improved the ability to retain liver tissue and thus function. Furthermore, transplant surgery has advanced significantly and the identification of those patients most likely to benefit from liver replacement has resulted in better outcomes.[9]

This study reviews Scottish cancer registrations of hepatocellular carcinoma (HCC) linked with hospital admissions and death

data to determine trends in survival and factors influencing survival.

Materials and methods

Cases of cancer in Scotland are registered through a comprehensive system that collects data from several sources. These are combined to create a single case registration based on the primary cancer type. Data are collected from pathology, radiotherapy, oncology, neuro-oncology and haematology departments. Further data are collected from the national databases of hospital admissions, screening programmes, prospective cancer audits and death registrations. These records are linked by probability matching and merged to create a single record for each cancer diagnosis, which is linked to hospital admissions. Patients seen in private care are also registered on this system.

Individuals aged > 20 years who were registered with a diagnosis of primary liver cancer between 1 January 1985 and 31 December 2008 were selected. These included all patients coded with ICD-9 code 155.0, ICD-10 code C22.0 and corresponding morphology codes ICD-O(1–3) 8170–8176.[10] Patients with cholangiocarcinoma [ICD-9 155.1, ICD-10 C22.1 and morphology codes ICD-O(1–3) 8050, 8140–8141, 8160–8161, 8260, 8440, 8480–8500, 8570–8572] were excluded from the analysis of survival, as were patients with unknown morphology in view of the high risk for misclassifying secondary tumours. Patients who were identified by death certificate only (DCO) were also excluded. Patients without histological verification were included in the analysis.

Information on tumour morphology, registration type, age at diagnosis, gender and postcode was extracted from the cancer registry data. Data on hospital admissions (within the 5 years prior to diagnosis) for liver cirrhosis, primary biliary cirrhosis, haematochromatosis, viral hepatitis, diabetes and ischaemic heart disease were extracted from the electronic database of hospital admissions (SMR01). Data on diabetes and ischaemic heart disease were extracted to give a measure of the impact of non-alcoholic fatty liver disease (NAFLD) on disease risk. Alcohol-related diseases were selected according to the predefined list of conditions used by the Information Services Division's substance misuse team, which have been published elsewhere.[11] The cancer registry has no information on tumour staging of liver cancers and thus a proxy for disease severity was devised; patients with an admission to hospital for metastatic disease (ICD-10 codes C77, C78, C79 and ICD-9 codes 196, 197, 198) within 4 weeks of diagnosis were defined as having more severe disease. At present, no data on primary liver malignancies are collected from screening or prospective cancer audits by the Scottish Cancer Registry. Socioeconomic deprivation was measured using the Scottish Index of Multiple Deprivation, a geographic indicator based on 37 indicators across income, employment, health, education, skills and training, geographic access, crime and housing.[12]

The hospital admissions database (SMR01) contained information on procedures and operations. These data were extracted to identify those individuals who had undergone resection or transplantation. The coding was unable to distinguish between patients treated with ablation and chemoembolization, respectively, and these were coded into a category referred to as 'non-resection treatments'.

The cohort of patients with HCC was divided according to periods of diagnosis and the proportions of patients with each risk factor were calculated within these categories.

Age-standardized incidence rates were calculated by sex using the European standard population. Date and cause of death were extracted from the linked data on death certifications. Relative survival rates were calculated for 1 year, 3 years and 5 years for the population diagnosed between 1985 and 31 December 2007 using the 'strel' program developed by the London School of Hygiene and Tropical Medicine (LSHTM) for calculating relative survival with the statistical analysis program STATA (StataCorp LP, College Station, TX, USA).[13,14] Relative survival is a measure of survival based on the ratio of observed to expected survival for that age group and location. Expected mortality rates are based on actuarial life tables compiled by the General Register Office for Scotland (now part of National Records of Scotland) and converted into a STATA format by the LSHTM. Right-hand censor date was limited to the end of 2007 because life tables for the strel program were not available for the years 2008 and 2009. STATA Version 11 was used for all other statistical analyses.

The relationship between risk factors and cancer-specific survival was calculated using Cox regression for patients diagnosed between the years 1997 and 2008. These years were selected as data on treatment were available from 1997, when regional cancer registries in Scotland were centralized. The proportional hazards assumption was tested using the sphtest program based on Schoenfield residuals, and violation of the proportional hazards assumption was assumed at $P < 0.05$. Survival dates were right-hand censored at 31 December 2008. Cancer-specific deaths were those defined as any death by neoplasm (ICD-9 codes 140–239 and ICD-10 codes C00–D48). All deaths by other causes were treated as right-hand censored at the date of death.

Results

Of the initial dataset of 5846 primary cancers, 264 (4.5%) were DCO diagnoses and were excluded from analysis. During the 23-year study period, 2802 patients were diagnosed with HCC as defined by topography and morphology code. The proportion of histologically verified registrations of HCC was 80.6%, but this fell to 42.5% over the study period (Table 1). The remainder of the registrations referred to cholangiocarcinoma, were of non-specific morphology or had a mixed topography and morphology (i.e. topography of biliary cancer with a morphology code for HCC).

The annual age-standardized incidence of HCC increased between 1985 and 2008 (Fig. 1). In 1997, a temporary rise in registrations coincided with the centralization of the regional registries into a single national registry. The rate of increase rose