Title: Trends in relative survival of patients diagnosed with hepatocellular carcinoma: A population-based cohort study

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Abstract

Background: Hepatocellular carcinoma (HCC) incidence and mortality continues to increase globally. However, the population-level impact on survival has been challenging to assess. Our objectives were to estimate the relative survival of HCC patients in Ontario, Canada over time and to examine potential factors associated with excess mortality risk.

Methods: A retrospective cohort study of patients diagnosed with HCC in Ontario, Canada, from 1990-2009 was performed using Ontario Cancer Registry (OCR) data. Standardized mortality ratios (SMRs) were calculated using observed deaths from the OCR and expected deaths from Ontario life tables. Relative survival was estimated by controlling for background mortality. A generalized linear model was used to estimate the excess mortality risk for important factors.

Results: 5,645 patients were diagnosed with HCC over the study period of which 78% were males. The SMR for both sexes was highest during 1990-1994 (F:29.3 95%CI 18.7-39.9; M:19.6, 95%CI 10.9-28.3), but decreased by 2005-2009 (F:16.6 95%CI 8.6-24.6; M:14.3, 95%CI 6.9-21.8). Significant improvements were observed for 1-year relative survival across all age groups over the study period; the highest was among those diagnosed at age <60 years during 2005-2009. Overall, the 5-year relative survival did not exceed 28%, however. The excess mortality risk decreased with increased years of follow-up, recent diagnosis, and curative or non-curative HCC treatments, while increased with age.

Interpretation: Although improving, the prognosis for HCC remains poor. Our findings highlight the importance of prevention and treatment of HCC to reduce the burden of disease and improve the healthcare systems and society.

Introduction

Liver cancer is the sixth most common cancer and third most frequent cause of cancer-related death worldwide.[1] Hepatocellular carcinoma (HCC) represents more than 80% of primary liver cancers and is an increasing public health concern. It is among the fastest growing cancers in Canada,[2-4] with incidence rates increasing for both females (2.2% per year) and males (3.4% per year) over the past 30 years.[2,3] Although screening and treatment options for HCC have advanced, a minority of patients are treated early,[5] with treatment often initiating at advanced stages of disease.[6] Survival after HCC diagnosis is poor, with a 5-year survival estimate of approximately 7%.[6] However, studies have shown that with early diagnosis and treatment, 5-year survival can be improved by more than 50%.[7-18]

Cancer survival estimates are often complicated by other causes of mortality. Identifying definitive cancer-associated mortality can be challenging and relies on accurate information regarding patient cause of death.[19,20] The issue is further confounded by the question of whether treatment-associated mortality should be attributable to the disease, an issue not often addressed with mortality estimates.

One solution is the use of relative survival methodology, which focuses on the population burden of mortality from a specific cancer by comparing survival among cancer diagnosed patients to an otherwise similar general population known not to have cancer.[19-23] The advantage of this methodology is that mortality both directly and indirectly attributable to cancer can be accounted for.[19-21] Relative survival analysis is useful for identifying the extent to which advances in cancer treatments have impacted the disease at a population level, as it places changes in survival in the context of population level change.[24] The objectives of this study are to estimate the relative survival of patients diagnosed with HCC in Ontario, Canada over a 20-year period and to examine potential factors associated with excess mortality risk.

Methods

Study design and population

A retrospective cohort study of all eligible patients diagnosed with HCC in Ontario, Canada, between January 1, 1990 and December 31, 2009 was conducted. The Ontario Cancer Registry (OCR)[25] was used to create the study cohort. The OCR captures approximately 95% of all diagnosed cancer cases in Ontario and has been shown to be both highly accurate and reliable.[26,27] The International Statistical Classification of Diseases and Related Health Problems, 9th Revision (ICD-9) site code 155.0 was used to identify primary hepatic neoplasms in addition to the International Classification of Diseases for Oncology, Third Edition (ICD-O-3) histology codes 8170-8175. HCC patients were followed from the date of their diagnosis to the date of their death, or until the end of the study period December 31, 2010. Patients were excluded if they were diagnosed with HCC on the same day they died.

Ethics approval for the study was granted by the University of Toronto Health Sciences Research Ethics Board.

Outcome measure

The analyses focused on the relative survival of HCC patients, which is the ratio of survival in patients diagnosed with HCC (i.e. observed survival) compared to the survival from the Ontario general population (i.e. expected survival) accounting for background mortality.[19,20] The secondary outcome was the relative excess hazard ratios (HRs) for mortality (excess mortality risk) to examine the impact of the potential prognostic factors.

Study variables

The OCR includes information on age at diagnosis, gender, date of diagnosis, cause of death, and date of death. Date of HCC diagnosis and date of death were ascertained from the OCR to calculate the length of survival after diagnosis. The OCR cohort was linked to health administrative data to assess baseline Charlson-Deyo Comorbidity Index (CCI) using the hospitalization record at diagnosis date from the Canadian Institute for Health Information Discharge Abstract Database[28] and considering two years before diagnosis if cases did not have a hospitalization record at diagnosis date.[29,30] The CCI was calculated using the methods described by Charlson *et al*.[31] and Deyo *et al*.,[32] applying an ICD-9 coding algorithm to the diagnostic field codes from the hospitalization data (excluding diagnoses for liver disease and metastatic cancer). Conditions were weighted and then summed up to provide an overall CCI for a given episode, which was then categorized into one of five groups (CCI of 0, 1, 2, ≥3, or no hospitalization record) representing different degrees of comorbidity. HCC treatments considered were: potentially curative treatment (i.e. liver resection, liver transplant, or radiofrequency ablation); non-curative treatment (i.e. chemotherapy or transarterial chemoembolization); palliative care; and no treatment. We have used these definitions of comorbidity and HCC treatments in our previous studies.[29,30] Codes used to identify HCC treatments can be found in Appendix Table A1.

Statistical analysis

Standardized-mortality-ratios

Standardized-mortality-ratios (SMRs) were calculated using observed deaths from the OCR and expected deaths from Ontario life tables (1990-2010).[33] SMRs were estimated by year of diagnosis (1990-1994, 1995-1999, 2000-2004, and 2005-2009) and age at diagnosis (<60, 60-69, 70-79, and ≥80 years) for both sexes. The percent change for each time period was calculated using the previous time period as the comparator.

Relative survival analysis

Relative survival estimates for 1-year and 5-year survival, by year of diagnosis, age at diagnosis, and gender were estimated by comparing the actual survival of patients diagnosed with HCC to that expected in the Ontario general population using the methodology described by Dickman *et al*.[21] Expected survival estimates were calculated for a cohort of patients diagnosed with HCC from the Ontario general population life tables[33] matched by year of diagnosis, age at diagnosis, and gender using the Ederer II method[34]—considering the matched individuals to be at risk until the corresponding cancer patient died or was censored. Survival estimates were calculated as a ratio and expressed as a percentage, and considered significantly different if the 95% confidence intervals (CIs) did not overlap.

A period analysis approach was also used to estimate 5-year relative survival for those diagnosed in 2005-2009 and those who were diagnosed earlier but were alive on January 1, 2005. Partial survival probabilities for each year of diagnosis during the most recent period (2005-2009) with available follow-up data were combined for this analysis[35-38] with the advantage of better survival estimates for newly diagnosed patients.[35-37]

Regression modelling of relative survival

A generalized linear model was used with a Poisson error structure to estimate the adjusted effect of the potential prognostic covariates (including year of diagnosis, follow-up year after diagnosis, age at diagnosis, gender, CCI, and HCC treatments) on the relative excess mortality risk.[21] The hazard function at any given time after diagnosis was modelled as the sum of the expected hazard from the general population (Ontario life tables) and the excess hazard from an HCC diagnosis.[21] The hazard was assumed to be piecewise constant hazards for each year. Survival data was collapsed in order to

allow for standard regression diagnostics to be performed.[21] A p-value of <0.05 was considered statistically significant. Interactions were considered between age at diagnosis and gender, year of diagnosis, follow-up after diagnosis, CCI and HCC treatments to allow changes in excess hazard after diagnosis to vary across age groups.[21] The interactions between age at diagnosis and gender, year of diagnosis and palliative care were found to be significant and they were used in the model. We evaluated the model goodness-of-fit using the deviance statistic, with the value divided by the degrees of freedom close to 1 (>0.85 and <1.5) being considered a reasonable fit.

Results

Standardized-mortality-ratios

Table 1 summarises the number of HCC-diagnosed patients by year of diagnosis, gender, and age at diagnosis along with the SMR and period percent changes. Further patient demographics are summarised in Appendix Table A2. Between 1990 and 2009, there were 5,645 patients diagnosed with primary HCC, with a 3-fold increase in the number of cases over time for both sexes, peaking in the 2005-2009 period. The majority of patients were male (78.2%) and most HCC cases were diagnosed at age ≥70 years for females (46.1%), and <60 years for males (35.8%). Overall, the SMR for both sexes was highest during 1990-1994 and decreased moderately thereafter.

Relative survival

The 1-year and 5-year relative survival estimates after HCC diagnosis are summarised in Table 2. For both sexes, there were significant improvements in the 1-year relative survival for all age groups when comparing 1990-1994 to 2005-2009 (Figures 1). 1-year relative survival of females was not significantly higher than the 1-year relative survival of males (Figure 2). The highest 1-year

survival for females was 70.9% (95% CI: 62.2, 78.0%) compared to 56.9% (95% CI: 53.2, 60.5%) for males, both of which correspond to those diagnosed at age <60 years during 2005-2009.

During 1990-1994, females diagnosed at age <60 years had a significantly higher 5-year relative survival of 17.4% (95% CI: 9.5, 27.5%) compared to males whose survival was 7.1% (95% CI: 3.8, 11.8%). Over time, the 5-year survival for males diagnosed at age <60 years saw significant improvements; in addition, significant improvements were seen in those diagnosed at age 60-69 and 70-79 years in the period of 2005-2009 when compared to 1990-1994. However, for females, a significant improvement was seen in those diagnosed at age ≥80 years in the periods of 2000-2004 and 2005-2009 when compared to 1990-1994. There were no significant differences in the relative survival estimates between the cohort analysis and period analysis for 2005-2009 (Figure 3), as well as no significant differences between males and females. Overall, the 5-year relative survival did not exceed 28% for either sex.

Relative excess hazard ratios for mortality

Model 1 in Table 3 shows the adjusted effect of the prognostic covariates on the relative excess mortality risk and Model 2 in Table 4 shows the same covariates but with the interaction terms. For Model 1, with the exception of gender (p=0.433) and age at diagnosis (overall p=0.08), all covariates were significant (p<0.001). Subsequent periods after 1990-1994 were associated with a protective relative excess mortality risk indicating decreased risk over time compared to 1990-1994; >1 year follow-ups after diagnosis were significantly associated with a decreased risk compared to 1 year after diagnosis; and HCC treatments (curative and non-curative) were associated with a decreased risk. Palliative care and no treatment were associated with an increased risk. CCIs >1 were associated with a protective relative risk of mortality likely representing patients who lived longer and thereby accumulated a greater maximal comorbidity score.[29]

In Model 2 (Table 4), interactions between age at diagnosis and gender (overall p=0.009), year of diagnosis (overall p=0.003) and palliative care (overall p<0.001) were found to be significant using the likelihood ratio Type 3 analysis, and all covariates with the exception of gender were also significant. Like Model 1, subsequent periods after 1990-1994, >1 year follow-ups after diagnosis, and curative and non-curative treatments were significantly associated with a protective relative excess mortality risk. For both sexes, being diagnosed at increasing age (≥70 years) was associated with an increased relative excess mortality risk when compared to those diagnosed at age <60 years. Both models seemed reasonable with the value/degrees of freedom close to 1. For Model 1, the value was 3901.73 and the degrees of freedom for the residuals were 2851. For Model 2 with the interaction term, the deviance was 3844.21 and the degrees of freedom for the residuals were 2836.

Interpretation

This study attempted to estimate the relative survival of patients diagnosed with HCC between 1990 and 2009 in Ontario, Canada. The results indicate significant improvements in 1-year relative survival by 2005-2009 using the period of 1990-1994 as a reference. One-year survival was highest amongst those diagnosed at age <60 years in the period of 2005-2009, with survival exceeding 50% for both sexes; however, 5-year relative survival improvements were minimal, with significant improvements occurring only for males diagnosed at age 60-69 and 70-79 years. The 5-year relative survival in both sexes never exceeded 28%. This is concerning from a population perspective because the frequency of new HCC cases is expected to continue to increase due to hepatitis C viral control challenges and aging of the Canadian population.[4]

When compared to the 5-year relative survival estimates for primary liver cancer in Canada during 2006-2008 made by the Canadian Cancer Society (CCS),[4] our estimates for both sexes age

≥80 years in Ontario were slightly higher. CCS estimates for 5-year relative survival for females diagnosed at age 60-69, 70-79, and 80-99 are 21.0% (95% CI: 15.0, 28.0%), 12.0% (95% CI: 7.0, 18.0%), and 7.0% (95% CI: 3.0, 13.0%), respectively.[4] In comparison, our estimates during 2005-2009 were 19.9% (95% CI: 12.4, 28.7%), 12.2% (95% CI: 6.7, 19.6%), and 8.2% (95% CI: 2.0, 21.3%), respectively. A similar pattern was present for males. These divergences may be attributable to differences in the data sources as well as slightly different time periods used. In addition, the estimates made by the CCS were done utilising data from the Canadian Cancer Registry and the Canadian Vital Statistics Death database.[4] CCS estimates account for all of Canada (except Quebec), whereas our analysis was limited to Ontario cases. Differences in our study are consistent with findings for other highly fatal cancers that show survival rates biased towards higher values in Ontario (Diane Nishri, Cancer Care Ontario, personal communication), presumed to be related to lost follow-up; however, cancers with a poorer prognosis tended to be associated with relatively small differences.[39]

The other major aspect of this study is estimating the impact of common covariates on the relative excess mortality risk. Being diagnosed at a later age was significantly associated with an increased relative excess mortality risk. A long-term follow-up after diagnosis and curative treatment were significantly associated with the most protective relative excess mortality risk.

This study is particularly relevant when considering the 5-year relative survival of non-hepatic cancers in Canada. For example, studies by Coleman *et al*.[33,38] estimated the 5-year relative survival for breast cancer in Ontario from 1990-1999 to be 81.6% (95% CI: 80.9, 82.3%). For other cancers such as colon, rectum, and colorectal, the 5-year relative survival in Ontario ranged from 51.0% to 59.1%.[38,40] Routine analysis and documentation of cancer survival is necessary to identify successes and failures of medical intervention and to expose disparities in care that can be addressed and these interventions continue to evolve.

Limitations

There are some limitations in the data used in this study. Data from the OCR only included cancer staging sub-categorization from 2004 onwards; however, more complete cancer staging is available only in recent years. Therefore we did not include cancer staging in this study. This is an important limitation as successful treatment of HCC is dependent on the stage at which treatment is initiated.[29,41] Additionally, behavioural factors that impact disease course and treatment decisions[3,42] such as alcohol use and body-mass index were not accounted for.[3,39] Finally, small sample size may lead to unstable survival estimates for the age at diagnosis group ≥70 years. We performed a sensitivity analysis to estimate relative survival, merging age at diagnosis 70-79 and ≥80 years; however, there were no significant differences from the initial results (see Appendix Table A3).

Conclusion

The results of this study show that while survival has improved, the prognosis for HCC remains poor. Due to the expected increase in HCC cases in the coming years and the high cost of care, investments may be best directed toward early detection through screening and surveillance efforts. The modest improvement seen may be accounted for by treatment of disease detected early in its course. Indeed, significant advances in therapeutic interventions such as radiofrequency ablation, liver transplant, and small molecule tumour inhibitors (sorafenib) is also likely contributing to improved outcomes amongst HCC patients. In an approaching era of safe, highly effective interferon-free directly acting antiviral therapies and a treatment time that may reduce with tolerable side effects, many barriers to treatment of hepatitis C, a major cause of the increasing incidence of HCC, will likely fall. With the perspective of more effective antiviral therapies, the potential of

future therapeutic strategies to prevent progression of liver disease and its associated health and economic burden is considerable.

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Table 1. Number of hepatocellular carcinoma cases, standardized-mortality-ratios, and period percentage changes by sex, year of diagnosis, and age at diagnosis

Year of Diagnosis	Female		Male	
	N (%)	SMR (95% CI) [% change]	N (%)	SMR (95% CI) [% change]
Total	**1233 (100.00)**		**4412 (100.00)**	
1990-1994	177 (14.36)	29.30 (18.69, 39.90) [N/A]	541 (12.26)	19.59 (10.91, 28.26) [N/A]
1995-1999	229 (18.57)	19.75 (11.04, 28.46) [-32.59]	820 (18.59)	15.39 (7.70, 23.08) [-21.42]
2000-2004	352 (28.55)	18.09 (9.75, 26.42) [-8.43]	1229 (27.86)	14.95 (7.37, 22.53) [-2.87]
2005-2009	475 (38.52)	16.61 (8.62, 24.60) [-8.15]	1822 (41.30)	14.34 (6.92, 21.76) [-4.07]
Age at Diagnosis				
<60 years, N (%)	**320 (100.00)**		**1580 (100.00)**	
1990-1994	62 (19.38)	126.84 (104.77, 148.92) [N/A]	167 (10.57)	92.62 (73.76, 111.48) [N/A]
1995-1999	56 (17.50)	92.1 (73.29, 110.91) [-27.39]	262 (16.58)	76.59 (59.44, 93.74) [-17.31]
2000-2004	77 (24.06)	110.51 (89.91, 131.11) [19.99]	468 (29.62)	58.07 (43.13, 73.00) [-24.18]
2005-2009	125 (39.06)	86.84 (68.57, 105.10) [-21.42]	683 (43.23)	63.95 (48.27, 79.62) [10.12]
60-69 years, N (%)	**345 (100.00)**		**1307 (100.00)**	
1990-1994	57 (16.52)	41.67 (29.02, 54.32) [N/A]	213 (16.30)	22.13 (12.91, 31.35) [N/A]
1995-1999	73 (21.16)	29.62 (18.95, 40.29) [-28.92]	266 (20.35)	23.35 (13.88, 32.82) [5.50]
2000-2004	102 (29.57)	36.08 (24.31, 47.85) [21.81]	349 (26.70)	23.32 (13.85, 32.78) [-0.11]
2005-2009	113 (32.75)	37.76 (25.72, 49.80) [4.66]	479 (36.65)	23.20 (13.76, 32.64) [-0.50]
70-79 years, N (%)	**399 (100.00)**		**1196 (100.00)**	
1990-1994	38 (9.52)	26.32 (16.27, 36.38) [N/A]	133 (11.12)	11.78 (5.05, 18.51) [N/A]

1995-1999	79 (19.80)	19.54 (10.87, 28.20) [-25.78]	244 (20.40)	9.36 (3.36, 15.36) [-20.56]
2000-2004	132 (33.08)	16.83 (8.79, 24.87) [-13.88]	334 (27.93)	9.25 (3.29, 15.21) [-1.16]
2005-2009	150 (37.59)	16.38 (8.45, 24.31) [-2.66]	485 (40.55)	10.38 (4.06, 16.69) [12.16]
≥80 years, N (%)	**169 (100.00)**		**329 (100.00)**	
1990-1994	20 (11.83)	8.71 (2.92, 14.49) [N/A]	28 (8.51)	6.99 (1.81, 12.18) [N/A]
1995-1999	21 (12.43)	5.62 (0.98, 10.27) [-35.43]	48 (14.59)	4.71 (0.46, 8.96) [-32.66]
2000-2004	41 (24.26)	5.83 (1.10, 10.56) [3.63]	78 (23.71)	5.19 (0.73, 9.66) [10.28]
2005-2009	87 (51.48)	7.59 (2.19, 12.99) [30.31]	175 (53.19)	4.75 (0.48, 9.02) [-8.53]

SMR, standardized mortality ratio; CI, confidence intervals; N/A, not applicable.

Table 2. Relative survival after diagnosis of hepatocellular carcinoma by sex, year of diagnosis, and age at diagnosis

Year of Diagnosis	Age at Diagnosis (years)	Cases (N)	Events (N)	1-year Relative Survival % (95% CI)	5-year Relative Survival % (95% CI)
			Cohort Analysis		
			Female		
1990-1994	<60	62	48	38.27 (27.09, 49.35)	17.44 (9.45, 27.48)
	60-69	57	49	28.97 (18.74, 40.01)	11.01 (4.92, 19.95)
	70-79	38	37	14.42 (7.23, 24.02)	0.43 (0.01, 4.34)*
	≥80	20	20	7.46 (2.08, 17.71)	0.09 (0.00, 0.99)
1995-1999	<60	56	38	49.19 (36.10, 61.04)	25.92 (15.10, 38.17)
	60-69	73	56	54.51 (43.21, 64.52)	19.28 (11.28, 28.99)
	70-79	79	72	22.54 (15.33, 30.64)	6.14 (2.31, 12.78)
	≥80	21	19	25.32 (11.97, 41.55)	10.12 (1.89, 29.03)
2000-2004	<60	77	56	51.77 (40.65, 61.79)	20.44 (11.90, 30.62)
	60-69	102	80	42.00 (32.85, 50.89)	17.61 (10.75, 25.94)
	70-79	132	119	47.34 (38.54, 55.69)	9.78 (5.21, 16.16)
	≥80	41	37	41.72 (27.49, 55.76)	12.29 (3.48, 28.69)
2005-2009	<60	125	65	70.93 (62.18, 78.03)	27.69 (18.27, 37.93)
	60-69	113	81	54.27 (44.83, 62.80)	19.36 (11.87, 28.29)
	70-79	150	120	51.52 (43.41, 59.08)	12.91 (7.38, 20.15)
	≥80	87	81	40.81 (30.38, 51.17)	4.85 (0.83, 15.62)
			Male		
1990-1994	<60	167	142	31.81 (25.52, 38.27)	7.13 (3.84, 11.80)
	60-69	213	185	28.08 (23.00, 33.37)	10.56 (7.04, 14.93)
	70-79	133	125	21.03 (15.31, 27.41)	5.08 (2.11, 10.16)
	≥80	28	28	8.39 (2.24, 20.17)	0.96 (0.02, 8.04)†
1995-1999	<60	262	204	35.82 (30.62, 41.05)	15.14 (11.14, 19.71)
	60-69	266	223	34.53 (29.32, 39.80)	12.61 (8.90, 17.04)
	70-79	244	216	35.76 (30.33, 41.25)	10.77 (7.08, 15.41)
	≥80	48	44	14.63 (7.95, 23.42)	7.88 (2.18, 19.94)
2000-2004	<60	468	296	52.47 (48.07, 56.67)	27.53 (23.33, 31.89)
	60-69	349	278	43.98 (38.92, 48.94)	17.33 (13.40, 21.71)
	70-79	334	290	47.59 (42.37, 52.67)	13.31 (9.62, 17.67)
	≥80	78	75	30.54 (21.05, 40.79)	3.67 (0.72, 11.66)
2005-2009	<60	683	439	56.94 (53.20, 60.50)	25.13 (21.39, 29.04)
	60-69	479	339	52.68 (48.26, 56.91)	22.85 (18.76, 27.22)

	70-79	485	390	55.90 (51.34, 60.24)	15.34 (11.66, 19.55)
	≥80	175	159	39.85 (32.52, 47.22)	12.13 (6.23, 20.73)
Period Analysis: Estimates of 5-Year Relative Survival Available in 2005-2009					
Female	<60			70.93 (62.18, 78.03)	26.57 (16.77, 37.43)
	60-69			54.27 (44.83, 62.80)	19.87 (12.42, 28.66)
	70-79			51.52 (43.41, 59.08)	12.20 (6.68, 19.61)
	≥80			40.81 (30.38, 51.17)	8.21 (2.01, 21.31)
Male	<60			56.94 (53.20, 60.50)	27.59 (23.77, 31.53)
	60-69			52.68 (48.26, 56.91)	21.75 (17.60, 26.24)
	70-79			55.9 (51.34, 60.24)	13.91 (10.24, 18.19)
	≥80			39.85 (32.52, 47.22)	8.86 (3.39, 18.43)

CI, confidence intervals. *4-year relative survival. †2-year relative survival.

Table 3. Generalized linear model using Poisson error structure to model relative excess hazard ratio for mortality after diagnosis of hepatocellular carcinoma using expected hazard from Ontario life tables, 1990-2009: Model 1

Parameters	Level	β coefficient	SE	Relative Excess Hazard Ratio (95% CI)	P-value
Intercept		0.545	0.088	1.724 (1.451, 2.047)	<0.001
Year of diagnosis	1990-1994	Reference	Reference	Reference	
	1995-1999	-0.239	0.055	0.787 (0.706, 0.877)	<0.001
	2000-2004	-0.314	0.053	0.730 (0.659, 0.810)	<0.001
	2005-2009	-0.258	0.052	0.773 (0.698, 0.855)	<0.001
Follow-up after diagnosis	1 year	Reference	Reference	Reference	
	2 years	-0.521	0.043	0.594 (0.546, 0.646)	<0.001
	3 years	-0.669	0.060	0.512 (0.455, 0.576)	<0.001
	4 years	-0.615	0.074	0.541 (0.468, 0.625)	<0.001
	5 years	-1.055	0.115	0.348 (0.278, 0.437)	<0.001
Age at diagnosis	<60 years	Reference	Reference	Reference	
	60-69 years	-0.041	0.041	0.960 (0.886, 1.041)	0.323
	70-79 years	-0.096	0.042	0.909 (0.837, 0.986)	0.022
	≥80 years	0.020	0.062	1.020 (0.903, 1.152)	0.754
Gender	Female	Reference	Reference	Reference	
	Male	0.030	0.038	1.031 (0.956, 1.111)	0.433
Charlson-Deyo Comorbidity Index	0	Reference	Reference	Reference	
	1	-0.234	0.044	0.791 (0.726, 0.863)	<0.001
	2	-0.595	0.054	0.551 (0.496, 0.612)	<0.001
	≥3	-0.692	0.059	0.500 (0.446, 0.562)	<0.001
	No hospitalization record	-0.649	0.043	0.523 (0.480, 0.568)	<0.001
HCC treatments		Reference	Reference	Reference	
	Curative	-1.474	0.058	0.229 (0.204, 0.257)	<0.001
	Non-curative	-0.410	0.049	0.664 (0.603, 0.731)	<0.001
	Palliative care	0.331	0.060	1.393 (1.238, 1.566)	<0.001
	No treatment	0.378	0.069	1.459 (1.276, 1.670)	<0.001

Model 1 (overall p-value): year of diagnosis (p<0.001); follow-up after diagnosis (p<0.001); age at diagnosis (p=0.08); Charlson-Deyo Comorbidity Index (p<0.001).

Table 4. Generalized linear model using Poisson error structure to model relative excess hazard ratio for mortality after diagnosis of hepatocellular carcinoma using expected hazard from Ontario life tables, 1990-2009; Model 2: Interactions between age at diagnosis and gender, year of diagnosis and palliative care are used in the model

Parameters	Level	β coefficient	SE	Relative Excess Hazard Ratio (95% CI)	P-value
Intercept		0.445	0.115	1.561 (1.246, 1.955)	<0.001
Year of diagnosis	1990-1994	Reference	Reference	Reference	
	1995-1999	-0.281	0.099	0.755 (0.622, 0.917)	0.005
	2000-2004	-0.322	0.093	0.724 (0.603, 0.870)	0.001
	2005-2009	-0.312	0.089	0.732 (0.615, 0.871)	<0.001
Follow-up after diagnosis	1 year	Reference	Reference	Reference	
	2 years	-0.509	0.043	0.601 (0.552, 0.654)	<0.001
	3 years	-0.656	0.060	0.519 (0.461, 0.584)	<0.001
	4 years	-0.596	0.074	0.551 (0.477, 0.637)	<0.001
	5 years	-1.025	0.115	0.359 (0.286, 0.450)	<0.001
Age at diagnosis	<60 years	Reference	Reference	Reference	
	60-69 years	-0.034	0.129	0.967 (0.750, 1.246)	0.794
	70-79 years	0.298	0.136	1.347 (1.032, 1.757)	0.028
	≥80 years	0.530	0.192	1.698 (1.165, 2.475)	0.006
Gender	Female	Reference	Reference	Reference	
	Male	0.116	0.077	1.123 (0.965, 1.307)	0.133
Charlson-Deyo Comorbidity Index	0	Reference	Reference	Reference	
	1	-0.239	0.044	0.788 (0.722, 0.859)	<0.001
	2	-0.604	0.054	0.547 (0.492, 0.607)	<0.001
	≥3	-0.701	0.060	0.496 (0.442, 0.558)	<0.001
	No hospitalization record	-0.654	0.043	0.520 (0.478, 0.566)	<0.001
HCC treatments	No specific treatment	Reference	Reference	Reference	
	Curative	-1.500	0.058	0.223 (0.199, 0.250)	<0.001
	Non-curative	-0.430	0.050	0.651 (0.590, 0.717)	<0.001
	Palliative care	0.528	0.073	1.696 (1.470, 1.957)	<0.001
	No treatment	0.338	0.070	1.403 (1.223, 1.608)	<0.001
Interactions:					
Age at diagnosis*gender	Female/<60 years Male	Reference	Reference	Reference	
	60-69 years	0.0682	0.117	1.071 (0.851, 1.347)	0.560

	70-79 years	0.130	0.126	1.139 (0.889, 1.458)	0.304
	≥80 years	0.654	0.186	1.923 (1.335, 2.772)	0.001
Age at diagnosis*year of diagnosis	1990-1994/<60 years	Reference	Reference	Reference	
1995-1999	60-69 years	-0.190	0.128	0.827 (0.644, 1.062)	0.137
2000-2004	60-69 years	-0.139	0.126	0.870 (0.680, 1.114)	0.270
2005-2009	60-69 years	-0.121	0.125	0.887 (0.694, 1.133)	0.336
1995-1999	70-79 years	0.014	0.127	1.014 (0.791, 1.299)	0.913
2000-2004	70-79 years	-0.193	0.121	0.825 (0.650, 1.046)	0.111
2005-2009	70-79 years	0.018	0.123	1.018 (0.801, 1.295)	0.882
1995-1999	≥80 years	0.133	0.182	1.142 (0.799, 1.632)	0.465
2000-2004	≥80 years	-0.243	0.165	0.784 (0.568, 1.084)	0.141
2005-2009	≥80 years	-0.288	0.158	0.750 (0.550, 1.023)	0.069
Age at diagnosis*palliative care	No palliative care/<60 years	Reference	Reference	Reference	
Palliative care	60-69 years	0.136	0.145	1.146 (0.863, 1.523)	0.347
	70-79 years	0.515	0.155	1.674 (1.236, 2.267)	0.001
	≥80 years	0.822	0.220	2.275 (1.48, 3.499)	<0.001

Model 2 (overall p-value): year of diagnosis (p=0.004); follow-up after diagnosis (p<0.001); age at diagnosis (p=0.004); Charlson-Deyo Comorbidity Index (p<0.001). Interactions between age at diagnosis and gender (p=0.009), year of diagnosis (p=0.003) and palliative care (p<0.001). Interactions between age at diagnosis and follow-up after diagnosis, Charlson-Deyo Comorbidity Index, curative treatment, non-curative treatment and no treatment were not significant.

FIGURE LEGEND:

Figure 1: Overall age-standardized 1- and 5-year relative survival trends (1995-2009) for hepatocellular carcinoma, Ontario

Figure 2: Age-standardized 1- and 5-year relative survival trends (1995-2009) for hepatocellular carcinoma by gender, Ontario

Figure 3: Age-standardized 5-year relative survival: period analysis vs. cohort analysis by gender and age at diagnosis

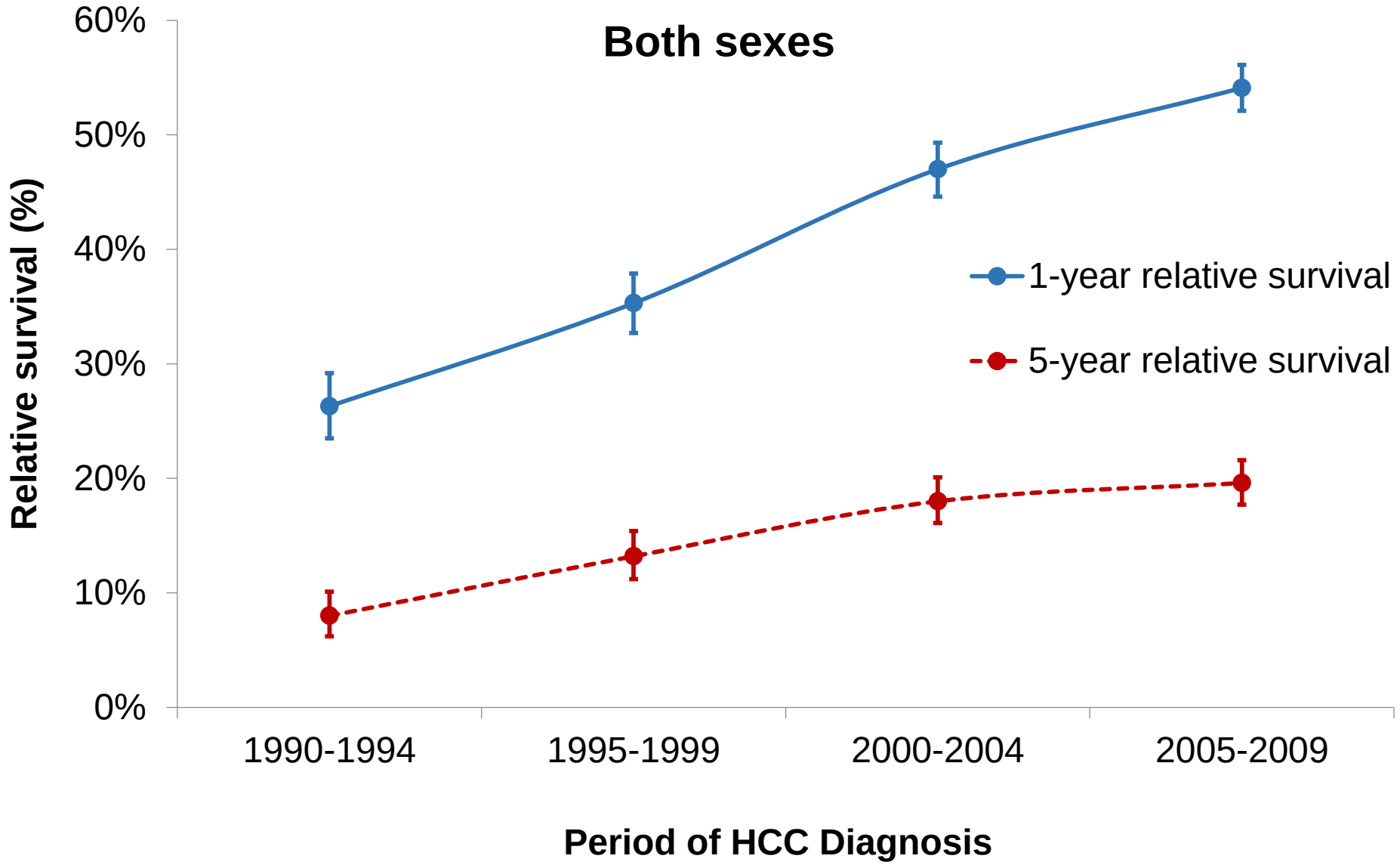
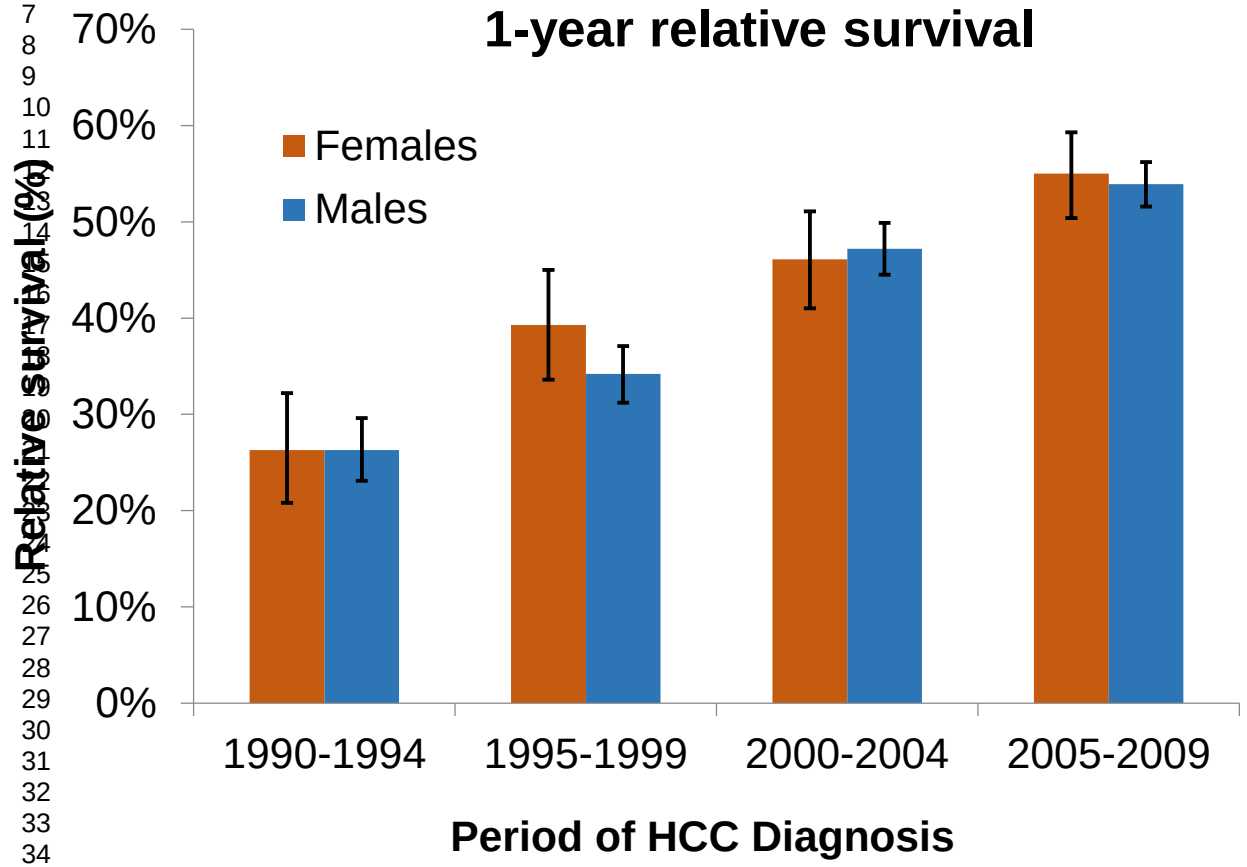


Figure 1.


1-year relative survival
Females
Males
70%
60%
50%
40%
30%
20%
10%
0%
Relative survival (%)
1990-1994
1995-1999
2000-2004
2005-2009
Period of HCC Diagnosis

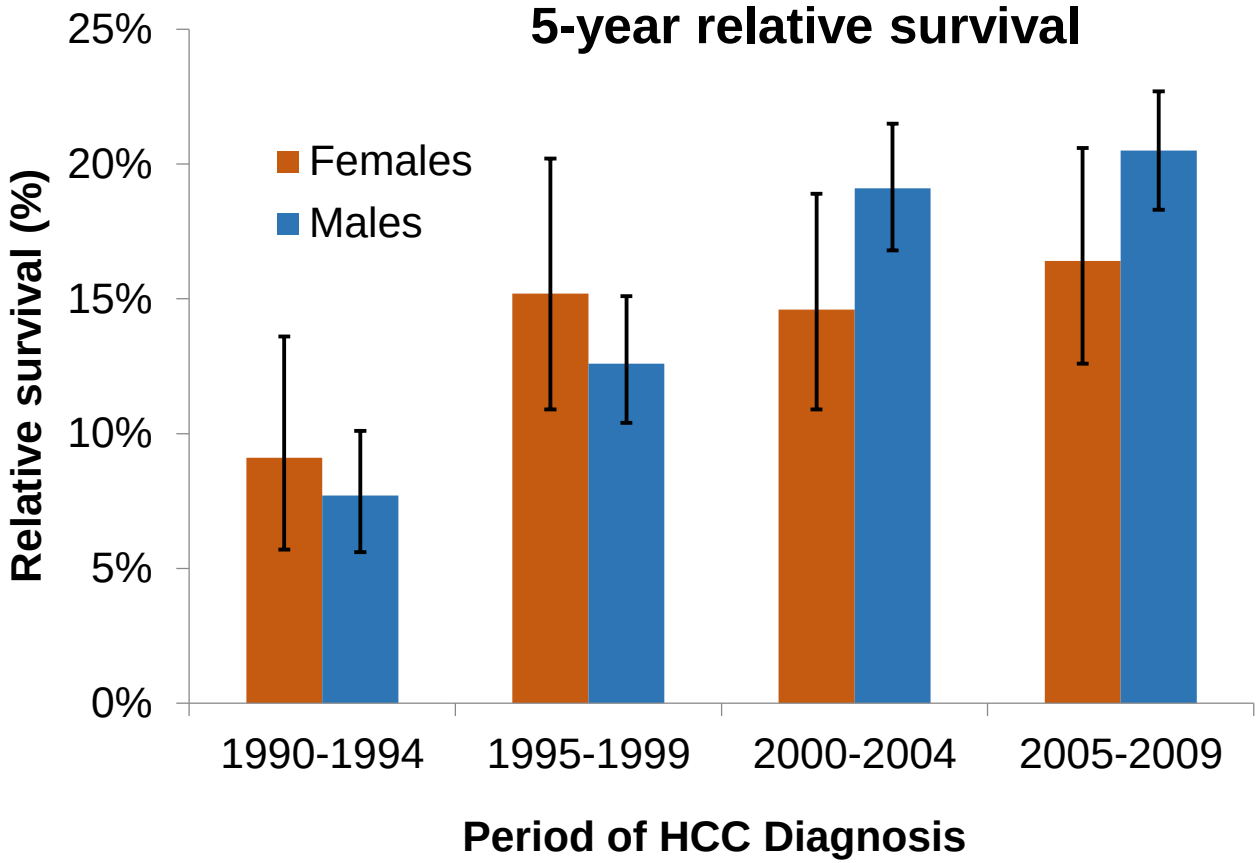
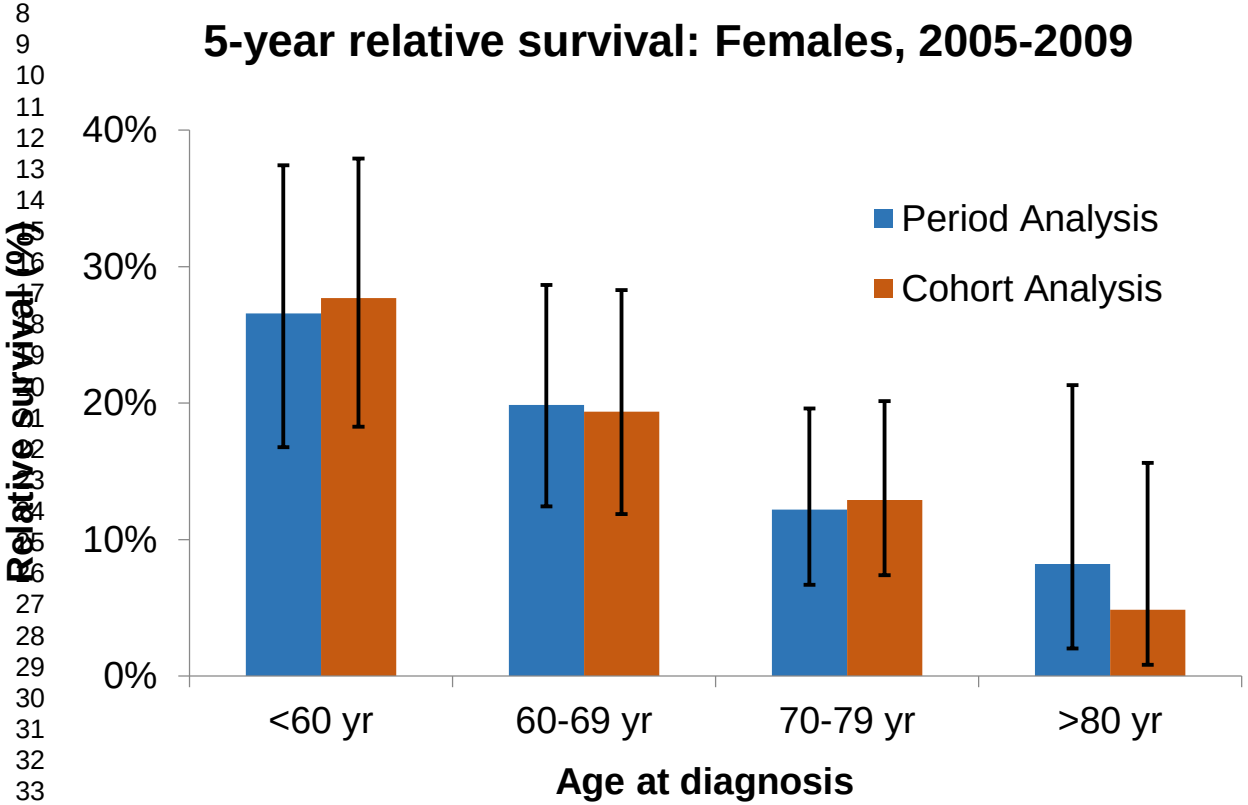

5-year relative survival
Females
Males
25%
20%
15%
10%
5%
0%
Relative survival (%)
1990-1994
1995-1999
2000-2004
2005-2009
Period of HCC Diagnosis

Figure 2.



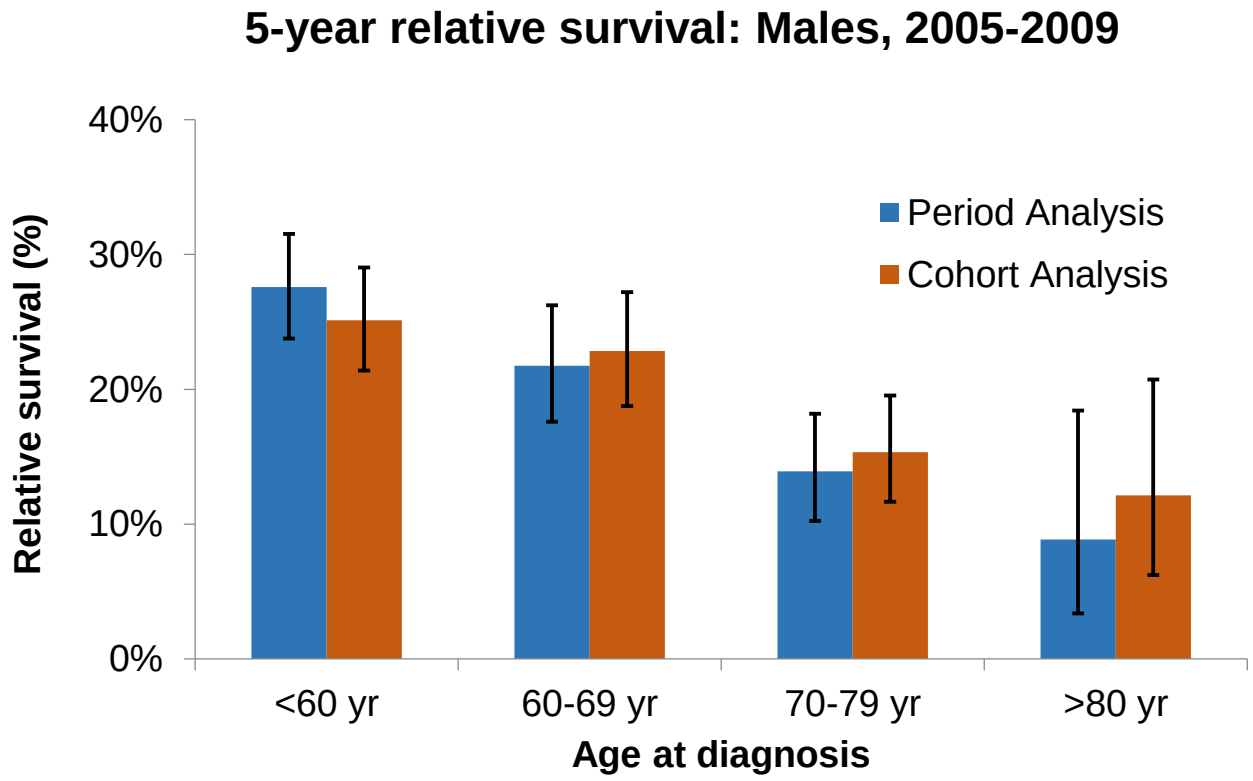


Figure 3.

Appendix

Table A1. Treatment procedures for persons diagnosed with hepatocellular carcinoma

	CCP code	CCI code	OHIP code
Potentially curative therapy			
Local excision or destruction of lesion or tissue of liver	62.1		
Partial hepatectomy	62.12		
Other destruction of lesion of liver	62.19		
Lobectomy of liver	62.20		
Excision partial, liver using endoscopic (laparoscopic)approach		1OA87DA	
Excision partial, liver using open approach		1OA87LA	
Excision partial, liver using ultrasonic aspirator device (for dissection) and open approach		1OA87LAAZ	
Liver excision-complete left/right lobectomy			S267
Liver excision-of lesion			S269
Liver excision-hepatectomy left lateral segmental excision			S270
Liver excision-extended right lobectomy			S271
Liver excision-partial lobectomy			S275
Total hepatectomy	62.3		
Liver transplant	62.4		
Auxiliary liver transplant	62.41		
Other transplant of liver	62.49		
Transplant, liver of a deceased donor full size liver		1OA85LAXXK	
Transplant, liver of a deceased donor multi organ liver with intestine/ pancreas/spleen/stomach (or any combination of)		1OA85VCXXK	
Transplant, liver of a living donor split liver		1OA85WLXXJ	
Transplant, liver of a deceased donor split liver (or reduced paediatric-size liver)		1OA85WLXXK	
Living donor orthotopic liver transplantation recipient			S266
Liver excision-liver transplant-recipient			S294
Digestive system-liver-repeat liver transplant			S295
Destruction, liver endoscopic (laparoscopic) approach using radiofrequency		1OA59DAAW	
Destruction, liver percutaneous approach using radiofrequency		1OA59HAAW	
Destruction, liver open approach using radiofrequency		1OA59LAAW	
Radiofrequency ablation			J069
Non-curative therapy			
Percutaneous ablation			

Destruction, liver endoscopic (abdominal) approach using cryoprobe	1OA59DAAD	
Destruction, liver endoscopic (abdominal) approach using laser	1OA59DAAG	
Destruction, liver endoscopic (abdominal) approach using device NEC	1OA59DAGX	
Destruction, liver endoscopic (abdominal) approach using chemical cautery agent (e.g. ethanol)	1OA59DAX7	
Destruction, liver percutaneous approach using chemical cautery agent (e.g. ethanol)	1OA59HAX7	
Destruction, liver open approach using cryoprobe	1OA59LAAD	
Destruction, liver open approach using laser	1OA59LAAG	
Destruction, liver open approach using device NEC	1OA59LAGX	
Destruction, liver open approach using chemical cautery agent (e.g. ethanol)	1OA59LAX7	
Chemotherapy		
Diagnostic and therapeutic injection(s)/infusion(s) test dose (bleomycin&l-asparatiginase once per patient per drug)		G075
Diagnostic and therapeutic injection/infusion-intravenous chemotherapy-each additional injection to		G281
Single agent intravenous chemotherapy i.e. doxorubicin, daunorubicin, epirubicin, mitoxintrone, cisplatin or bleomycin (greater than 10 units per metre square)		G339
Taxol, rituximab, trastuzumab, bortezomib, docetaxel administration or multiple agent intravenous chemotherapy including at least one of either doxorubicin, daunorubicin, epirubicin, mitoxintrone, cisplatin or bleomycin (greater than 10 units per metre square)		G345
Special single agent chemotherapy utilizing either high-dose methotrexate with folinic acid rescue - methotrexate given in a dose of greater than 1 g/m2, high dose cisplatin greater than 75 mg/m2 given concurrently with hydration and osmotic diuresis, high dose cystosine, arabinoside (greater than 2g/m2), or high dose cyclophosphamide (greater than 1g/m2)		G359
Single injection (for agents other than doxorubicin, cisplatin, bleomycin or high dose methotrexate)		G381
Supervision of chemotherapy (marrow suppressant) for malignant or autoimmune disease by telephone - monthly		G382
Arteries-cannulation-chemotherapy-hepatic (TACE)		R776
Supportive/Palliative care		
General/Family Practice special palliative care consultation		A945
Special palliative care consultation hospital in patient		C945
Palliative care		C982
Palliative care support individual care 1/2 hr. or major part		K023

CCI, Canadian Classification of Health Interventions – is the new national standard for classifying health care procedures. CCI is the companion classification system to ICD-10-CA. CCI replaces the Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures (CCP) and the intervention portion of ICD-9-CM in Canada. CCP was originally developed by Statistics Canada in 1978 to meet Canadian needs for a procedural classification to be used in conjunction with ICD-9. The Ontario Health Insurance Plan (OHIP), physician billing claims dataset contains service and diagnosis information for outpatient visits in Ontario.

Table A2. Characteristics of individuals diagnosed with hepatocellular carcinoma by gender and year of diagnosis

	Female					Male				
	1990-1994	1995-1999	2000-2004	2005-2009	Total	1990-1994	1995-1999	2000-2004	2005-2009	Total
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Age at diagnosis (years)	N=177	N=229	N=352	N=475	N=1233	N=541	N=820	N=1229	N=1822	N=4412
<60	62 (35.03)	56 (24.45)	77 (21.88)	125 (26.32)	320 (25.95)	167 (30.87)	262 (31.95)	468 (38.08)	683 (37.49)	1580 (35.81)
60-69	57 (32.20)	73 (31.88)	102 (28.98)	113 (23.79)	345 (27.98)	213 (39.37)	266 (32.44)	349 (28.40)	479 (26.29)	1307 (29.62)
70-79	38 (21.47)	79 (34.50)	132 (37.50)	150 (31.58)	399 (32.36)	133 (24.58)	244 (29.76)	334 (27.18)	485 (26.62)	1196 (27.11)
≥80	20 (11.30)	21 (9.17)	41 (11.65)	87 (18.32)	169 (13.71)	28 (5.18)	48 (5.85)	78 (6.35)	175 (9.60)	329 (7.46)
Charlson-Deyo Comorbidity Index										
0	55 (31.07)	101 (44.10)	135 (38.35)	162 (34.11)	453 (36.74)	169 (31.24)	330 (40.24)	432 (35.15)	540 (29.64)	1471 (33.34)
1	21 (11.86)	31 (13.54)	71 (20.17)	89 (18.74)	212 (17.19)	104 (19.22)	187 (22.8)	234 (19.04)	379 (20.80)	904 (20.49)
2	17 (9.60)	37 (16.16)	40 (11.36)	73 (15.37)	167 (13.54)	45 (8.32)	94 (11.46)	156 (12.69)	238 (13.06)	533 (12.08)
≥3	6 (3.39)	22 (9.61)	35 (9.94)	42 (8.84)	105 (8.52)	19 (3.51)	77 (9.39)	143 (11.64)	222 (12.18)	461 (10.45)
No hospitalization record	78 (44.07)	38 (16.59)	71 (20.17)	109 (22.95)	296 (24.01)	204 (37.71)	132 (16.1)	264 (21.48)	443 (24.31)	1043 (23.64)
HCC treatments										
Curative	29 (16.38)	59 (25.76)	105 (29.83)	179 (37.68)	372 (30.17)	82 (15.16)	193 (23.54)	400 (32.55)	688 (37.76)	1363 (30.89)
Noncurative	24 (13.56)	32 (13.97)	54 (15.34)	96 (20.21)	206 (16.71)	77 (14.23)	98 (11.95)	223 (18.14)	417 (22.89)	815 (18.47)
Palliative care	17 (9.60)	80 (34.93)	160 (45.45)	220 (46.32)	477 (38.69)	72 (13.31)	233 (28.41)	542 (44.10)	841 (46.16)	1688 (38.26)
No treatment	120 (67.80)	105 (45.85)	119 (33.81)	116 (24.42)	460 (37.31)	352 (65.06)	412 (50.24)	372 (30.27)	400 (21.95)	1536 (34.81)

Table A3. Relative survival after diagnosis of hepatocellular carcinoma by sex, year of diagnosis, and age at diagnosis: Sensitivity analysis, merging age at diagnosis 70-79 and ≥80 years

Year of Diagnosis	Age at Diagnosis (years)	Cases (N)	Events (N)	1-year Relative Survival % (95% CI)	5-year Relative Survival % (95% CI)
	Cohort Analysis				
	Female				
1990-1994	< 60	62	48	38.27 (27.09, 49.35)	17.44 (9.45, 27.48)
	60-69	57	45	28.97 (18.74, 40.01)	11.01 (4.92, 19.95)
	≥70	58	54	11.85 (6.62, 18.78)	0.03 (0.00, 0.42)
1995-1999	< 60	56	29	49.19 (36.10, 61.04)	25.92 (15.10, 38.17)
	60-69	73	42	54.51 (43.21, 64.52)	19.28 (11.28, 28.99)
	≥70	100	80	23.09 (16.59, 30.27)	6.97 (3.12, 13.11)
2000-2004	< 60	77	45	51.77 (40.65, 61.79)	20.44 (11.90, 30.62)
	60-69	102	65	42.00 (32.85, 50.89)	17.61 (10.75, 25.94)
	≥70	173	127	46.16 (38.61, 53.43)	10.12 (5.85, 15.86)
2005-2009	< 60	125	47	70.93 (62.18, 78.03)	27.69 (18.27, 37.93)
	60-69	113	63	54.27 (44.83, 62.80)	19.36 (11.87, 28.29)
	≥70	237	164	47.60 (41.17, 53.81)	10.00 (5.92, 15.44)
	Male				
1990-1994	< 60	167	120	31.81 (25.52, 38.27)	7.13 (3.84, 11.80)
	60-69	213	165	28.08 (23.00, 33.37)	10.56 (7.04, 14.93)
	≥70	161	142	18.61 (13.7, 24.16)	4.15 (1.73, 8.38)
1995-1999	< 60	262	175	35.82 (30.62, 41.05)	15.14 (11.14, 19.71)
	60-69	266	191	34.53 (29.32, 39.80)	12.61 (8.90, 17.04)
	≥70	292	218	32.29 (27.54, 37.15)	10.26 (6.93, 14.43)
2000-2004	< 60	468	239	52.47 (48.07, 56.67)	27.53 (23.33, 31.89)
	60-69	349	234	43.98 (38.92, 48.94)	17.33 (13.40, 21.71)
	≥70	412	280	44.41 (39.74, 49.01)	11.64 (8.48, 15.41)
2005-2009	< 60	683	373	56.94 (53.20, 60.50)	25.13 (21.39, 29.04)
	60-69	479	269	52.68 (48.26, 56.91)	22.85 (18.76, 27.22)
	≥70	660	439	51.72 (47.8, 55.52)	14.35 (11.17, 17.98)

CI, confidence intervals.