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Survival of hepatocellular carcinoma patients is significantly improving: a population-based study from southern Switzerland

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ABSTRACT

Background: During the last 20 years, relevant diagnostic procedures and advanced treatments have been progressively introduced in the management of hepatocellular carcinoma (HCC).

The aim of the present study was to assess up-to-date survival trends for HCC in southern Switzerland, a region with one of the highest incidence rates in the country.

Methods: HCCs diagnosed in 1996–2009 were selected by the Ticino Cancer Registry. Cancer-specific survival (CSS) analysis was performed using the Kaplan–Meier method by calendar period: 1996–2000, 2001–2005 and 2006–2009. The log-rank test was used to detect differences in survival curves. Simultaneous assessment of prognostic factors was performed by a multivariate analysis using the Cox proportional-hazards regression model.

Results: 619 HCCs were analysed. There was a significant increase of patients undergoing transarterial chemoembolisation (TACE), whereas patients undergoing curative or palliative supportive treatments remained unchanged ($p < 0.0001$). No shift to earlier stages was detected. Significant differences in CCS were observed by age-group ($p < 0.0001$), diagnosis period ($p < 0.0001$), diagnosis technique ($p = 0.0035$), Barcelona-Clinic liver cancer stage ($p < 0.0001$), treatment ($p < 0.0001$). Multivariate analysis confirmed the independent impact on CSS of factors above mentioned, not including the diagnosis technique. Death risk was higher for patients diagnosed in 1996–2000 (HR: 1.32; 95% CI: 1.03; 1.68) and 2001–2005 (HR: 1.33; 95% CI: 1.05; 1.67) in comparison with 2006–2009 (reference group).

Conclusions: The current population-based report describes a major increase in HCC survival. Simultaneously an increased use of TACE has been detected, probable cofactor of the observed survival increase. Possibly additional efforts could be made to decrease the HCC stage at diagnosis through active surveillance of cirrhotic patients to allow an increase in curative treatments. For sure efforts should be made to comply with a standardised staging system for HCC, particularly for comparative population-based issues.

represents the third most common cause of death from cancer worldwide. The prognosis is therefore very poor, with a very low survival probability (<5–10% at five years from diagnosis) [3–6]. Most of the burden is in developing countries, where almost 85% of the cases occur, and in men, with a male:female ratio of 2.4. In Switzerland, the highest incidence of HCC is observed in the Latin regions, particularly in Canton Ticino, the southern Italian-speaking area, where the rate is twofold higher for men compared to the rest of the country [7–9].

During the last 20 years, relevant diagnostic procedures, such as ultrasonography, computed tomography and magnetic resonance imaging, have been introduced to detect HCC at an earlier stage. Furthermore, novel and effective treatments, including surgical resection, liver transplantation, percutaneous ablation treatments, transarterial chemoembolisation (TACE) and targeted drugs, have also been progressively introduced in the management of HCC [10]. As observed in previous reports in both the United States and Europe, these events have contributed to increase patient survival, particularly in the short term [3–6].

The aim of the present study was to assess up-to-date survival trends for HCC in southern Switzerland and investigate the influence of population-based clinical and pathological prognostic factors.

2. Patients and methods

2.1. Case selection

All patients from the archives of the population-based Ticino Cancer Registry with primary HCC diagnosed in southern Switzerland between 1996 and 2009 were analysed.

Information was actively collected from pathology reports and public and private hospital discharge letters. Each single patient's report was analysed and consistent information were extracted by trained data-managers and revised by a medical doctor. Data were recorded prospectively. HCC patients were defined in accordance with the International Classification of Diseases for Oncology (ICD-O-III) and the WHO Classification of Gastrointestinal Tumours. Tumour localisation C22 (liver) and morphology 81703–81753 (HCC and subtypes) were selected for the analysis [11,12]. Case registration, comparability, validity and consistency checks were performed according to the International Agency for Research on Cancer (IARC) guidelines and the European Network of Cancer Registries (ENCR) recommendations [13–15]. Quality controls on multiple primaries, comparability, validity and consistency of data are carried out by means of the IARC checks programme [13,16].

Patients were categorised into three subgroups according to the calendar period of diagnosis: 1996–2000, 2001–2005 and 2006–2009.

Essential clinical–pathological characteristics were analysed, including patient age and sex, basis of diagnosis, tumour stage and treatment procedures. The method of diagnosis was classified into microscopic (cytological and/or histological confirmation) and non-microscopic (alpha-fetoprotein and/or imaging). HCC stage was defined and recoded through a revision of single-patient medical records according to the Barcelona Clinic liver cancer (BCLC) staging system, as follows: early stage (BCLC A, i.e., single HCC $\leq$5 cm or 3 nodules $\leq$3 cm); intermediate stage (BCLC B, i.e., large multinodular); advanced stage (BCLC C, i.e., portal/vascular invasion or presence of lymph node (N1) or distant metastases (M1)); terminal stage (D) [17]. For analysis, patients with a BCLC D stage were included with the subgroup of BCLC C cases because of the small sample size.

The treatment procedures were classified as follows: curative ((liver hepatectomy or segmentectomy or lobectomy or transplantation or radio-frequency thermal ablation (RFA)) ± neo-adjuvant TACE), palliative interventional (only TACE, percutaneous ethanol injection (PEI)), palliative supportive (chemotherapy, hormonal therapy, targeted therapies (i.e., sorafenib), radiotherapy on metastasis) and no treatment [18].

2.2. Statistical analyses

Mean and median values were used for patient age, whereas proportions were used to report categorical variables. Differences among period subtypes were evaluated using one-way analysis of variance (ANOVA) for patient age. Median values were compared by the non-parametric K-sample test, which evaluates the null hypothesis that samples were drawn from populations with the same median. The chi-square test or Fisher's exact test was used for discrete variables, such as sex, basis of diagnosis, BCLC stage and treatments [19,20].

Cancer-specific survival (CSS) analysis was conducted considering only deaths due to malignancies of the liver, reducing the likelihood of bias in survival results due to co-morbidity. The active follow-up (31 December 2011) consisted of systematic checks of patient vital status through a record-linkage procedure between the local Cancer Registry database and the regional Office of Population Registry Rosters. To extract and increase the quality and reliability of cancer-specific causes of death, we constructed a specific variable (death due to HCC; death due to another cancer; death due to causes not related to cancer) derived from the following sources of information: the Swiss Federal Office of Statistics, which provides to the Registry the single death certificates with cancer diagnosis and the list of death cancer codes; public and private hospitals, which systematically send medical documents, reports and discharge letters; and physicians, who fill in ad-hoc questionnaires provided by the Registry. Cases coming first to the attention of the Registry by death certificate and for which the trace back was unsuccessful were excluded from the analysis. Indeed, the only evidence of a tumour for these cases, commonly defined in a cancer registry setting as death certificate-only cases (DCOs), was provided by the death certificate, but the real date of diagnosis was unknown.

Survival curves were assessed according to the Kaplan–Meier method. Survival trends were provided by the 3 calendar periods of observation: 1996–2000, 2001–2005 and 2006–2009. The log-rank test was used to detect statistically significant differences in survival curves according to age group (<75 vs $\geq$75 years), gender, calendar period of observation, method of diagnosis, BCLC stage and treatment [19]. For multiple comparisons, the Sidak correction was computed to adjust the paired log-rank tests.

Simultaneous assessment of all prognostic factors mentioned above was performed through a multivariate analysis using the Cox proportional-hazards regression model, with the backward selection method and a significance level for removing an explanatory variable from the model equal to 0.1 (i.e., 10%). The magnitude of the effect of each independent covariate, adjusted for the other main clinical–pathological variables, was estimated by the hazard ratio (HR) for cancer-specific deaths with the corresponding 95% confidence intervals (95% CIs) [19]. Statistical significance was determined at $p < 0.05$. The SAS System Version V9.1 (SAS Institute Inc., Cary, NC) was used for analysis.

3. Results

Between 1996 and 2009, 673 patients with HCC were identified at the Ticino Cancer Registry. Fifty-four cases were excluded because they were DCO cases. The remaining 619 HCCs were included in the analysis.

3.1. Patient and tumour characteristics

Table 1 reports the main clinical–pathological characteristics of the 619 HCCs. The overall M:F ratio was 4.42, and the median age was 68 years (range: 30–91 years). No significant difference was detected in patient age or sex among the three periods. Considering the diagnostic technique, a significant association with the incidence period was observed: cases with microscopic confirmation decreased from 62.2% in 1996–2000 to 38.9% in 2006–2009 ($p < 0.0001$). BCLC stage classification was significantly associated with the period of diagnosis ($p = 0.0044$). Additionally, an increase of BCLC B and BCLC C/D cases was accompanied by a decrease of BCLC A and unknown cases.

When cases were stratified according to treatment, we observed a substantial constant trend of patients undergoing a curative approach (approximately 20% throughout the entire study period) accompanied by an increase in patients treated with a palliative interventional approach or palliative supportive procedures (from 5.6% in 1996–2000 to 26.0% in 2006–2009, $p < 0.0001$). Simultaneously, the number of untreated patients significantly decreased. Patients with a previous neoplasm increased from 4.1% in 1996–2000 to 12.5% in 2006–2009 ($p = 0.0103$).

3.2. Survival analysis of HCC

The CSS rates at 1, 2 and 3 years from the date of diagnosis are reported in Table 2 according to the main clinical–pathological characteristics. Overall, patients with HCC showed 1-, 2- and 3-year CSS rates equal to 49.1%, 36.5% and 28.6%, respectively.

Significant differences in survival curves were observed when cases were stratified according to age group ($p < 0.0001$), period of diagnosis ($p < 0.0001$), type of diagnosis confirmation ($p = 0.0035$), BCLC stage ($p < 0.0001$) and treatment approach ($p < 0.0001$). By contrast, no significant survival difference was detected between patients with or without a previous neoplasm ($p = 0.3037$). There was a significant increase in survival across the three study calendar periods: patients diagnosed in the last period (i.e., 2005–2009) had the highest CCS (Fig. 1). The adjusted multiple comparisons analysis confirmed a significant difference between the periods 1996–2000 and 2005–2009 ($p = 0.0009$). Survival curves stratified according to BCLC stage classification are reported in Fig. 2 ($p < 0.0001$). Moreover, all paired comparisons among BCLC stage subgroups were statistically significant: A vs B ($p = 0.0020$); A vs C/D ($p < 0.0001$), A vs unknown ($p < 0.0001$), B vs C/D ($p < 0.0001$), B vs unknown ($p < 0.0001$), and C/D vs unknown ($p = 0.0032$). As reported in Fig. 3, patients treated with a curative intent had the best outcome, followed by those patients undergoing a palliative interventional or palliative supportive approach and untreated patients ($p < 0.0001$). All paired comparisons were statistically significant: curative vs palliative interventional ($p = 0.0065$), curative vs palliative supportive ($p < 0.0001$), curative vs no treatment ($p < 0.0001$), palliative interventional vs palliative supportive ($p < 0.0001$), palliative interventional vs no treatment ($p < 0.0001$), palliative supportive vs no treatment ($p < 0.0029$).

The multivariate Cox model analysis confirmed the significant and independent impact of the period of diagnosis on CSS (Table 3). In fact, the hazard risk of death due to liver cancer was higher for patients diagnosed in the periods 1996–2000 (HR: 1.32; 95% CI: 1.03; 1.68) and 2001–2005 (HR: 1.33; 95% CI: 1.05; 1.67) compared to patients diagnosed in 2006–2009 (reference group), confirming the significant increase in HCC survival. The other significant variables included in the final Cox model were age group, BCLC stage classification and treatment approach (Table 3). Considering that patients with BCLC stage C/D and BCLC unknown showed

Table 1
Clinical–pathological characteristics of patients with hepatocellular carcinoma diagnosed in southern Switzerland according to the period of diagnosis (1996–2000, 2001–2005 and 2006–2009).

Variable	All cases $N=619$		1996–2000 $N=196$ (31.7%)		2001–2005 $N=215$ (34.7%)		2006–2009 $N=208$ (33.6%)		p-Value
Age									
Mean ± sd (years)	67.5 ± 10.6		67.5 ± 11.0		67.3 ± 10.5		67.8 ± 10.4		0.8974
Median	68		68		68		68		0.9933
Range	30–91		33–90		30–90		43–91		
Age-specific group, n (%)									
<75 years	447	(72.2%)	140	(71.4%)	155	(72.1%)	152	(73.1%)	0.9329
≥75 years	172	(27.8%)	56	(28.6%)	60	(27.9%)	56	(26.9%)	
Sex, n (%)									
M	505	(81.6%)	163	(83.2%)	181	(84.2%)	161	(77.4%)	0.1562
F	114	(18.4%)	33	(16.8%)	34	(15.8%)	47	(22.6%)	
Type of diagnosis confirmation, n (%)									
Histological	297	(48.0%)	122	(62.2%)	94	(43.7%)	81	(38.9%)	<0.0001
Non-histological	322	(52.0%)	74	(37.8%)	121	(56.3%)	127	(61.1%)	
BCLC stage classification, n (%)									
BCLC A	159	(25.7%)	59	(30.1%)	56	(26.1%)	44	(21.1%)	0.0044
BCLC B	184	(29.7%)	45	(23.0%)	65	(30.2%)	74	(35.6%)	
BCLC C/D	188	(30.4%)	52	(26.5%)	66	(30.7%)	70	(33.6%)	
BCLC unknown	88	(14.2%)	40	(20.4%)	28	(13.0%)	20	(9.6%)	
Treatment									
Curative[a]	130	(21.0%)	38	(19.4%)	49	(22.8%)	43	(20.7%)	<0.0001
Palliative interventional[b]	120	(19.4%)	11	(5.6%)	55	(25.5%)	54	(26.0%)	
Palliative supportive[c]	153	(24.7%)	45	(23.0%)	47	(21.9%)	61	(29.3%)	
No treatment	216	(34.9%)	102	(52.0%)	64	(29.8%)	50	(24.0%)	
Previous neoplasm									
Yes	55	(8.9%)	8	(4.1%)	21	(9.8%)	26	(12.5%)	0.0103
No	564	(91.1%)	188	(95.9%)	194	(90.2%)	182	(87.5%)	

[a] Curative: liver hepatectomy or segmentectomy or lobectomy or transplantation or radio-frequency thermal ablation (RFA) ± neo-adjuvant transarterial chemoembolisation (TACE).
[b] Palliative interventional: only TACE, percutaneous ethanol injection (PEI).
[c] Palliative supportive: chemotherapy, hormonal therapy, targeted therapies (i.e., sorafenib), radiotherapy on metastasis.

Table 2
Univariate analysis of 1-, 2- and 3-year cancer-specific survival of patients with hepatocellular carcinoma diagnosed in southern Switzerland in the period 1996–2009 according to main clinical-pathological characteristics.

Variable	1-year CSS		2-year CSS		3-year CSS		Median survival (months)	p-Value[§]
	%	(95% CI)	%	(95% CI)	%	(95% CI)		
All patients	49.1	(45.0; 53.0)	36.5	(32.6; 40.4)	28.6	(24.9; 32.4)	11.2	–
Age-specific group								
<75 years	54.3	(49.4; 58.8)	41.1	(36.4; 45.8)	32.6	(28.0; 37.2)	14.9	<0.0001
≥75 years	35.5	(28.3; 42.8)	24.3	(17.9; 31.2)	17.9	(12.2; 24.5)	5.8	
Sex								
M	46.9	(42.4; 51.2)	35.2	(30.9; 39.6)	26.7	(22.7; 30.9)	9.7	0.1133
F	58.7	(49.0; 67.2)	42.2	(32.7; 51.3)	36.9	(27.7; 46.1)	16.3	
Period of diagnosis								
1996–2000	39.5	(32.6; 46.4)	27.0	(20.8; 33.6)	21.7	(14.0; 28.0)	7.6	0.0013[a]
2001–2005	49.8	(42.8; 56.3)	39.1	(32.4; 45.7)	28.6	(22.5; 35.0)	10.9	
2006–2009	57.4	(50.2; 63.9)	42.8	(35.6; 49.7)	35.4	(28.2; 42.6)	16.1	
Type of diagnosis confirmation								
Microscopic	51.9	(46.0; 57.5)	39.6	(33.8; 45.2)	31.8	(26.3; 37.4)	13.5	0.0035
Non-microscopic	46.5	(40.8; 51.9)	33.7	(28.4; 39.1)	25.6	(20.6; 30.8)	8.5	
BCLC stage classification								
BCLC A	78.4	(71.0; 84.2)	65.9	(57.7; 72.9)	55.6	(47.1; 63.3)	30.1	<0.0001[b]
BCLC B	60.0	(52.5; 66.8)	43.9	(36.3; 51.2)	32.8	(25.5; 40.2)	17.6	
BCLC C/D	24.7	(18.6; 31.2)	13.7	(9.0; 19.3)	7.6	(4.2; 12.5)	4.5	
BCLC unknown	24.6	(16.1; 34.2)	15.5	(8.6; 24.3)	14.0	(7.4; 22.6)	2.1	
Treatment								
Curative[c]	88.1	(81.1; 92.7)	75.8	(67.2; 82.4)	66.3	(57.1; 74.0)	53.2	<0.0001[b]
Palliative interventional[d]	81.3	(72.9; 87.2)	61.7	(51.9; 70.0)	42.5	(32.7; 51.9)	29.9	
Palliative supportive[e]	29.2	(22.0; 36.7)	14.9	(9.4; 21.5)	9.6	(5.1; 15.9)	5.2	
No treatment	20.7	(15.4; 26.5)	12.5	(8.3; 17.6)	9.3	(5.7; 14.1)	3.0	
Previous neoplasm								
Yes	54.3	(40.2; 66.3)	46.0	(32.3; 58.7)	38.4	(24.9; 51.8)	18.8	0.3037
No	48.6	(44.3; 52.7)	35.6	(31.5; 39.7)	27.6	(23.8; 31.6)	10.6	

[§] *P*-value of the log-rank test to assess the equality of survival curves over strata.
[a] Among all strata comparisons, the only significant difference was between the period 1996–2000 and 2005–2009, $p = 0.0009$ (the paired log-rank test was adjusted for multiple comparisons using the Sidak correction).
[b] All strata comparisons were statistically significant (the paired log-rank tests were adjusted for multiple comparisons, using the Sidak correction).
[c] Curative: liver hepatectomy or segmentectomy or lobectomy or transplantation or radio-frequency thermal ablation (RFA) ± neo-adjuvant transarterial chemoembolisation (TACE).
[d] Palliative interventional: only TACE, percutaneous ethanol injection (PEI).
[e] Palliative supportive: chemotherapy, hormonal therapy, targeted therapies (i.e., sorafenib), radiotherapy on metastasis.

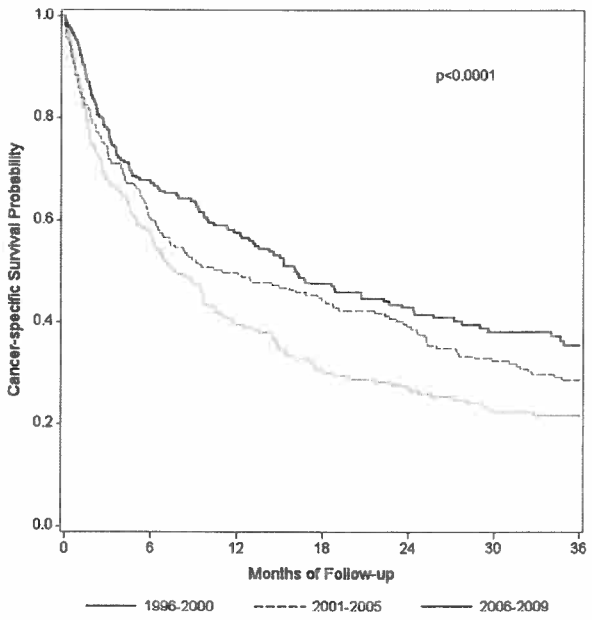

Fig. 1. Three-year cancer-specific survival of patients with hepatocellular carcinoma diagnosed in southern Switzerland across three calendar periods.

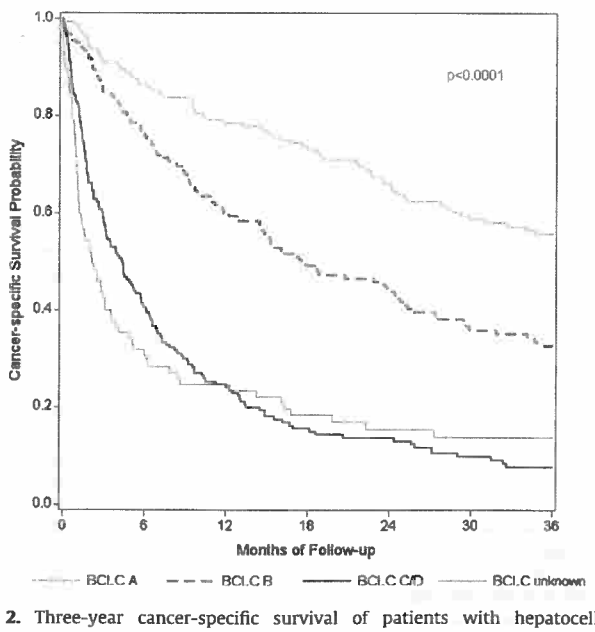

Fig. 2. Three-year cancer-specific survival of patients with hepatocellular carcinoma diagnosed in southern Switzerland according to the Barcelona-Clinic liver cancer (BCLC) staging system.

similar survival curves in the univariate analysis (Fig. 2), we clustered them in a single group (i.e., BCLC stage C/D/unknown) for the multivariate survival analysis. The increase of BCLC stage translated into an increase of the hazard of death due to HCC. The probability of death was 59% higher in patients with BCLC B stage compared with BCLC A. Moreover, BCLC C/D/unknown patients had

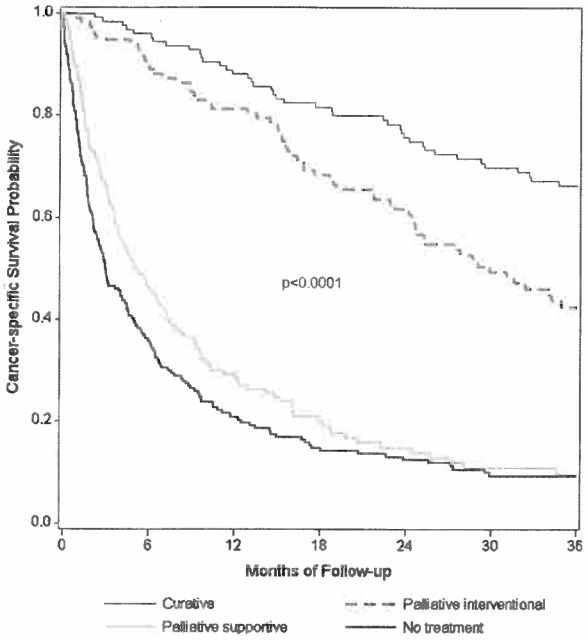

Fig. 3. Three-year cancer-specific survival of patients with hepatocellular carcinoma diagnosed in southern Switzerland according to the treatment approach.

Table 3
Multivariate Cox model analysis of 3-year cancer-specific survival of patients with hepatocellular carcinoma diagnosed in southern Switzerland in the period 1996–2009.

Variable	Hazard ratio[d]	(95% CI)	*p*-Value
Period of diagnosis			
2006–2009	1	–	–
2001–2005	1.33	(1.05; 1.67)	0.0180
1996–2000	1.32	(1.03; 1.68)	0.0280
Age-specific group			
<75 years	1	–	–
≥75 years	1.30	(1.06;1.58)	0.0118
BCLC stage classification			
BCLC A	1	–	–
BCLC B	1.59	(1.21; 2.09)	0.0009
BCLC C/D/Unknown	2.63	(2.01; 3.44)	<0.0001
Treatment			
curative[a]	1	–	–
palliative interventional[b]	1.57	(1.12; 2.19)	0.0088
palliative supportive[c]	3.62	(2.60; 5.02)	<0.0001
no treatment	4.69	(3.43; 6.41)	<0.0001

[a] Curative: liver hepatectomy or segmentectomy or lobectomy or transplantation or radio-frequency thermal ablation (RFA) ± neo-adjuvant transarterial chemoembolisation (TACE).
[b] Palliative interventional: only TACE, percutaneous ethanol injection (PEI).
[c] Palliative supportive: chemotherapy, hormonal therapy, targeted therapies (i.e., sorafenib), radiotherapy on metastasis.
[d] Hazard ratios are adjusted for all other variables.

a 2.6-fold greater hazard compared to BCLC A patients. Considering the therapeutic approaches, patients undergoing palliative interventional or palliative supportive treatments or no treatment had a significantly higher risk of death in comparison with patients treated with a curative intent (reference group); the corresponding HRs were equal to 1.57 (95% CI: 1.12; 2.19), 3.62 (95% CI: 2.60; 5.02) and 4.69 (95% CI: 3.43; 6.41), respectively.

4. Discussion

In our study period, we observed a relative increase in three-year HCC survival, which almost doubled (from 21.7% in 1996–2000 to 35.4% in 2006–2009). There was a significant increase in patients undergoing palliative interventional treatment with TACE, whereas surgery and supportive palliative treatment remained stable. The significant increase in patients staged at diagnosis was not accompanied by a shift to earlier stages. The observed important shift of the diagnostic method (from histological verification to radiology only based diagnosis) seemed not to influence survival in the multivariate analysis.

Considering the stability of patients treated with curative surgery and the absence of a shift to earlier stages at diagnosis, the increase of survival probability could be due to an increase in patients undergoing TACE and possibly to an increase in accurately staged patients, thus enabling specific treatment. Detailed population-based studies are still lacking and further descriptive research is needed for comparative purposes.

The different factors cited above deserve additional discussion.

First, a survival increase of 45–65% between 1996 and 2009 was uniformly observed at 1, 2 and 3 years from diagnosis. Survival probability trends increased in southern Switzerland similarly to what has been reported in the US and Europe, even if CSS remains higher in Switzerland compared to the US and France (at three years, 24% in the US for 2000–2002, 17% in France for 1996–2005, 11% in Scotland in 2000–2004 and 28% in Switzerland for 2001–2005) [6,21,22].

Second, we re-staged all study patients through an extensive revision of single-patient medical reports according to the BCLC staging system, which is widely used in the clinical setting and encompasses all HCC patients (cirrhotic and not cirrhotic), with the aim of analysing an homogeneously staged population during the study period [23]. The current report is most likely the first at the population-based level using the BCLC staging system to assess survival trends retrospectively during a 15-year period. Moreover, due to the lack of similar reports in the literature, it can be used for future comparisons of survival results stratified by stage.

Patients with unknown BCLC stage had a survival probability similar to patients staged as BCLC C/D, suggesting that they corresponded to patients with a worse prognosis and were thus effectively not staged in the clinical setting, rather than truly missing at the cancer registry level. In fact, patients with unknown BCLC stage were most likely advanced cases who arrived to the physicians' attention too late to benefit from treatment or complete the staging.

Contrary to what was expected and observed in the US, we did not observe any relevant stage shifts to earlier forms during the study period, thus making this less likely to be associated with the observed survival increase in southern Switzerland [21]. A recent German study showed an increasing trend of advanced HCC and a reduction of earlier stages, more similar to our findings [24]. In the literature, it is hypothesised that because of the greater awareness concerning HCC, an increasing number of patients are being diagnosed with early disease via active screening, employing abdominal ultrasonography, serum alpha-fetoprotein testing and other means of diagnostic imaging [21,25]. Some studies and guidelines suggest active surveillance of patients at high risk of HCC using screening tools to reduce mortality [23,25,26]. In particular, according to different guidelines and studies, active surveillance is advocated for patients with chronic hepatitis B (CHB) and/or C (CHC), non-alcoholic or alcoholic steatohepatitis with liver cirrhosis, non-cirrhotic CHB with a high serum viral load and CHC with liver fibrosis as well as patients with hepatic iron overload by means of alpha-fetoprotein determination and periodic abdominal ultrasonography [10,23,25]. In our study, we interpret the increase of BCLC B and C/D patients as a real increase of patients being staged to receive the most appropriate treatment, confirmed by the observed reduction of HCC with missing stage along the study period. At the same time, the lack of increase in the number of stage A patients is difficult to explain.

Lacking comparable population-based studies analysing the BCLC staging system precludes us from performing a comparative discussion. The fact that age at diagnosis remained stable throughout the study period appears fully compatible with the lack of a shift of the population to earlier stages. Theoretically, if the pattern of risk factors was unchanged over time, short-term survival could be enhanced by diagnostic anticipation (lead-time bias), and diagnostic anticipation should also be associated with earlier age at diagnosis. The lack of decrease of age at diagnosis is therefore compatible with the lack of stage shift that was observed, thus supporting the hypothesis that lead-time bias is not responsible for the observed survival increase.

Third, we observed a statistically significant increase in HCC diagnosed without histological proof, confirming that the diagnosis of HCC is more often based on imaging than microscopy. Similar results have been observed in a recent study in France [6]. Currently, different guidelines accept the use of non-invasive imaging approaches to confirm an HCC diagnosis, particularly for cirrhotic patients using multiple-phase CT scan or dynamic contrast MRI [23,25,27]. Although a non-microscopical based diagnosis could also lead to a HCC over/under diagnosis or misdiagnosis with a possible impact on the survival results, the method used to confirm the diagnosis was not an independent prognostic factor of survival in the final multivariate regression model.

Finally, considering the discussion above, the treatment approach could have played a major role in the observed survival change. We documented a clear increase in patients receiving TACE, whereas the proportion of patients undergoing curative surgery remained stable, which is compatible with the measured BCLC stage distribution trends. Moreover, TACE has been associated with improved survival in different clinical trials, particularly for patients with preserved liver function [28,29]. A meta-analysis in 2004 confirmed the survival benefit of TACE [30]. Similar results were observed in the US in the most recent analysis of Surveillance Epidemiology and End Results data in the period 1997–2004, where an increase in treated patients was clearly observed, and in Germany in a clinical observational study [21,24].

In conclusion, the current report describes a major increase in the survival of HCC patients. The documented increased use of palliative interventional treatment as well as the increased number of staged patients, allowing a more effective treatment, could have played a relevant role in the survival improvement. Possibly, additional efforts should be made to diagnose HCC at earlier stages through active surveillance of patients at risk and thus offer the benefits of curative treatments to a larger number of patients, but further studies are needed. For sure efforts should be made to comply with a standardised staging system for HCC, particularly for comparative population-based issues.

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Conflict of interest statement

The authors indicate no potential conflicts of interest.

Authorship contribution

We declare that all authors of this research paper have met the criteria for authorship as established by the International Committee of Medical Journal Editors. All authors directly participated in the planning, execution or analysis of the study and have full access to all of the data to verify the validity of the results reported. All authors take responsibility for the integrity of the data and the accuracy of the data analysis and believe that the paper represents honest work. All authors have read and approved the final version of the submitted paper.

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