Original article

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Treatment patterns and survival in patients with hepatocellular carcinoma in the Swedish national registry SweLiv

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Background: **Consistent data on clinical features, treatment modalities and long-term survival in patients with hepatocellular carcinoma (HCC) using nationwide quality registers are lacking. This study aimed to describe treatment patterns and survival outcomes in patients diagnosed with HCC using a national maintained database.**

Methods: **Characteristics and treatment patterns in patients diagnosed with HCC and registered in the national register of liver and bile duct tumours (SweLiv) between 2009 and 2016 were reviewed. Overall survival (OS) was estimated using Kaplan–Meier analysis and the log rank test to compare subgroups for clinical features, treatment modalities and outcomes according to the year of treatment.**

Results: **A total of 3376 patients with HCC were registered over 8 years, 246 (7·3 per cent) of whom underwent transplantation. Some 501 (14·8 per cent) and 390 patients (11·6 per cent) had resection and ablation as primary treatment. Transarterial chemoembolization and systemic sorafenib treatment were intended in 476 (14·1 per cent) and 426 patients (12·6 per cent) respectively; the remaining 1337 (39·6 per cent) were registered but referred for best supportive care (BSC). The 5-year survival rate was approximately 75 per cent in the transplantation group. Median OS was 4·6 (i.q.r. 2·0 to not reached) years after resection and 3·1 (2·3–6·7) years following ablation. In patients referred for palliative treatment, median survival was 1·4 (0·8–2·9), 0·5 (0·3–1·2) and 0·3 (0·1–1·0) years for the TACE, sorafenib and BSC groups respectively ($P < 0·001$). Median survival was 0·9 years for the total HCC cohort in 2009–2012, before publication of the Swedish national treatment programme, increasing to 1·4 years in 2013–2016 ($P < 0·001$).**

Conclusion: **The survival outcomes reported were in line with previous results from smaller cohorts. The introduction of national guidelines may have contributed to improved survival among patients with HCC in Sweden.**

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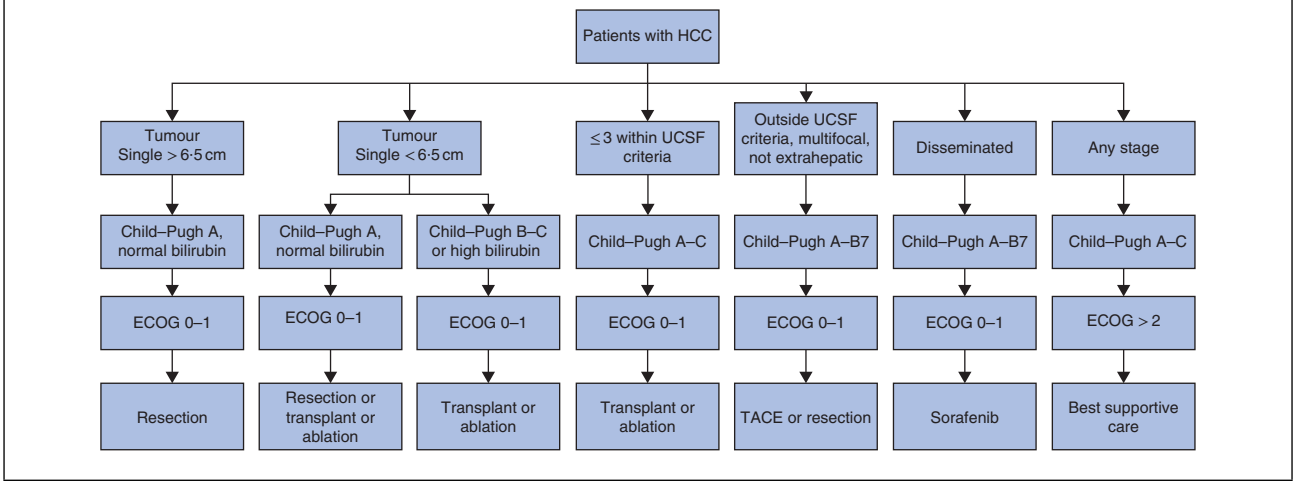
Introduction

Hepatocellular carcinoma (HCC) is the most common type of liver cancer worldwide[1]. In Sweden, the incidence of HCC is approximately five per 100 000 in men aged 55 years, with an age-increasing trend that reaches a peak of 30 per 100 000 in men aged 75 years[2]. In women, the HCC incidence is approximately one-third that of men of the same age[2].

About 500 patients with HCC among the ten million Swedish inhabitants are diagnosed every year. Six referral centres provide curative treatments, two of which also perform transplantations. In these patients, clinical features such as tumour burden, general health status and liver

Fig. 1 Swedish treatment algorithm for hepatocellular carcinoma



HCC, hepatocellular carcinoma; UCSF, University of California, San Francisco; ECOG, Eastern Cooperative Oncology Group performance status; TACE, transarterial chemoembolization.

function are all considered when deciding on the appropriate management[3].

The Swedish SweLiv registry was launched in 2008, and aimed to include all patients with malignancies of the liver, gallbladder and bile ducts, covering about 95 per cent of the patients treated in Sweden[2]. The registry includes also interventions (resections, ablations and transplantations) related to both primary and secondary liver malignancy[3], and was validated in 2014[4].

Furthermore, a national treatment programme for patients with HCC was launched in 2012 and updated in 2015. This programme includes a treatment algorithm that is closely related to the Barcelona Clinic Liver Cancer (BCLC) algorithm.

A contemporary nationwide data set of HCC including patient characteristics, treatment patterns and related outcomes has not been investigated so far. This study aimed to describe the HCC national cohort, including treatments and interventions, and to investigate long-term survival outcomes.

Methods

Ethical approval for the study was granted by the ethical vetting board at Linköping University (Dnr 2017/29-31).

SweLiv

Patient registration is based on four modules: the initial entry module includes diagnosis, staging and treatment recommendations; the intervention module consists of tumour treatment by ablation, resection or transplantation; the third module covers complications and pathology; and the follow-up module, introduced in 2014, covers information regarding recurrence based on a 2-year follow-up after the first registration. The survival status of the patients entered into the register is updated continuously by linkage to the Swedish national population register.

Patients

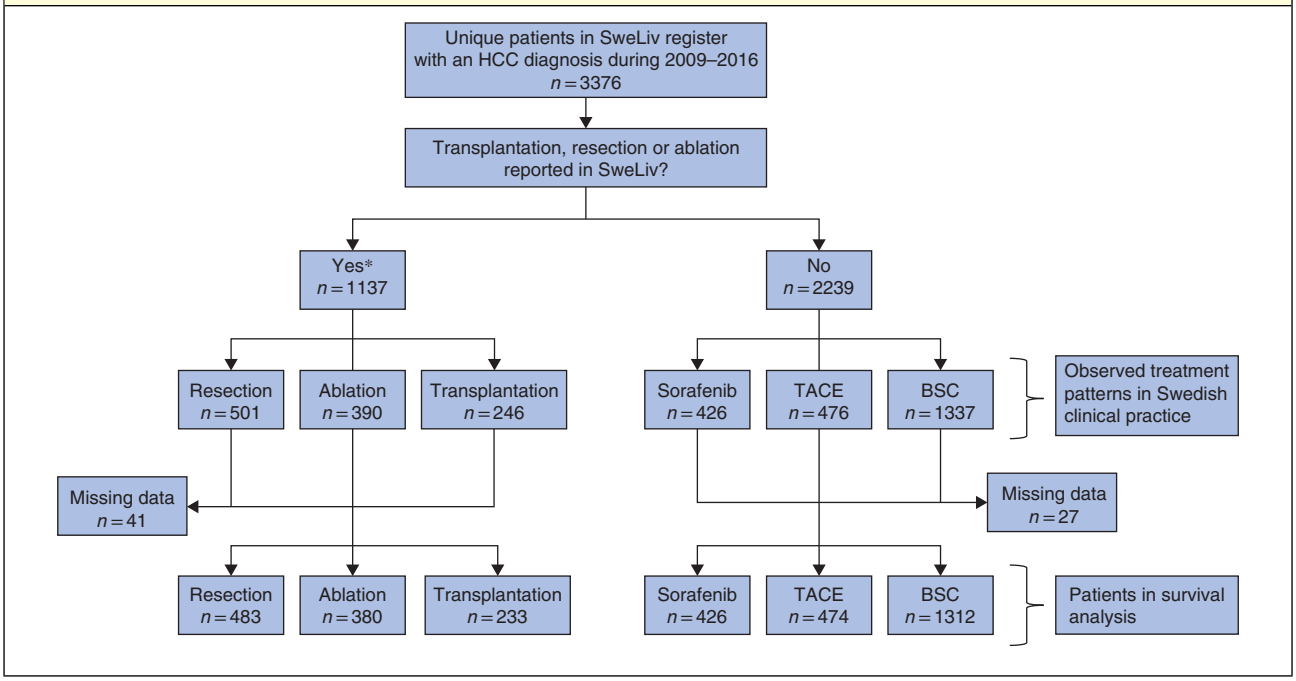
All patients registered with a diagnosis of HCC (ICD-10 code C22.0) between 1 January 2009 and 31 December 2016 (approximately 95 per cent of all patients with HCC in Sweden) were reviewed and included in the present analysis. Patients were analysed independently from age, sex, tumour location and histological type. Patient characteristics including age, sex, Eastern Cooperative Oncology Group (ECOG) score and BCLC stage were extracted from the SweLiv to provide a baseline description of the study population. In the registry, ECOG score was used to describe not only the effect of HCC on the ECOG score but also the overall performance status.

In addition, the proportion of patients being referred to and evaluated at one of the six hepatobiliary multidisciplinary centres was reported.

Treatment

Treatment patterns were described according to the intervention module and recommendations offered to patients, including a palliative treatment plan with

Fig. 2 Treatment patterns and patients available for analysis



*Patients with multiple treatments reported in SweLiv were categorized as follows: transplantation if the patient underwent transplantation at any point regardless of preceding treatments; resection if the patient had a resection before ablation and did not undergo transplantation; ablation if the patient underwent ablation before resection and did not receive a transplant. Missing data: starting date or event/censoring date was missing or an event indicator was missing. HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization; BSC, best supportive care.

transarterial chemoembolization (TACE), medical treatment (sorafenib) or best supportive care (BSC), as reported in the initial entry module. Notably, there was no information available in the registry regarding whether palliative treatment was actually provided. *Fig. 1* illustrates the flow diagram for treatment of HCC according to the national programme launched in 2012.

Patients were categorized according to the following treatments: transplantation, if the patient was transplanted during the study period; resection, if the patient underwent resection before ablation and did not undergo transplantation; ablation, if the patient underwent ablation before resection and did not receive a transplant; TACE, if the patient was planned for TACE only; sorafenib, if the patient was planned for only this treatment; or BSC, if the patient had no active treatment as reported in SweLiv during the study interval. The starting date in the analysis was the reported date of treatment for patients who underwent transplantation, resection or ablation. For patients receiving TACE, sorafenib or BSC, the date of treatment recommendation was defined as the starting date. If this date was missing, the date of multidisciplinary management or the date of diagnosis was imputed as the starting date.

Outcomes

Overall survival (OS) was defined as the time from the treatment or palliative care decision to the date of death or the last date for survival status updates (10 August 2017).

Statistical analysis

Clinical features are reported as proportions and compared with the χ^2 test if categorical, and as mean(s.d.) or median (range) values and compared using one-way ANOVA and Mann–Whitney *U* tests respectively, if continuous variables. Kaplan–Meier analysis was used to estimate survival conditional on the treatment category and subgroup, and compared with the log rank test. Median survival was reported for each treatment group using years and interquartile ranges.

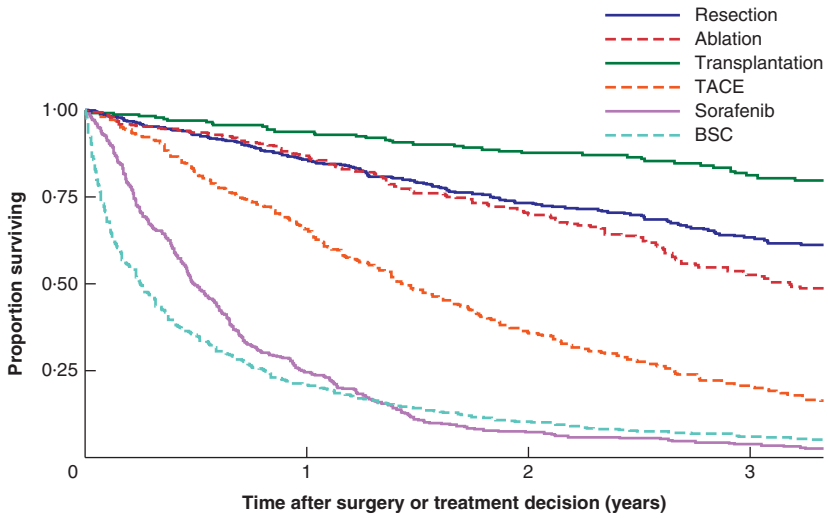
Survival for Child–Pugh A *versus* B grades was analysed in patients treated with TACE, sorafenib or BSC. OS was also investigated according to cirrhosis status at diagnosis and in patients with an ECOG score of 2. The impact of the introduction of national guidelines on OS in the HCC cohort was explored by comparing survival before

Table 1 Baseline characteristics by treatment strategy

	All patients (*n* = 3308)	Treatment category						*P*¶
		Transplantation (*n* = 233)	Ablation (*n* = 380)	Resection (*n* = 483)	TACE (*n* = 474)	Sorafenib (*n* = 426)	BSC (*n* = 1312)	
Age (years)*	68 (16–94)	59 (19–73)	67 (33–86)	69 (18–88)	69 (29–89)	67 (16–91)	72 (25–94)	< 0·001#
Sex								0·005
M	2492 (75·3)	190 (81·5)	300 (78·9)	338 (70·0)	352 (74·3)	331 (77·7)	981 (74·8)	
F	816 (24·7)	43 (18·5)	80 (21·1)	145 (30·0)	122 (25·7)	95 (22·3)	331 (25·2)	
Multidisciplinary conference	*n* = 3261	*n* = 233	*n* = 380	*n* = 481	*n* = 473	*n* = 424	*n* = 1270	< 0·001
Yes	2723 (83·5)	205 (88·0)	359 (94·5)	453 (94·2)	444 (93·9)	377 (88·9)	885 (69·7)	
No	538 (16·5)	28 (12·0)	21 (5·5)	28 (5·8)	29 (6·1)	47 (11·1)	385 (30·3)	
Underlying liver disease	*n* = 3206	*n* = 226	*n* = 374	*n* = 453	*n* = 467	*n* = 416	*n* = 1270	< 0·001
Yes (any)	1973 (61·5)	217 (96·0)	318 (85·0)	244 (53·9)	313 (67·0)	225 (54·1)	656 (51·7)	
No	1233 (38·5)	9 (4·0)	56 (15·0)	209 (46·1)	154 (33·0)	191 (45·9)	614 (48·3)	
Type of liver disease‡								
Porphyria	20 (0·6)	0 (0)	2 (0·5)	14 (3·1)	2 (0·4)	0 (0)	2 (0·2)	< 0·001
Hepatitis B infection	196 (6·1)	25 (11·1)	21 (5·6)	36 (7·9)	28 (6·0)	33 (7·9)	53 (4·2)	< 0·001
Hepatitis C infection	949 (29·6)	130 (57·5)	166 (44·4)	112 (24·7)	154 (33·0)	110 (26·4)	277 (21·8)	< 0·001
Haemochromatosis	40 (1·2)	3 (1·3)	5 (1·3)	11 (2·4)	4 (0·9)	6 (1·4)	11 (0·9)	0·195
Alcohol-associated	803 (25·0)	59 (26·1)	164 (43·9)	60 (13·2)	125 (26·8)	85 (20·4)	310 (24·4)	< 0·001
ECOG performance status	*n* = 2013	*n* = 144	*n* = 297	*n* = 348	*n* = 318	*n* = 244	*n* = 662	
0–1	1327 (65·9)	115 (79·9)	253 (85·2)	324 (93·1)	251 (78·9)	162 (66·4)	222 (33·5)	< 0·001
2	425 (21·1)	25 (17·4)	39 (13·1)	23 (6·6)	62 (19·5)	67 (27·5)	209 (31·6)	
3–4	261 (13·0)	4 (2·8)	5 (1·7)	1 (0·3)	5 (1·6)	15 (6·1)	231 (34·9)	
Child–Pugh grade	*n* = 2137	*n* = 188	*n* = 276	*n* = 319	*n* = 347	*n* = 256	*n* = 751	
A	1191 (55·7)	97 (51·6)	192 (69·6)	285 (89·3)	230 (66·3)	151 (59·0)	236 (31·4)	< 0·001
B	733 (34·3)	64 (34·0)	83 (30·1)	34 (10·7)	110 (31·7)	95 (37·1)	347 (46·2)	
C	213 (10·0)	27 (14·4)	1 (0·4)	0 (0)	7 (2·0)	10 (3·9)	168 (22·4)	
Size of largest tumour	*n* = 2924	*n* = 226	*n* = 377	*n* = 477	*n* = 453	*n* = 355	*n* = 1036	
Diameter (mm)†	63(52)	32(24)	27(30)	59(43)	64(47)	90(62)	76(53)	< 0·001**
≤ 20	480 (16·4)	69 (30·5)	161 (42·7)	80 (16·8)	19 (4·2)	27 (7·6)	124 (12·0)	< 0·001
21–50	1120 (38·3)	137 (60·6)	204 (54·1)	203 (42·6)	206 (45·5)	77 (21·7)	293 (28·3)	
> 50	1324 (45·3)	20 (8·8)	12 (3·2)	194 (40·7)	228 (50·3)	251 (70·7)	619 (59·7)	
No. of tumours	*n* = 2716	*n* = 217	*n* = 374	*n* = 463	*n* = 428	*n* = 299	*n* = 935	
No. of tumours†	2·22(2·76)	1·70(1·24)	1·59(0·99)	1·50(4·42)	2·60(2·65)	3·12(2·77)	2·48(2·29)	< 0·001**
1–3	2272 (83·7)	206 (94·9)	355 (94·9)	450 (97·2)	340 (79·4)	200 (66·9)	721 (77·1)	< 0·001
≥ 4	444 (16·3)	11 (5·1)	19 (5·1)	13 (2·8)	88 (20·6)	99 (33·1)	214 (22·9)	
M category	*n* = 2993	*n* = 216	*n* = 358	*n* = 385	*n* = 447	*n* = 411	*n* = 1176	< 0·001
M0	2403 (80·3)	210 (97·2)	349 (97·5)	373 (96·9)	418 (93·5)	252 (61·3)	801 (68·1)	
M1	490 (16·4)	1 (0·5)	5 (1·4)	6 (1·6)	16 (3·6)	146 (35·5)	316 (26·9)	
MX	100 (3·3)	5 (2·3)	4 (1·1)	6 (1·6)	13 (2·9)	13 (3·2)	59 (5·0)	
BCLC stage§	*n* = 1941	*n* = 120	*n* = 212	*n* = 241	*n* = 230	*n* = 305	*n* = 833	< 0·001
0	40 (2·1)	3 (2·5)	20 (9·4)	14 (5·8)	1 (0·4)	0 (0)	2 (0·2)	
A	302 (15·6)	39 (32·5)	77 (36·3)	127 (52·7)	38 (16·5)	8 (2·6)	13 (1·6)	
B	47 (2·4)	3 (2·5)	10 (4·7)	3 (1·2)	20 (8·7)	6 (2·0)	5 (0·6)	
C	1118 (57·6)	47 (39·2)	99 (46·7)	96 (39·8)	159 (69·1)	266 (87·2)	451 (54·1)	
D	434 (22·4)	28 (23·3)	6 (2·8)	1 (0·4)	12 (5·2)	25 (8·2)	362 (43·5)	

Values in parentheses are percentages unless indicated otherwise; values are *median (range) and †mean(s.d.). ‡As patients may have had more than one underlying liver disease reported, the total number of patients with a specified liver disease may exceed that reported for patients with any liver disease. §Barcelona Clinic Liver Cancer (BCLC) stage was derived from information in SweLiv using the following algorithm: stage 0 if one tumour smaller than 2 cm, Eastern Cooperative Oncology Group (ECOG) score 0, and Child–Pugh grade A; stage A if one tumour only or up to three tumours with largest diameter 3 cm or more, ECOG score 0, and Child–Pugh grade A or B; stage B if more than three tumours, ECOG score 0, and Child–Pugh grade A or B; stage C if N1 or M1 category or surgical invasion, ECOG score 1 or 2, and Child–Pugh grade A or B; or stage D if ECOG score 3 or 4, or Child–Pugh grade C. TACE, transarterial chemoembolization; BSC, best supportive care. ¶χ^2 test, except #Mann–Whitney *U* test and **ANOVA.

Fig. 3 Overall survival according to treatment performed or strategy planned



No. at risk				
Resection	483	376	246	158
Ablation	380	284	177	94
Transplantation	233	207	167	114
TACE	474	280	119	57
Sorafenib	426	95	26	12
BSC	1312	247	104	53

For transplantation, resection and ablation groups, survival was estimated from the day of operation. For transarterial chemoembolization (TACE), sorafenib and best supportive care (BSC) groups, survival was estimated from the day of treatment recommendation at multidisciplinary conference. Note that treatment groups are not comparable due to different tumour burden and ECOG score. $P < 0{\cdot}001$ (log rank test).

2013 (year of guideline introduction) with that from 2013 onwards.

Results

Of 3376 patients with HCC registered in SweLiv during the study period, 2039 (60·4 per cent) were recommended to receive treatment, either curative or palliative. A total of 246 (7·3 per cent), 501 (14·8 per cent) and 390 patients (11·6 per cent) underwent transplantation, resection and ablation respectively. TACE and systemic sorafenib treatment were intended in 476 (14·1 per cent) and 426 (12·6 per cent) patients respectively, whereas 1337 patients (39·6 per cent) were referred for BSC (*Fig. 2*).

The mean patient age was 67·8 years, and the male : female ratio was 3 : 1. The two main causes of HCC were hepatitis C infection and alcohol-associated liver disease, which represented more than half of the patients, whereas no associated liver disease was reported in more than one-third (*Table 1*). In 39·9 per cent of the patients (48·7 per cent of women and 37·1 per cent of men), no cirrhosis was detected. Non-alcohol-induced steatohepatitis has been registered in SweLiv since 2013 (57·2 per cent of the present patients), and was reported in 3·6 per cent of the patients; diabetes was reported in 3·8 per cent. Patients undergoing transplantation were younger than those in the other treatment categories (median 59 years *versus* 72 years in the BSC group; $P < 0{\cdot}001$ for overall difference between treatment categories).

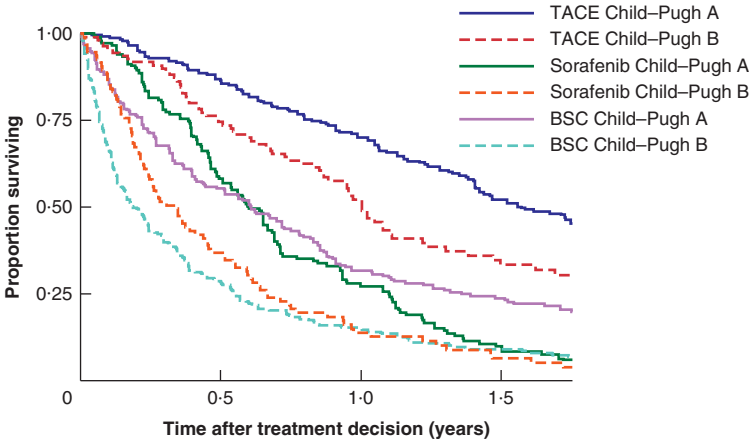
Overall, patient characteristics at baseline were statistically significantly different across treatment modalities (*Table 1*).

The majority of the patients (83·5 per cent) were referred to and evaluated in a multidisciplinary conference at one of the six liver centres in Sweden. Some 16·5 per cent of patients with advanced disease and severe co-morbidity (ECOG 3–4) were treated at primary hospitals with BSC.

Survival outcomes

Fig. 3 shows OS across treatment categories. As expected, the transplantation group had the most improved outcome, with an estimated 5-year survival rate of approximately 75 per cent. Median OS was 4·6 (i.q.r. 2·0 to not reached) years

Fig. 4 Overall survival of patients referred to palliative treatment according to Child–Pugh grade



No. at risk				
TACE Child–Pugh A	230	198	145	96
TACE Child–Pugh B	110	82	48	25
Sorafenib Child–Pugh A	151	88	37	13
Sorafenib Child–Pugh B	95	35	12	5
BSC Child–Pugh A	236	130	64	43
BSC Child–Pugh B	347	97	49	26

TACE, transarterial chemoembolization; BSC, best supportive care. $P < 0{\cdot}001$ (log rank test).

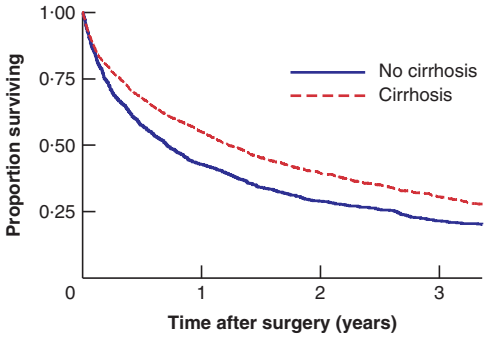
after resection and 3·1 (2·3–6·7) years after ablation. For patients in whom palliative treatment was planned, median survival calculated starting from the treatment decision was 1·4 (0·8–2·9), 0·5 (0·3–1·2) and 0·3 (0·1–1·0) years for the TACE, sorafenib and BSC groups respectively ($P < 0{\cdot}001$).

Fig. 4 shows survival according to Child–Pugh grade in three different treatment groups: among patients with Child–Pugh grade B disease, median survival was 1·0 (i.q.r. 0·5–2·0) years in the TACE group, 0·3 (0·2–0·7) years in the sorafenib group and 0·2 (0·1–0·6) years in the BSC group ($P < 0{\cdot}001$). Accordingly, in patients with Child–Pugh grade B disease, the survival duration was approximately 1·7 months longer in patients planned for sorafenib treatment than in those receiving BSC. In patients with Child–Pugh grade A disease, median survival was similar for BSC and planned sorafenib treatment (approximately 0·5 years in both groups), although the BSC group contained an apparently higher proportion of patients surviving in the longer term (1·5–2·5 years) ($P < 0{\cdot}001$).

Median survival of patients with cirrhosis at diagnosis was 0·5 years greater than that of patients without cirrhosis ($P < 0{\cdot}001$) (*Fig. 5*).

Survival rates for the 20·5 per cent of patients (87 of 425) with an ECOG score of 2 who were treated with transplantation, resection or ablation are presented in *Fig. 6*. Median survival for the ablation subgroup was 2·7 years, whereas median survival was not reached in the transplantation and resection subgroups ($P < 0{\cdot}001$).

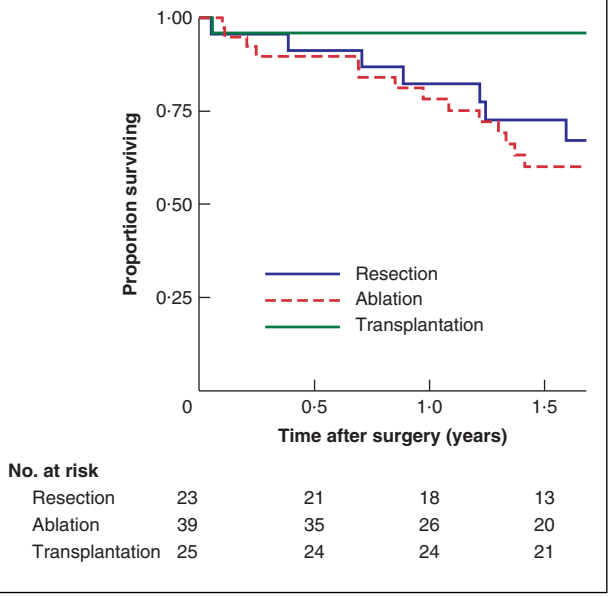
Fig. 5 Overall survival of patients according to cirrhosis status



No. at risk				
No cirrhosis	1325	519	291	165
Cirrhosis	1895	931	524	308

$P < 0{\cdot}001$ (log rank test).

Fig. 6 Overall survival of patients with an ECOG score of 2 who underwent transplantation, resection or ablation



$P < 0{\cdot}001$ (log rank test).

Treatment recommendations in Swedish national guidelines

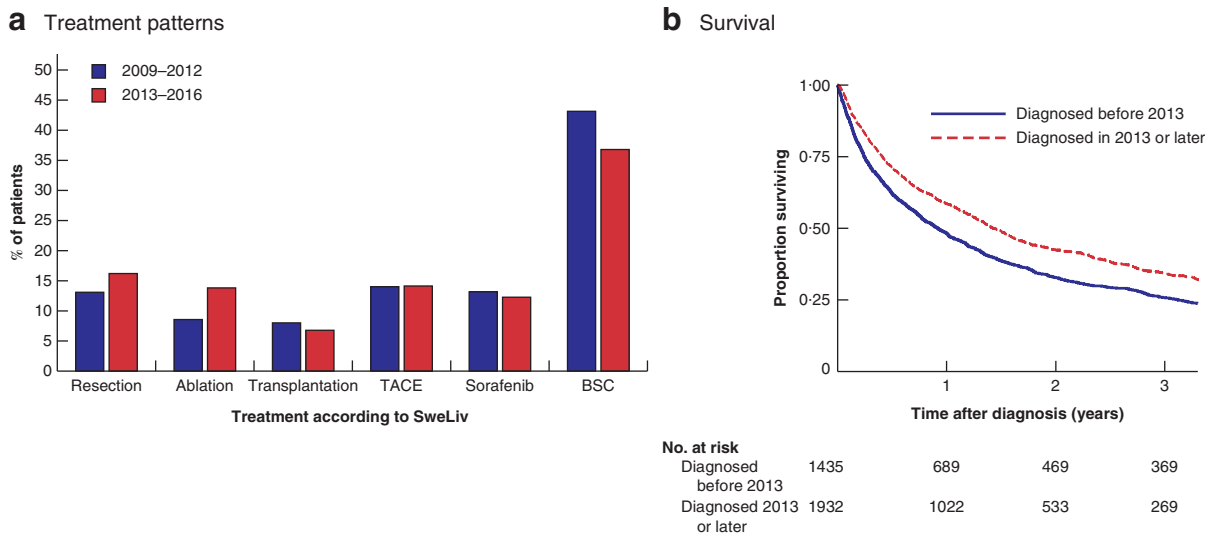
Overall treatment patterns differed between the two time periods before and after the introduction of national guidelines ($P < 0{\cdot}001$). The proportion of patients treated with ablation increased from 8·6 to 13·8 per cent, and the proportion treated with resection increased from 13·1 to 16·2 per cent. In contrast, the proportion of patients planned for BSC reduced from 43·1 to 36·8 per cent in the two time periods (*Fig*. 7*a*).

Median survival was 0·9 years for the total HCC cohort in 2009–2012, before the Swedish national treatment programme was published, and increased to 1·4 years in 2013–2016, after its publication ($P < 0{\cdot}001$) (*Fig*. 7*b*).

Discussion

Since 2012, national guidelines for the treatment of HCC have been published in Sweden, and updated to keep up with current evidence. The introduction of these guidelines may have contributed to the increased median survival of more than 6 months for the whole cohort when patients diagnosed before 2013 were compared with those diagnosed subsequently. For example, the proportion of patients receiving curative treatment increased in recent years: one-third of all patients were treated with transplantation, resection or ablation, and these groups had overall 5-year survival rates of 73·9, 47·1 and 30·1 per cent respectively. Although national data are sparse, data from the SEER (Surveillance, Epidemiology, and End Results) registry, covering approximately 28 per cent of the US

Fig. 7 Overall treatment patterns and survival before and after introduction of the national guidelines



a Treatment patterns and **b** survival in patients diagnosed in 2009–2012 and 2013–2016. TACE, transarterial chemoembolization; BSC, best supportive care. **b** $P < 0{\cdot}001$ (log rank test).

population, for 2000–2010 showed that 23 per cent of the patients received potentially curative treatment, although this proportion did not increase over time[5]; the curative treatment rate was lower than the 34 per cent found in the present study. As reported by others[6], the survival rate after liver transplantation for HCC exceeds that observed after resection, although the groups are hardly comparable because patients selected for resection are usually older with larger tumours and lower Child–Pugh grade and BCLC stage.

More than 20 per cent of all patients with an ECOG score of 2 were offered transplantation, resection or ablation outside the recommended guidelines. Survival of these patients was clearly better than that of patients with planned BSC, who thus also need active evaluation in a multidisciplinary setting.

TACE is performed mainly with drug-eluting beads in Sweden. The median OS of 1·4 years for patients in the TACE group was similar to that reported by large single centres[7], although patients in the present cohort were older. There was a notably small survival difference between sorafenib-treated patients and those who received BSC, although the latter patients were older and had a higher ECOG score. However, the lack of data on actual doses administered in this study does not allow any conclusions to be drawn, as the tolerability of sorafenib treatment varies highly between individuals[8]. Survival of patients with Child–Pugh grade B disease was lower than that of patients with Child–Pugh grade A disease in both the sorafenib and TACE groups, based on subgroup analysis, an effect also observed by others[9,10]. Survival was better in the cohort of patients with liver cirrhosis than in those without cirrhosis. This could be related to the fact that patients with cirrhosis are diagnosed at an earlier stage with smaller tumours, possibly in the setting of a surveillance programme as included in the national guidelines.

A surprisingly large proportion of patients offered BSC had an ECOG score of 0–1 and a low Child–Pugh grade, possibly indicating that there is still a margin for improvement in the treatment of HCC in Sweden.

Up to 40 per cent of patients in the registry had no radiological signs of cirrhosis, in contrast to other findings[11]. In addition, in more than one-third of patients there was no known associated liver disease, indicating a large group of patients with unknown aetiology. A deeper analysis of these groups is needed to clarify these findings.

The strengths of the SweLiv registry are its high coverage, more than 95 per cent of the population, and the ability to validate the coverage against the Swedish cancer registry, using the Swedish social security number system, to ensure that as few patients as possible are missing. The main strength of this study was that it included a nationwide cohort of patients with HCC retrieved from a validated registry with high coverage, thereby eliminating the selection bias inherent to smaller, isolated cohorts. However, the SweLiv register has some important limitations that affect interpretation of the findings, such as the lack of data on actual administration of TACE, sorafenib and BSC. Thus, the results are based on what treatment was recommended during multidisciplinary management. Further analysis of these patient groups would be of value to ascertain correct survival outcomes in these groups and, ultimately, to record data on these treatments in the SweLiv registry. Furthermore, the data were not complete for some of the parameters, as noted in *Table 1*. As future research may include risk stratification and survival outcomes in more refined subgroups, it is important to increase data completeness in the registry. Indeed, recent measures have been undertaken to ensure such improvements, and to enable more refined research questions to be explored. These findings suggest that the survival outcomes in this national cohort are in line with previously reported outcomes in smaller cohorts, and that the introduction of national guidelines may have contributed to improved survival among patients with HCC.

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