ACTA ONCOLOGICA, 2016
VOL. 55, NO. 3, 297–302
http://dx.doi.org/10.3109/0284186X.2015.1080857

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ORIGINAL ARTICLE

Staging and therapy for patients with hepatocellular cancer in a defined population from 2000 to 2011 – active palliative treatment improved overall survival

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ABSTRACT

Background: Sweden's western region has successively introduced the use of validated non-invasive diagnostic algorithms and treatment allocation for hepatocellular cancer (HCC). The aim was to analyse whether between 2000 and 2011 these changes in strategy had an impact on survival.

Methods: Data concerning diagnosis, survival and treatment for 687 individuals with HCC were retrieved from the regional cancer centre's register and hospital charts. The 12-year period was divided into three four-year cohorts (A-B-C).

Results: There was an increase in the crude incidence rate of HCC from 2.7 to 4.2 per 100 000 inhabitants ($p < 0.0001$) over the period studied. Imaging was increasingly used for diagnosis over the three time periods (1.4%, 7.9% and 29%; $p < 0.0001$). Alcohol abuse was the most common aetiology for underlying liver disease (42%). The median survival time for all HCC patients improved over time – period A: 3.8 months, period B: 5.1 months and period C: 7.0 months ($p = 0.0007$). The 209 patients without any underlying liver disease had a worse survival than the 377 with a reported underlying liver disease ($p = 0.0001$). Active palliative treatment (APT) increased from 17% to 35% during period C ($p < 0.0001$). For these patients, median survival increased from 8.8 months to 14.2 months. Best supportive care was used less over time.

Discussion: Overall survival improved when more patients had APT, mainly trans arterial chemoembolisation (TACE).

HISTORY
Received 13 April 2015
Revised 29 July 2015
Accepted 3 August 2015
Published online
29 September 2015

To more clearly understand the impact of new diagnosis and treatment strategies it is important to use the entire cohort of persons with the disease. Such a total survival analysis must include pre-hospital mortality data along with individuals hospitalised with advanced disease who have non-intervention care. Few hepatocellular cancer (HCC) studies describe the entire cohort for a defined geographical area.

The diagnosis of HCC depends on the carcinogenic process in the liver that evolves over a subclinical period for several years. In a majority of patients, between 60% and 70% in Sweden, there is underlying liver disease, mainly liver cirrhosis. In a cirrhotic liver there is an ongoing low-grade cell death that causes a continuous regeneration of liver cells and, as a further consequence, a high rate of cell duplication and cell dysplasia.

Clinical staging instruments have been validated in restricted populations, such as liver resection cohorts and exclude persons with an extremely poor prognosis. Algorithms have been introduced, like the Barcelona Clinic Liver Cancer (BCLC), which facilitate correct use of the therapeutic options available [1]. The BCLC classification defines treatment allocation not only by tumour stage, but also by liver function and patient performance.

Refined diagnostic methods have been increasingly used in recent decades to diagnose HCC at an earlier stage [1]. These methods are based on the vascularisation of the HCC, i.e. loading and washout of contrast media. Magnetic resonance imaging (MRI) with liver-specific contrast media has shown to have the highest sensitivity (81%) and specificity (85%) for HCC [2]. Observations of changes in vascularisation when a dysplastic nodule undergoes malignant transformation have been the basis for the introduction of non-invasive HCC diagnostic algorithms. These algorithms, accepted by European Association for Study of the Liver (EASL) and American Association for Study of Liver Disease (AASLD), were introduced in Sweden during the study's time period.

Liver transplantation (Tx) offers a curative option for patients with an underlying liver disease and no clinical evidence of vascular invasion or extra-hepatic cancer. The five-year survival is similar to survival for Tx in patients without HCC; i.e. 60–75% [3,4] if transplant is within the Milan or University of California San Fransisco (UCSF)-criteria.

Liver resection (Rx) is a curative option in patients with a resectable tumour and adequate liver function [5–7]. A meta-analysis has identified a 10% increase in five-year survival for

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Tx versus Rx for individuals with HCC who fall within the Milan criteria [8].

Local radiofrequency ablation (RFA) of HCC is described as almost equivalent to Rx in selected patients with tumour(s) smaller than 3 cm [9,10].

Among active palliative procedures (APT), i.e. treatment without curative intention, chemoembolisation [trans arterial chemoembolization (TACE)] offers a prolonged median survival of more than one year when there is no extra hepatic growth and there is a Child-Pugh grade A liver function [11]. During the last decade TACE has been standardised and the complication rate has decreased through the usage of doxorubicin-loaded beads [12]. Systemic therapy using the kinase inhibitor sorafenib, which targets VEGF, PDGF and Raf-kinases, was introduced in 2007. Sorafenib (Nexavar®) prolongs survival from 8 to 11 months among individuals classed as Child-Pugh A [13].

The aim of the present study was to analyse all persons with HCC in a well defined region of Sweden during 2000–2011 to explore if changes in diagnostic procedures and therapeutic strategies had an impact on survival for the complete population with the diagnosis of HCC.

Study population and data collection

The Healthcare Region of Western Sweden served by the Regional Cancer Center (RCC) has a population between 1.65 and 1.76 million during the study period. The management of HCC is centralised at one university hospital. The liver surgery unit administers all treatment for HCC; from palliative to transplantation.

This study was based on the reported HCC-cases to the RCC.

This study used RCC register as it contained the area's complete HCC diagnostic record. This register records all individuals with a histopathologically verified diagnosis of HCC. When a physician made a clinical diagnosis of HCC was established in accordance with the EASL-protocol [e.g. radiography, alpha-fetoprotein (AFP) and underlying liver disease] [14] the register was notified. EASL-guidelines were implemented in 2007. Clinical staging was based on computed tomography (CT), MRI or ultrasound analysis of the abdomen and chest. In the event of a diagnostic exploratory laparoscopy/laparotomy, these findings were included in the clinical tumour-node-metastasis (TNM) staging. The histomorphologic grading of the surgical specimen was based on the Edmondson-Steiner scale. Included in the notification to RCC was the stage of the cancer, based on clinical and imaging findings. This was converted into TNM criteria (TNM 6 or 7) for the report to the register. Clinical and pathological information was retrieved from RCC records for this study. Additional information was obtained by reviewing individual patient charts. When several therapeutic procedures were described, the most important therapy was ranked as the instituted therapy. Forty-one patients were treated with several procedures and with an increasing number by time.

The importance of the therapies was ranked in order: Tx, Rx, RFA, TACE and sorafenib/sirolimus.

Data on pre- and postoperative adjuvant therapy was not collected. MDT conferences were introduced successively from 2004.

To help assess whether there was a continuous improvement in outcome, the data was divided into three equal time cohorts: Period A 2000–2003, Period B 2004–2007 and Period C 2008–2011.

Statistics

Survival time was calculated from date of diagnosis to date of death or last follow-up. The date of diagnosis was established by histopathologically or clinically. Observation time was more than 36 months or until death in all cases. Survival estimates were made using the Kaplan-Meier method and compared using the log-rank test. All statistics were calculated using StatView software, version 5.0 and Graph Pad Prism version 6.0. A p-value less than 5% was used as the level for statistical significance.

Ethics

The research was conducted in accordance with the Helsinki declaration on ethical principles for medical research involving human subjects.

Results

In total, 685 persons with HCC were included in the regional cancer register during 2000–11. In period A $n = 180$, period B $n = 214$ and period C $n = 291$ (Table I). There was an increase of 64% in crude incidence rate from period A to period C or from 2.7 to 4.2 per 100000 inhabitants ($p < 0.0001$).

There were less cases diagnosed with HCC at date of death (at autopsy) over time: in cohort A 24%, in cohort B 6% and in C 7% ($p < 0.0001$). These 79 cases were not included in further analyses.

Among the remaining 606 cases the diagnosis was verified by histopathology in 500, including cytology ($n = 30$). For 103 individuals, the diagnosis was based on clinical and radiological findings and supported by increased AFP above 200 units in 49 of them. There was an increasing number diagnosed by radiology over the three periods (1.4%, 7.9% and 29%; $p < 0.0001$). For three cases the method of diagnosis was not identified.

The male/female ratio was 2.4/1. The mean age among women was 71 years at the time of HCC diagnosis. Age at diagnosis was significantly lower for men (67 years; $p = 0.0002$). Those under the age of 50 diagnosed with HCC comprised 5.6% of the population (Table I). The proportion of persons older than 70 years decreased over the three periods, 59%, 51% and 43% ($p = 0.009$). Underlying liver disease increased from 51% in period A to 70% in period C ($p = 0.003$). The male/female ratio for those with an underlying liver disease was 3.7/1 and without underlying disease was 1.3/1. Alcohol abuse alone or in combination with other liver diseases was the most common aetiology for underlying liver disease and was seen in 42% of the total population. There was an increase in those with ethyl abuse in relation to the total number of patients

Table I. Demographics.

	2000–2003	2004–2007	2008–2011	Total	*p*-value
n (all)	180	214	291	685	
Post-mortem diagnosis	44	13	22	79	<0.0001
n (in analysis)	136	201	269	606	
Male/female	94/42	148/53	185/84	427/179	0.462
Ratio	2.2	2.8	2.2	2.4	
Mean age	70	68.4	67.4	68.3	0.144
Age cohorts					
20–49	5	12	17	34	0.533
50–59	21	34	56	111	
60–69	30	52	79	161	
70–79	52	67	64	183	
>80	28	36	53	117	0.795
	136	201	269	606	
No underlying liver disease	65	65	77	207	
Underlying liver disease	68 (51%)	130 (67%)	180 (70%)	378	0.003
Not stated	3	6	12	21	

Table II. Reported underlying liver disease.

	2000–2003	2004–2007	2008–2011	Total
Cirrhosis unspec.	17	35	36	87
Hep B	3	3	14	20
Hep C	12	28	24	64
Hep B + C	1	3	4	8
Ethylismus	15	27	35	77
Ethylismus + Hep B	0	2	1	3
Ethylismus + Hep C	8	16	37	61
Ethylismus + Hep B + C	1	3	8	12
Haemochromatosis	5	3	3	11
NASH + Steatosis unspec.	1	3	6	10
PBC	1	1	6	8
PSC	0	2	3	5
Other[a]	4	4	5	13
Not stated	3	6	12	21
Total	71	136	192	399

[a]Other includes alfa-1 deficiency, autoimmune disease, chronic hepatitis unspecified, fibrosis unspecified and porphyria.

Table III. Clinical staging, largest tumour size (percentage of cases with size revealed) and Child-Pugh's calculation of liver function.

Clinical staging	2000–2003	2004–2007	2008–2011	Total
T0	3 (2%)	7 (3%)	4 (1%)	14 (23%)
T1	33 (24%)	49 (24%)	75 (27%)	157 (26%)
T2	14 (10%)	16 (8%)	33 (12%)	63 (10%)
T3	39 (29%)	56 (28%)	80 (30%)	175 (29%)
T4	1 (1%)	0 (0%)	1 (0.4%)	2 (0.3%)
N1	6 (4%)	9 (4%)	15 (6%)	30 (5%)
M+	23 (17%)	45 (22%)	44 (17%)	112 (18%)
Not stated	17 (12%)	19 (9%)	17 (6%)	54 (9%)
Total	136	201	269	606
Size cm	8.3 (59%)	7.9 (66%)	7.0 (84%)	
Child-Pugh				
A	55 (40%)	76 (38%)	102 (38%)	233 (38%)
B	22 (16%)	24 (12%)	70 (26%)	116 (19%)
C	12 (9%)	33 (16%)	36 (13%)	81 (13%)
Not stated	47 (35%)	68 (34%)	61 (22%)	176 (29%)
	136	201	269	606

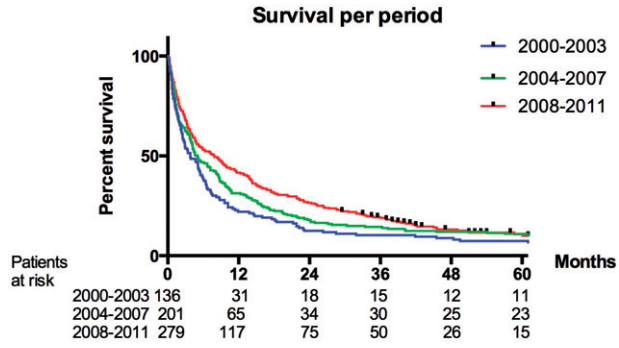

Figure 1. Survival curves for three time cohorts. Between period A and C there is an increase in overall survival ($p = 0.0007$), but not between period A and B ($p = 0.163$) and B and C ($p = 0.105$).

with HCC from 19% in period A to 32% in period C ($p = 0.01$). In relation to patients with underlying liver disease, the increase went from 31% to 47%. Hepatitis C was the second most common cause for underlying liver disease (38%) and was associated with alcohol abuse among 53% (Table II) of the population. The proportion with hepatitis C increased in the total HCC population ($p = 0.047$).

TNM-clinical staging (ICD 10) was made for 92% of the population. No staging migration could be identified from period A to period C (Table III). There were 14 patients in whom the diagnosis of HCC was not identified in the preoperative work-up, i.e. clinical T0 but the HCC was identified incidentally at abdominal exploration for other disease or by explanted liver histopathology.

Using radiological tools to estimate tumour size increased over the life of the study (A:59%, B:66%, C:84%). Actual tumour size decreased (from 8.3 cm in period A to 7.0 cm in period C; $p = 0.031$). For those with underlying liver disease the mean size was 6.3±4.3 cm. Among those with an underlying liver disease there was a size decrease between period B and C (6.9–5.8 cm; $p = 0.052$). Those without underlying disease had a mean size of 10.0±4.5 cm throughout the study (Table III).

There was an increased number of histomorphological grading performed over time (64% period A and 81% period C; $p = 0.0009$). There was significantly worse survival for those cases, whose biopsies' specimen not were graded ($p = 0.0048$) and there was no correlation between grading and clinical TNM-staging. The relative number of low differentiated cancers was 22% in patients with underlying liver disease and 27% in patients without underlying liver disease.

The median survival from the date of diagnosis for the 606 patients with HCC was 5.2 months. There were 14.5% people who survived for more than three years and 7.2% survived more than five years. Overall survival improved over time, between period A and C the increase was significant ($p = 0.0007$), but between period A and B and between B and C it was not significant (Figure 1). The median survival time for all HCC patients in each of the three periods was – period A: 3.8 months, period B: 5.1 months and period C: 7.0 months. Gender did not change survival time ($p = 0.34$).

The 209 persons without any information on underlying liver disease had a worse survival rate than the 378 with a reported underlying liver disease ($p = 0.0001$) (Figure 2). There was a trend that those with underlying liver disease had improved survival over time ($p = 0.06$). The group without underlying disease did not experience a similar improvement ($p = 0.27$). Compared to patients with other causes of liver disease, there was a better survival for those with HCV ($p = 0.03$) but not for persons with a history of alcohol abuse ($p = 0.77$). The Child-Pugh classification was utilized more frequently over time (Table III).

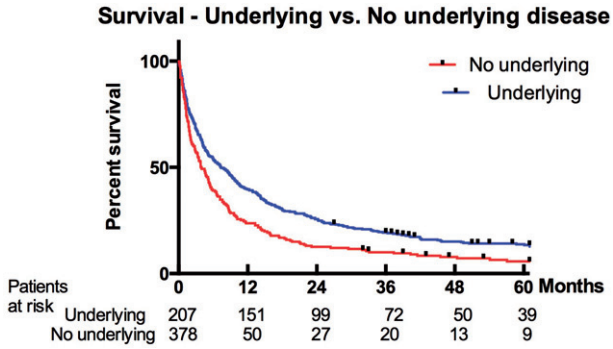

Figure 2. Overall survival with and without underlying liver disease ($p < 0.0001$).

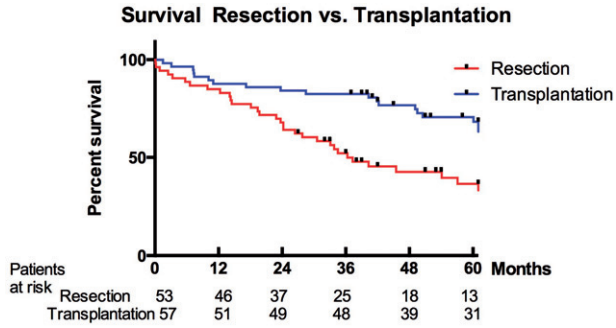

Figure 3. Overall survival from date of diagnosis for patients subjected to Tx ($n = 57$) and Rx ($n = 53$) ($p < 0.0003$).

Table IV. Therapy per period.

	2000–2003	2004–2007	2008–2011	Total
Curative	21 (15%)	41 (20%)	47 (17%)	109 (17%)
Transplantation	14 (10%)	18 (9%)	25 (9%)	57 (9%)
Liver resection	7 (5%)	23 (11%)	23 (8%)	53 (9%)
Active palliative	23 (17%)	31 (15%)	95 (35%)	149 (25%)
Chemotherapy	1 (1%)	1 (0.5%)	2 (0.7%)	4 (0.7%)
Cox 2	11 (8%)	2 (1%)	1 (0.4%)	14 (2%)
RFA	1 (1%)	6 (3%)	13 (5%)	20 (3%)
Sirolimus	5 (4%)	16 (8%)	1 (0.4%)	22 (4%)
Sorafenib	0	2 (1%)	41 (15%)	43 (7%)
TACE	5 (4%)	4 (2%)	35 (13%)	44 (7%)
Miscellaneous[a]			2[a] (0.7%)	2 (3%)
Best supportive care	92 (68%)	129 (64%)	126 (47%)	347 (57%)
Total	136	201	269	606

[a]Miscellaneous = ethanol one, Yttrium 90 one.

Therapeutic measures were the curatively aimed procedures of Tx and Rx along with active palliative therapy (APT) and best supportive care (BSC) (Table IV). Curatively aimed surgery (Tx + Rx) was used for 15% of the population during period A, during period B the rate was 21% and for period C it was 17%. Patients with resectable tumour and adequate liver function did undergo Rx and Tx was reserved for individuals that were not resectable due to underlying liver disease. There were 57 Tx and 53 Rx during the 12 years of this study. In six cases Tx was preceded by TACE. The five-year survival rate for those receiving Tx was 70% and 45% for patients who had Rx. The survival curves were significantly separated ($p < 0.0001$) (Figure 3).

The number of persons receiving APT increased successively between period A (17%) and period C (35%) ($p < 0.0001$) and a decreased number were given BSC (from 67% to 47%; $p = 0.0001$) (Table IV). Median survival time for patients receiving BSC was 2.0 months.

One hundred and thirty patients had APT and 20 patients were treated with RFA. In periods A and B there were 21 persons who participated in a pilot study using sirolimus [15]. Forty-three patients were treated with sorafenib (Nexavar®). There was a significant improvement in the overall survival for those receiving APT between the three periods ($p = 0.02$). Median survival was 8.8, 10.8 and 14.0 months for periods A, B and C, respectively.

Discussion

This is a complete population-based analysis of all individuals with HCC from a Swedish health region covering the 12-year period from 2000 to 2011. The participants were divided into three time cohorts and hence had an observation time from date of diagnosis of more than 36 months. There was almost a doubling in the number of HCC cases from period A to period C and the rate of underlying liver disease increased from 51% to 67%.

Whether the observed increase in the incidence of HCC was a true increase in the population or the consequence of a better reporting system is an open question. It could be related to factors such as better and earlier diagnoses due to improved radiology [2] and care facilities better supporting efforts to get an exact diagnoses for these individuals. That the relative number of participants with no clinical staging declined from 12% to 6% supports the idea of diagnostic improvement over population increase. The establishment of a regional multidisciplinary board from 2004 during period B and the adoption of the EASL guidelines for non-invasive diagnostics in 2007 have supposedly improved the establishment of correct diagnosis and improve treatment allocation.

In 2008–2009 the Swedish Registry for Cancer in the Liver, Gallbladder and Bile ducts (SweLiv) was founded. Registration in SweLiv leads automatically to a registration in the Regional Cancer Registry. The establishment of SweLiv might have led to an increased awareness of HCC among physicians and been an incentive for registration of clinically diagnosed cases of HCC but the impact of the registry in this analysis is of minor importance.

The validity of the RCC registry is continuously controlled and is estimated to have coverage of 95–98% of the individuals (not published information from RCC).

More persons have contracted hepatitis C rate in western countries during the last part of the 20th century and the HCC rate has similarly increased [16,17] so it is difficult to rule out a true increase in HCC incidence. A programme for screening of individuals with liver cirrhosis was not in effect during the time of this study. However individuals with liver cirrhosis were being more actively monitored with ultrasound and this might also have contributed to the increase in HCC incidence and the decreased size of tumours at the time of diagnosis. Other factors that may have affected that rate were better and earlier diagnosis due to improved radiology [2] and efforts by the multidisciplinary board to get an exact diagnosis. This is supported by the fact that the relative numbers of persons in whom no clinical staging was done was reduced from 12% to 6% and that 81% of those not

staged were more than 70 years of age. There was a concomitant increase in underlying liver disease (from 51% to 67%). This relative increase in underlying liver disease was mainly among those with a history of alcohol abuse and hepatitis C; this change could be the result of better detection through improved surveillance.

Determining the true incidence of HCC in the region studied is hampered by the autopsy rate; significantly reduced over the last decades [18,19]. This can explain why in the first period (A) there were 0.6 cases per 100 000 inhabitants diagnosed at autopsy and in the last period C 0.3 cases per 100 000 inhabitants diagnosed at autopsy.

While survival is still dismal, there was an encouraging improvement in overall survival. This improvement was seen only among patients with an underlying liver disease. There was no apparent staging migration that might have affected the data. Tumour size at time of diagnosis was smaller among those with underlying liver disease. These factors support a conclusion that more individuals are being diagnosed earlier and more precisely and reflect most likely that patients with underlying liver disease benefit from more surveillance over time.

In the population with an underlying liver disease there was a shift in the use of APT from 24% to 45% and fewer were subjected to BSC. APT consisted mainly of TACE, which has been shown to prolong survival [11]. The median survival for patients receiving TACE was 18 months during period C; this strategy improved the outcome for the entire period C population.

No changes were observed between study periods, with regard to outcome for curatively aimed treatments. Eighteen per cent had treatment that included Tx or Rx. While Milan or UCSF criteria were not fully implemented during period A (2000–2003), there was no change over time that suggested any difference. Similar figures are reported in other surveys [20]. In a study where 28% of the tumours were detected by screening, 25% were treated with a curative aim [21] – the same results should be achievable in a Swedish population with liver disease if every person were to be thoroughly screened.

Rx and RFA are alternatives to transplantation. A five-year survival in the range of 60% in selected series of Rx has been described [22].

Even very large cancers can be resected with acceptable results among patients without an underlying liver disease [23]. In the present analysis, four patients without underlying liver disease with a tumour larger than 18 cm underwent Rx. Survival ranged from 20 to 73 months. This emphasises the value of an aggressive surgical approach for this group.

Overall survival and progression-free survival was significantly better after Tx than Rx. The survival after Tx was within the range expected when current guidelines, UCSF-expanded criteria [3], were followed. In the present study, 12 patients had Tx after terminal liver failure; histopathology of their explanted livers revealed HCC. These patients had an excellent outcome and improved the survival rate for the Tx cohort. When these T0 patients are excluded, the survival rate from date of diagnosis or date of surgery shows no difference between Tx and Rx.

Survival time in this analysis is calculated from date of diagnosis. Those receiving curatively aimed treatment, mainly Tx, had added survival time because of the wait for liver grafts in comparison to survival calculated from the date of surgery.

The measured outcome of Rx was negatively influenced by three cases of ruptured and bleeding tumours acutely operated on for haemostatic reasons. Their survival was short (0.2, 2.5 and 6.6 months). These cases should be considered when analysing Tx versus Rx survival. In a meta-analysis with a low grade of evidence, five-year overall survival after Tx was 58% and Rx 34% [24]. The five-year survival rate in the present analysis corresponds closely with these results. In one meta-analysis, Rx was described as superior to RFA for tumours more than 3 cm, but the authors were cautious as the available data was limited [10]. At our institution Rx or Tx have been considered as the curative options for treatment which in combination with the short survival observed after RFA in this series led to the decision that RFA was not included when curative treatments were analysed. It can be discussed whether RFA should be transferred to curative procedures. Such a transfer reduces median survival in APT group to 10.6 months.

Those receiving APT where TACE was used had a median survival of 16 months (1.5–58); which is consistent with findings reported elsewhere [11]. Period C (2008–2011) saw the introduction of a standardised TACE treatment that used beads. The median survival for individuals in time period C when TACE was used was 18 months.

As the outcomes of the curative treatment options (Tx and Rx) did not improve over time, the increased use of APT (TACE and sorafenib) was the treatment strategy that more successfully extended survival time. By implementing TACE for those with liver restricted disease and a Child-Pugh classification of A ($<$7 points), the use of APT may extend life expectancy for up to half a year – improving the survival rate for the whole population with HCC.

For patients treated only with best supportive care (BSC), median survival was two months and that rate did not improve over the life of the study. In a recent report by Cabibbo an overall median survival of 6.8 months and one-year survival of 32% was reported for those who received treatment comparable to BSC, i.e. best comfort care [25]. The shorter survival time in the present analysis might be more representative of outcome for a complete population of HCC patients receiving BSC – the diagnosis of HCC was substantiated histopathologically for 84% (285/338). Of those, 8% (27/338) survived more than one year and five individuals survived more than three years. It is of significant interest that four of the five three-year survivors were more than 80 years old at time of diagnosis. This may indicate that HCC in persons older than 80 years often has a slow growth speed. These long-time survivors underline the unpredictable outcome for those diagnosed with HCC and that therapy for those of high age should be more restricted than for younger individuals.

Based on a local study [26] that showed prolonged survival after treatment with Cox-2 inhibitor, Cox 2 inhibitors were considered as APT, even if the treatment most often would be thought of as palliative. Transfer of those patients to the BSC-group did not change the outcome of the study.

In conclusion, there was an increase in the reported number of patients with HCC during the three time periods in the defined region from 2.5 to 4.1 per 100 000 inhabitants. During the same time period there was a decline in the number of individuals diagnosed during a post-mortem investigation. There was also an increase in the number of persons (from 51% to 70%) who had an underlying liver disease. There was no staging migration over time. There was a survival improvement over time – mainly due to more APTs with TACE and sorafenib. In the future, the outcome for the HCC population may be further improved through structured surveillance with an eventual expansion of both the screened population and the frequency of the surveillance. Effective hepatitis C treatments will in the future reduce the HCC incidence. Downsizing strategies before Tx and improved treatment allocation can improve the results for already affected individuals.

Declaration of interest: The study was supported by grants from the Swedish Cancer Research Foundation (Cancerfonden) no 5029 B06 02xBB, the OC of the VG region, Sweden. Director Professor Nils Conradi and Assistant Director Susanne Amsler Nordin of the Regional Cancer Center Western Sweden have generously supported this analysis. All surgeons in Transplant Institute, Sahlgrenska University Hospital, and Gothenburg, Sweden are acknowledged for their excellent clinical work with study subjects. The English was reviewed and corrected by Jonathan Stubbs, M.Sc. The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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