Trends in incidence, diagnosis, treatment and survival of hepatocellular carcinoma in a low-incidence country: data from the Netherlands in the period 2009-2016

Reinders, M.T.M.; Meer, S. van; Burgmans, M.C.; Jong, K.P. de; Klumpen, H.J.; Man, R.A. de; ... ; Dutch Hepatocellular & Cholangioca

European Journal of Cancer 137 (2020) 214–223

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Trends in incidence, diagnosis, treatment and survival of hepatocellular carcinoma in a low-incidence country: Data from the Netherlands in the period 2009–2016

Margot T.M. Reinders [a,b,*], Suzanne van Meer [b], Mark C. Burgmans [c], Koert P. de Jong [d], Heinz-Josef Klümpen [e], Robert A. de Man [f], D. (Sandjai) Ramsoekh [g], Dave Sprengers [f], Eric T.T.L. Tjwa [h], Judith de Vos-Geelen [i], Karel J. van Erpecum [b,1], Lydia G.M. van der Geest [j,1] In collaboration with the Dutch Hepatocellular & Cholangiocarcinoma Group (DHCG)

[a] *Department of Radiology & Nuclear Medicine, University Medical Centre Utrecht, P.O. Box 85500, 3508 GA Utrecht, the Netherlands*
[b] *Department of Gastroenterology & Hepatology, University Medical Centre Utrecht, P.O. Box 85500, 3508 GA Utrecht, the Netherlands*
[c] *Department of Radiology, Leiden University Medical Centre, P.O. Box 9600, 2300 RC Leiden, the Netherlands*
[d] *Department of Surgery, University Medical Centre Groningen, P.O. Box 30001, 9700 RB Groningen, the Netherlands*
[e] *Department of Medical Oncology, Amsterdam University Medical Centres, P.O. Box 22660, 1100 DD Amsterdam Zuidoost, the Netherlands*
[f] *Department of Gastroenterology & Hepatology, Erasmus Medisch Centrum Rotterdam, P.O. Box 2040, 3000 CA Rotterdam, the Netherlands*
[g] *Department of Gastroenterology & Hepatology, Amsterdam University Medical Centres, P.O. Box 7057, 1007 MB Amsterdam, the Netherlands*
[h] *Department of Gastroenterology & Hepatology, Radboud University Medical Centre Nijmegen, P.O. Box 9101, 6500 HB Nijmegen, the Netherlands*
[i] *Department of Internal Medicine, Division of Medical Oncology, GROW – School for Oncology and Developmental Biology, Maastricht University Medical Centre, P.O. Box 5800, 6202 AZ Maastricht, the Netherlands*

Abbreviations: EAPC, Estimated Annual Percent Change; EoD, Extent of Disease; ESR, European Standard Rate; HCC, Hepatocellular carcinoma; IKNL, Netherlands Comprehensive Cancer Organisation; NCR, Netherlands Cancer Registry; NOTR, Dutch Organ Transplant Registry; PALGA, Nationwide network and registry of histo- and cytopathology in the Netherlands; RESR, Revised European Standard Rate; SIRT, Selective internal radiation therapy; SONCOS, Foundation of oncological collaboration; TACE, Transarterial chemoembolisation; TNM, Tumour-node-metastasis.

* *Corresponding author*: University Medical Centre Utrecht (UMCU) P.O. Box 85 500 3500 GA Utrecht, the Netherlands. Fax: +31 88 75 695 89.
E-mail address: m.t.m.reinders@umcutrecht.nl (M.T.M. Reinders), s.van.meer@antoniusziekenhuis.nl (S. van Meer), m.c.burgmans@lumc.nl (M.C. Burgmans), k.p.de.jong@umcg.nl (K.P. de Jong), h.klumpen@amsterdamumc.nl (H.-J. Klümpen), r.deman@erasmusmc.nl (R.A. de Man), d.ramsoekh@amsterdamumc.nl (D.(Sandjai) Ramsoekh), d.sprengers@erasmusmc.nl (D. Sprengers), eric.tjwa@radboudumc.nl (E.T.T.L. Tjwa), judith.de.vos@mumc.nl (J. de Vos-Geelen), k.j.vanerpecum@umcutrecht.nl (K.J. van Erpecum), l.vandergeest@iknl.nl (L.G.M. van der Geest).
[1] Shared last authorship.

https://doi.org/10.1016/j.ejca.2020.07.008

[j] The Netherlands Comprehensive Cancer Organisation, P.O. Box 19079, 3501 DB Utrecht, the Netherlands

Received 27 April 2020; received in revised form 1 July 2020; accepted 8 July 2020
Available online 13 August 2020

KEYWORDS
Hepatocellular carcinoma;
Liver cancer;
Cancer diagnostics;
Cancer treatment;
Survival

Abstract ***Objective:*** Evaluation of the trends in incidence, diagnostics, treatment and survival of patients with hepatocellular carcinoma (HCC) in the Netherlands.
Method: Data regarding incidence, diagnostics, primary treatment and survival of patients with HCC in the period 2009–2016 were obtained from the Netherlands Cancer Registry. Trends in incidence, diagnostics, various treatment modalities (except liver transplantation, due to inaccurate data) and regional treatment preferences were analysed. Survival was evaluated using Kaplan-Meier curves and multivariable Cox proportional hazard regression modelling.
Results: In the period of 2009–2016, 3838 patients were diagnosed with HCC. A distinct decrease in the percentage of patients who underwent tumour biopsy was observed (from 51% in 2009–2010 to 42% in 2015–2016). Percentage of patients who underwent cancer treatment increased markedly (from 49% in 2009–2010 to 57% in 2015–2016), mainly because of an increasing use of resection and ablation. The number of hospitals where resections were performed or sorafenib treatment prescribed decreased slightly. The number of hospitals sporadically (<1 ablation per year) performing ablations increased. There were significant differences between regions in the application of resection, ablation and transarterial chemoembolisation /radioembolisation ($p < 0.05$ after 'case mix'-correction). One-, 3- and 5-year survival of patients with HCC significantly improved in the studied period. Receiving cancer treatment was associated with increased survival, whereas increasing age and an advanced tumour stage were both associated with decreased survival.
Conclusion: From 2009 to 2016, patients with hepatocellular carcinoma more often received cancer treatment and their survival improved. There were significant differences in types of treatment between various regions.

1. Introduction

Primary liver cancer is the sixth most common cancer worldwide and the second most common cause of cancer-related death. Ninety percent of all liver tumours are hepatocellular carcinomas (HCCs). HCC most often occurs in patients with underlying liver cirrhosis [1,2].

Liver transplantation, resection and thermal ablation are potentially curative treatment options. Locoregional treatment options are transarterial chemoembolisation (TACE) and selective internal radiation therapy (SIRT), generally in palliative setting. Furthermore, patients with HCC can be considered for systemic therapy, such as sorafenib [3].

Although in the Netherlands HCC incidence is steadily increasing in recent decades, HCC remains an infrequent tumour compared with other European and Asian countries [4–6]. In 2013, the first Dutch guideline 'HCC' was published which recommends that diagnostics and treatment of HCC are performed in expert centres [7]. Such centralisation of care is believed to improve patient outcomes, also considering that new treatment modalities introduced in recent years are, in general, only available in expert centres.

In the present study, we explore incidence and trends in diagnostics and treatment patterns for HCC in the Netherlands during the last decade in relation to survival. In addition, we explore whether there is a trend to centralisation of care after introduction of the Dutch HCC guidelines.

1.1. Patients and methods

Data regarding incidence, diagnostics and treatment of HCC in the period 2009–2016 were extracted from the database of the Netherlands Cancer Registry (NCR) by selection of the diagnosis 'invasive malignancies primary localised in the liver' (ICD-10 code C22.0). The NCR is deemed to have 95% complete coverage in the Netherlands [8]. Patients aged younger than 18 years, residence abroad, histologically proven other hepatic malignancy than HCC, such as hepatoblastoma and lymphoma and HCC diagnosed at autopsy were excluded. The registry is based on notifications from the

automated pathological archive: Pathologisch-Anatomisch Landelijk Geautomatiseerd Archief (PALGA). In addition, data from the National Registry of Hospital Discharge Diagnoses were used. Survival data were obtained by annual linkage to the Municipal Personal Records Database. The survival length was calculated from the date of diagnosis until the date of death or end of follow-up on February 1st, 2018. Since 2012, tumour stage of all patients with HCC in the NCR database is registered and classified in accordance with the 7th edition of the 'Tumour-Node-Metastasis' (TNM) – classification [9]. Before 2012, HCC diagnoses without histological confirmation were registered with a one-digit 'Extent of Disease' (EoD) – classification: locally within initial organ, advanced outside initial organ or distant metastases [10]. To enable comparison of data from before and after 2012, all TNM stages were converted into EoD-classes, using a wide and a strict definition (Nx and/or Mx classified as 'local' or as 'unknown', refer also Table 1).

The NCR exclusively registers treatment performed according to the initial treatment plan after primary diagnosis, approximately at 9 months after diagnosis. In this study, the following treatment options are described: liver resection (transplantation excluded), locoregional therapy (radiofrequency and microwave ablation, TACE and SIRT), targeted systemic therapy (in the studied period sorafenib) and other systemic therapy. This study focusses on cancer treatments with accurate data available in the database (resection, ablation, TACE, SIRT and sorafenib) as opposed to best supportive care. Liver transplantation is performed in three academic hospitals in the Netherlands. Accurate data on liver transplantation are not available in the NCR database, owing to the fact that waiting time for this procedure in the Netherlands generally exceeds one year (beyond registration window of NCR: refer previously). Therefore transplantation data are excluded from the analyses regarding trends over time, regional differences and hospital volumes. Hospital volume was calculated based on the mean number of treatments per year in a period of 4 years (82 hospitals in reference year 2016) [5]. In the study period, 9 geographical cancer regions were defined by the Integraal Kankercentrum Nederland (Netherlands Comprehensive Cancer Organisation, IKNL) (anonymous except for IKNL), with

Table 1
Patient and tumour characteristics of 3838 patients with hepatocellular carcinoma in the Netherlands from 2009-2016. N (%): Absolute numbers, values between brackets are the percentages of the total number of patients in the specific period.

Period	Total	2009–2010	2011–2012	2013–2014	2015–2016	p-value
Number	3838	824	877	1010	1127	**<0.001**
Sex						0.671
Male	2929 (76)	626 (76)	666 (76)	785 (78)	852 (76)	
Female	909 (24)	198 (24)	211 (24)	225 (22)	275 (24)	
Age (years)						0.241
<60	854 (22)	204 (25)	209 (24)	210 (21)	231 (20)	
60–74	1881 (49)	383 (46)	421 (48)	503 (50)	574 (51)	
≥75	1103 (29)	237 (29)	247 (28)	297 (29)	322 (29)	
Country of origin						**<0.001**
The Netherlands	2821 (74)	618 (75)	672 (77)	714 (71)	817 (73)	
Asia – subSahara	281 (7)	79 (10)	57 (6)	73 (7)	72 (6)	
Different/unknown	736 (19)	127 (15)	148 (17)	223 (22)	238 (21)	
Social-economic status						0.058
High (1e-3e decile)	1173 (30)	260 (32)	261 (30)	318 (31)	334 (30)	
Medium (4e-7e decile)	1526 (40)	334 (40)	321 (36)	393 (39)	478 (42)	
Low (8e-10e decile)	1139 (30)	230 (28)	295 (34)	299 (30)	315 (28)	
Basis for diagnosis						**0.035**
Clinical performance or imaging	1650 (43)	313 (38)	377 (43)	447 (44)	513 (45)	
Cytology	51 (1)	10 (1)	10 (1)	13 (1)	18 (2)	
Histology[a]	2137 (56)	501 (61)	490 (56)	550 (55)	596 (53)	
Tumour stage[b]						0.141
1–2 (local)	1795 (47)	369 (45)	402 (46)	478 (47)	546 (48)	
3–4–5 (locally advanced)	404 (11)	100 (12)	99 (11)	110 (11)	95 (9)	
6 (distant metastases)	710 (18)	143 (17)	167 (19)	174 (17)	226 (20)	
9 (unknown)	929 (24)	212 (26)	209 (24)	248 (25)	260 (23)	
Tumour stage[c]						**<0.05**
1–2 (local)	2375 (62)	483 (59)	528 (60)	647 (64)	717 (64)	
3–4–5 (locally advanced)	416 (11)	110 (13)	100 (11)	110 (11)	96 (9)	
6 (distant metastases)	710 (19)	143 (17)	167 (19)	174 (17)	226 (20)	
9 (unknown)	337 (8)	88 (11)	82 (10)	79 (8)	88 (7)	

P-values <0.05 are considered statistically significant and presented in bold.
[a] From biopsy or resection.
[b] In case N- and/or M-status unknown, tumour stage considered as 'unknown' (strict definition).
[c] In case N- and/or M-status unknown and T = 0 or T = 1, tumour stage considered as 'local' (wide definition).

various degrees of multidisciplinary collaboration between participating hospitals.

1.2. Statistical analysis

Annual incidence rates were age standardised per 100,000 person years to the European standard population (1976) and the Revised European standard population (2013), resulting in the (Revised) European Standardised Rate ((R)ESR). Because of the ageing European Population, older persons receive a higher weighting in the RESR compared with the ESR [11]. We provide both rates to enable comparisons with previous and future literature. Using the estimated annual percentage change (EAPC) and corresponding p-value, changes in RESR and ESR were evaluated.

The study period 2009–2016 was divided into periods of 2 years, and most data are given for 2-year periods. However, data regarding number of hospitals and volume (treatments performed by hospitals) and variation between regions were given for 4-year periods, to allow meaningful statistical comparisons. Chi-squared tests for trend were used to evaluate changes over time. Kaplan-Meier curves and log-rank tests were used to evaluate survival and Cox-regression analysis for the influence of time period, sex, age, tumour stage (model 1) and treatment (model 2). Variables with a p-value <0.05 were included in the multivariable Cox-regression analysis.

For comparison of the cancer regions, standardised percentages ([observed/expected] x national percentage) were calculated with 'case mix'-adjustment based on sex, age, social-economic status and tumour stage. Of note, location of hospital where initial diagnosis was made, determined cancer region, but subsequent treatment could have been performed throughout the Netherlands. The standardised percentages are shown in a spider diagram in which every spoke represents an (anonymous) cancer region. Variation between regions was statistically tested with 'likelihood'-ratio tests. A two-sided p-value <0.05 was deemed significant. Statistical analyses were performed in RStudio, version 1.1.463 and STATA, version 12.

2. Results

In total 3838 patients were diagnosed with HCC in the Netherlands between 2009 and 2016. The number of patients increased from 406 cases in 2009 to 513 cases in 2016 (Fig. 1a). Between 2009 and 2016, the incidence increased from 2.94 to 3.69 per 100,000 person years based on the RESR ($p < 0.01$, Fig. 1b). The incidence was more than three times higher in men than in women, and an increasing incidence was particularly found in men (4.78–5.92 person years, $p < 0.01$, women: 1.38 to 1.69, $p = 0.09$). The ESR showed similar trends (Fig. 1c).

Three quarters of all patients were men and almost half were 60- to 74-year-olds (Table 1). Approximately 70% were born in the Netherlands. Based on the tumour stage (strict definition), 1795 patients (47%) exhibited local disease, 404 patients (11%) exhibited locally advanced disease, 710 patients (18%) exhibited distant metastases and for 929 patients (24%) tumour stage was unknown.

2.1. Trends in diagnostics and treatment

The percentage of diagnostic biopsies decreased significantly over the period 2009–2016. This procedure was performed in 51, 47, 43 and 42% of the patients, respectively, in the periods 2009–2010, 2011–2012, 2013–2014 and 2015–2016 (Table 2).

During the study period, cancer treatment in general was provided more frequently: 49, 53, 57 and 57% of all patients in the subsequent periods. The other patients received best supportive care exclusively. Twenty-nine percent of the treated patients received resection or ablation, whereas 27% of the patients received cancer

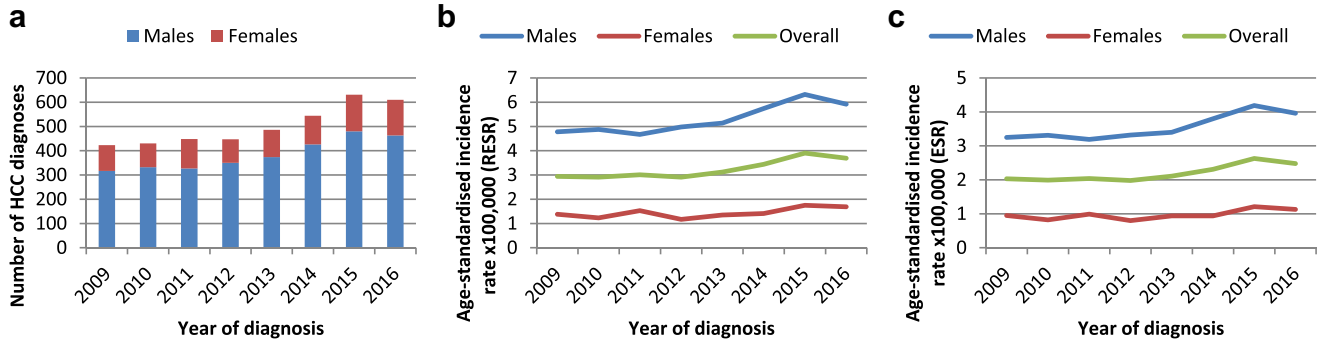

Fig. 1. Age-standardised incidence rate of patients with hepatocellular carcinoma stratified by sex in the study period 2009–2016 in the Netherlands. (*a*) Cumulative absolute number of HCC diagnoses per sex in the study period 2009–2016, (*b*) Age-standardised incidence rate based on the European Standard Population. Overall Estimated Annual Percent Change of 3.91% (p-value <0.05), (*c*) Age-standardised incidence rate based on the Revised European Standard Population. Overall Estimated Annual Percent Change of 4.28% (p-value <0.05).

Table 2
Diagnostics and treatments of 3838 patients with hepatocellular carcinoma in the Netherlands from 2009-2016. N (%): Absolute numbers, values between brackets are the percentages of the total number of patients in the specific period.

Period	Total	2009–2010	2011–2012	2013–2014	2015–2016	p-value
Number	3838	824	877	1010	1127	
Biopsy[a]	1741 (45)	422 (51)	410 (47)	439 (43)	470 (42)	**<0.001**
Treatment	2089 (54)	405 (49)	462 (53)	580 (57)	642 (57)	**<0.001**
Resection	572 (15)	99 (12)	122 (14)	178 (18)	173 (15)	**0.013**
Ablation	538 (14)	96 (12)	105 (12)	171 (17)	166 (15)	**0.007**
TACE[b]	439 (11)	92 (11)	102 (12)	127 (13)	118 (10)	0.713
SIRT[c]	78 (2)	4 (0)	9 (1)	17 (2)	48 (4)	**<0.001**
Sorafenib	504 (13)	116 (14)	130 (15)	126 (12)	132 (12)	**0.047**
Chemotherapy, other	31 (1)	10 (1)	10 (1)	5 (0)	6 (1)	0.059

P-values <0.05 are considered statistically significant and presented in bold.
[a] Without patients with PA-confirmation from resection.
[b] TACE = transarterial chemoembolisation.
[c] SIRT = selective internal radiation therapy.

treatments such as TACE, SIRT or sorafenib. In the period 2009–2016, 15% of all patients were treated with liver resection, 14% with ablation, 11% with TACE, 2% with SIRT and 13% with sorafenib. Of all treated patients, 19% received a combination of these treatment options.

The percentage of patients treated with liver resection and ablation showed an increase in the first part of the study period and remained relatively stable thereafter. The percentage of patients who underwent TACE or sorafenib was more or less stable in the period 2009–2016. The percentage of patients treated with SIRT was limited but showed a slight increase in the period 2015–2016 in comparison with periods before.

2.2. Trends in number of hospitals and hospital volume

Diagnostic biopsies were performed in almost every hospital in the periods 2009–2012 and 2013–2016. The percentage of hospitals where ablations were performed doubled in the last period from 12% to 24% of all hospitals. There was a slight decrease (from 33% to 29%) in the number of hospitals, where liver resections for HCC were performed. The percentage of hospitals providing

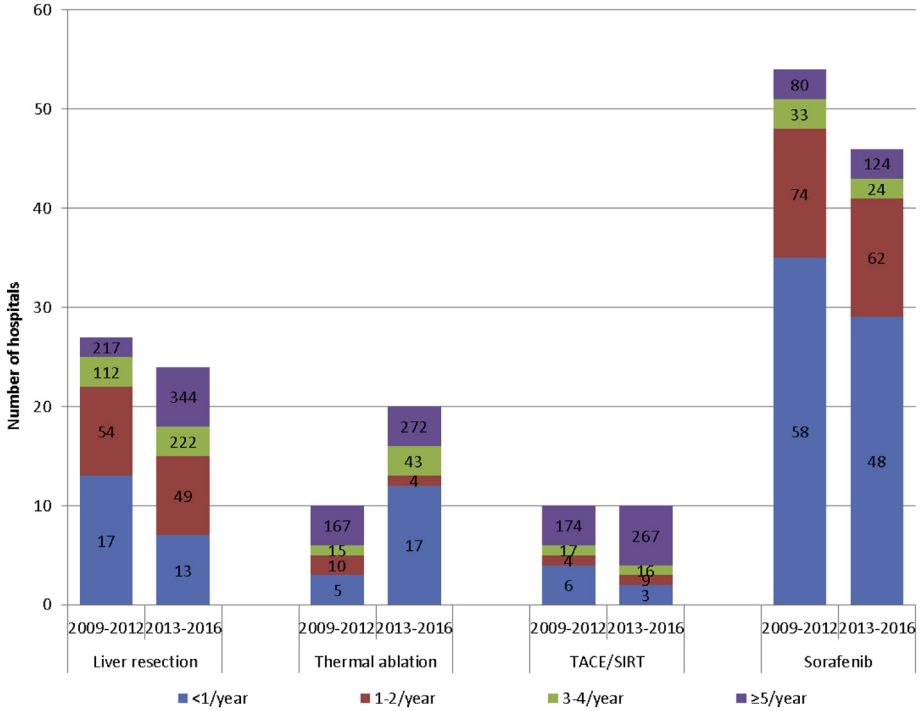

Fig. 2. The number of hospitals in the Netherlands with on average less than 1, 1–2, 3–4 or 5 or more liver resections, thermal ablations, transarterial chemoembolisation (TACE)/selective internal radiation therapy (SIRT) and sorafenib treatments per 4-year period (2009–2012 and 2013–2016, respectively). Numbers in various bars indicate absolute number of patients in 4-year periods in particular hospital volume category. Note: the discrepancy in total number of patients compared with Table 2 is caused by patients who were treated outside the Netherlands.

sorafenib treatment decreased from 66 to 56%. TACE and SIRT were performed in 12% of all hospitals.

In Fig. 2 resection and sorafenib treatment volumes in various hospitals are shown (<1, 1–2, 3–4 or ≥5 treatments per year) during the periods 2009–2012 and 2013–2016. The number of hospitals, where liver resection was sporadically (<1 per year) performed, decreased (from 13 to 7 hospitals, 17 and 13 patients in the 4-year periods, respectively, Fig. 2), whereas there was an increase in the number of hospitals, where at least 5 resections per year were performed (from 2 to 6 hospitals, 217 and 344 patients). The number of hospitals, where ablations were sporadically performed, increased considerably (from 3 to 12 hospitals, 5 and 17 patients). The number of hospitals, where at least 5 TACE and/or SIRT treatments per year were performed, slightly increased (from 4 to 6 hospitals, 174 and 267 patients). The number of hospitals, where sorafenib treatments were sporadically given, slightly decreased (from 35 to 29 hospitals, 58 and 48 patients).

2.3. Variation between regions

Significant differences are shown between the nine (anonymous) regions (based on hospital of first diagnosis) in the application of liver resection, ablation, and TACE/SIRT (all $p < 0.01$, Fig. 3) in both periods (2009–2012 and 2013–2016, case mix adjusted). There were no significant differences in use of sorafenib.

2.4. Trends in survival

A significant improvement occurred in survival of all patients with HCC within the period 2009–2016 with a 1-year survival of 40, 41, 50 and 46% in the consecutive 2-year periods, a 3- year survival of 20, 23, 27 and 27% and a 5- year survival of 14, 17 and 21% (calculation only possible for the first 3 periods: Fig. 4, log-rank test $p < 0.05$). Survival improvement in the course of the study period persists in a multivariable analysis after adjustment for age, tumour stage (model 1) and whether or not patients underwent specific cancer treatment (model 2, Table 3, Supplementary Table 1).

In the subgroup of patients with HCC who underwent liver resection, 1-, 3- and 5-year survival rates were 85, 65 and 55%, respectively. Survival did not significantly differ between consecutive 2-year periods (log-rank test $p = 0.62$). In addition, no significant difference over time was found in survival after ablation, with 1-, 3- and 5-year survival rates of 89, 62 and 42%, respectively (log-rank test $p = 0.84$). On the other hand, survival slightly improved in the subgroup treated with TACE: 1-year survival rates were, respectively, 75, 79, 82 and 82%, 3-year survival rates 28, 41, 38 and 49% and 5-year survival rates 15 and 30% (calculation only possible for the first 2 periods: log-rank test $p < 0.05$).

In addition, survival of patients with HCC treated with sorafenib improved significantly during the study period: 1-year survival rates after sorafenib treatment

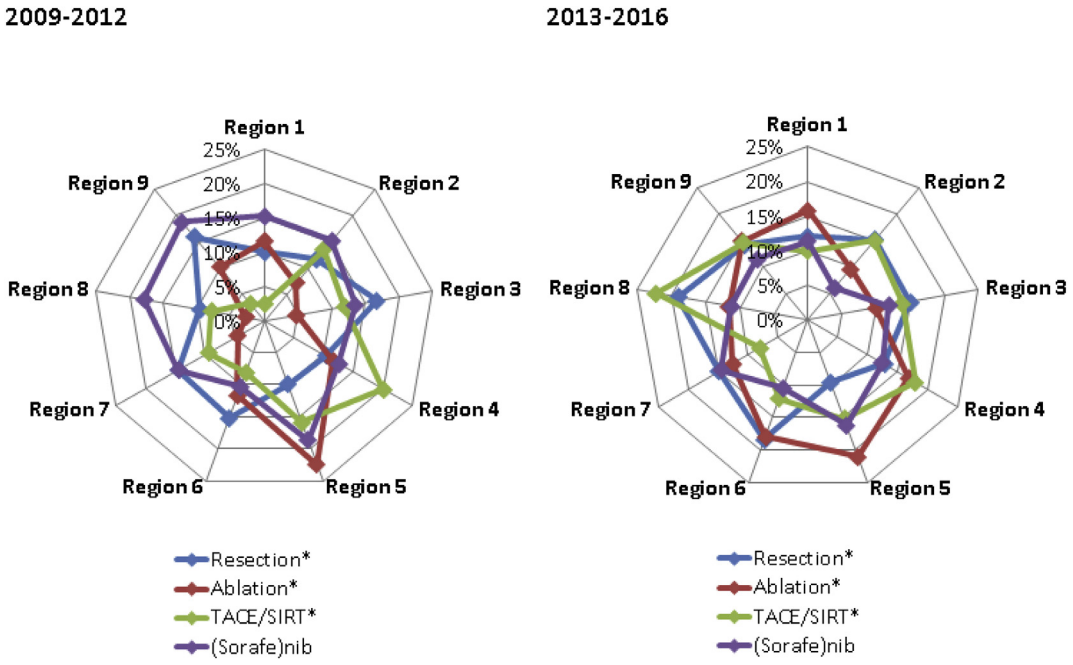

Fig. 3. Spider diagram with standardised percentages of patients per region that were treated with liver resection, radiofrequency and microwave ablation, transarterial chemoembolisation (TACE) or selective internal radiation therapy (SIRT) and sorafenib, in the periods 2009–2012 (a) and 2013–2016 (b), where every spoke represents a region. Standardisation is based on 'case mix'-adjustment for differences in age, sex, socio-economic status and tumour stage. *Significant differences in treatment application between regions $p < 0.05$.

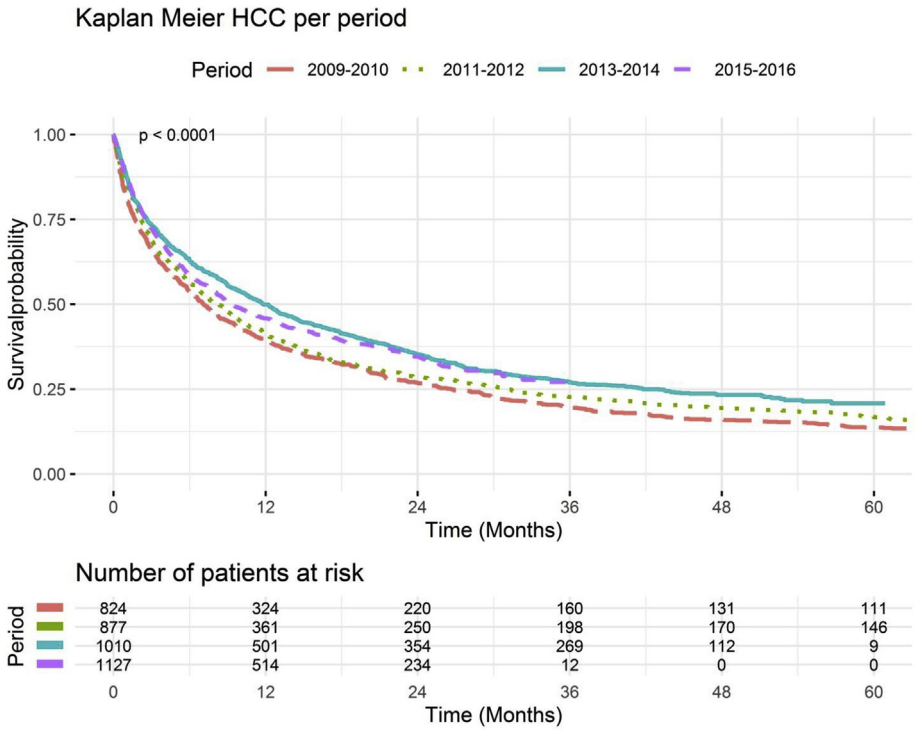

Fig. 4. The survival of patients with HCC in the Netherlands in the period 2009–2016 (log-rank test $p < 0.05$). Underneath the figure is the number of patients at risk at different time points.

were, respectively, 30, 26, 44 and 27% in the subsequent periods and 3-year survival rates 4, 7 and 9% (calculation only possible for the first 3 periods: log-rank test $p < 0.05$).

3. Discussion

An overview is presented of the trends in incidence, diagnosis, treatment and survival of patients with HCC

Table 3
Survival analysis (all patients) based on Cox Proportional hazard models.

Variables	Patients	Median survival	Univariable analysis		Multivariable analysis		Multivariable analysis including treatment	
	n = 3838	months	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Year of diagnosis								
2009–2010	824	7.1	ref		ref		ref	
2011–2012	877	8.3	0.92 (0.83–1.02)	**<0.001**	0.90 (0.82–1.00)	0.05	0.94 (0.85–1.04)	0.243
2013–2014	1010	11.9	0.78 (0.71–0.87)		0.77 (0.70–0.86)	**<0.001**	0.84 (0.76–0.93)	**<0.001**
2015–2016	1127	9.3	0.81 (0.73–0.90)		0.79 (0.71–0.88)	**<0.001**	0.86 (0.77–0.95)	**0.004**
Sex								
Male	2929	9.0	ref					
Female	909	9.3	0.96 (0.88–1.05)	0.356				
Age at diagnosis								
<60 jaar	854	13.4	ref		ref		ref	
60–74 jaar	1881	10.5	1.31 (1.19–1.45)	**<0.001**	1.23 (1.12–1.36)	**<0.001**	1.16 (1.05–1.28)	**0.004**
>75 jaar	1103	5.7	1.94 (1.75–2.20)		1.85 (1.67–2.06)	**<0.001**	1.18 (1.06–1.32)	**0.002**
Tumour stage[a]								
Local	1795	13.8	ref		ref		ref	
Locally advanced	404	5.2	1.92 (1.71–2.16)	**<0.001**	1.89 (1.68–2.12)	**<0.001**	1.60 (1.42–1.79)	**<0.001**
Distant metastases	710	2.3	3.26 (2.96–3.58)		3.29 (2.99–3.62)	**<0.001**	2.68 (2.43–2.95)	**<0.001**
Unknown	929	27.0	0.64 (0.58–0.71)		0.65 (0.59–0.72)	**<0.001**	0.78 (0.71–0.86)	**<0.001**
Cancer Treatment								
No	1693	2.4	ref				ref	
Yes	2145	26.1	0.21 (0.20–0.23)	**<0.001**	X		0.26 (0.24–0.28)	**<0.001**

Variables with a p-value <0.05 in the univariable analysis were used in the multivariable analysis.
P-values <0.05 are considered statistically significant and presented in bold.
95%CI = 95%-Confidence interval; HR = Hazard ratio.
[a] In case N- and/or M-status unknown, tumour stage considered as 'unknown' (strict definition).

in the Netherlands during the period 2009–2016. During this study period, a substantial increase of HCC incidence and cancer treatment was found in the Netherlands, and overall survival of patients with HCC significantly improved. The incidence of HCC in the Netherlands is relatively low but continues to rise since the start of the NCR in 1989, especially in men [6]. This increase may be explained by an increasing number of persons at risk for HCC (e.g. non-alcoholic fatty liver disease). In addition, an improvement of diagnostic modalities may have contributed.

Better general health care or better treatment of possible underlying liver disease may have contributed to a better survival of patients with HCC. The survival improvement in the course of the study period cannot solely be explained by the increased use of cancer treatment; after addition of cancer treatment to the multivariable Cox-regression model, the hazard ratios of the consecutive time periods moved towards 1, but significance did not 'disappear' (periods of diagnosis in model 2 vs. model 1 vs. univariable analysis, Table 3). In addition, earlier detection may have contributed to improved survival, as patients tended to be diagnosed with a lower tumour stage ($p = 0.14$, Table 1).

Despite an increase in cancer treatments in patients with HCC in comparison with the first decade of this century [5] (37% in 2003–2011 versus 57% in 2015–2016), there were significant regional differences in the application of liver resection, ablation and TACE/SIRT. In addition, in other Western countries, similar large regional differences are seen in the use of different therapies for HCC [12,13]. Possible explanations for this phenomenon are regional preferences or available expertise, which might be related to a different speed of implementation of new techniques. Since 2014, centres in the Netherlands collaborate in the Dutch Hepatocellular & Cholangiocarcinoma group to initiate joint clinical studies and improve the nationwide quality of health care for this specific patient group [14]. From 2020 onwards, HCC will be subject to national standards of the multidisciplinary oncological collaboration [15].

Because of the low incidence of HCC in the Netherlands, the current guideline (issued in 2013) advises to centralise diagnostics and treatment [7]. As opposed to previously, we see a slight decrease in the number of hospitals performing liver resections and sorafenib treatments during the period 2009–2016, whereas the number of hospitals, where patients with HCC were sporadically treated with ablations, increased substantially (Fig. 2), most probably because hospitals became experienced with this technique in patients with metastasised colorectal cancer. Previous research showed that survival of patients with HCC, with local or regional spread, is associated with the volume of treatments per hospital or treating physician [16–19]. The number of hospitals in the Netherlands with high treatment volumes is limited. Therefore, sporadic performance of therapies for HCC should be discouraged.

The limitations of this study include amongst others 'confounding by indication' as a consequence of the observational character of the NCR data in this study [20]. Furthermore, the 'Barcelona classification of liver cancer' stage is not available, in which the extensiveness of HCC, the Child-Pugh classifications as a measure for the severity of underlying liver disease, and the performance status are combined [2,7]. Furthermore, database entries are limited to treatments performed within 9 months after diagnosis as part of the initial treatment plan. As a result, we could not give accurate data on liver transplantation due to long waiting time for this procedure in the Netherlands (generally more than 12 months). To provide some information on liver transplantation for HCC, we made enquiries at the Dutch Organ Transplantation Registry. Liver transplantations were performed in 226, 242, 272 and 266 patients in the periods 2009–2010, 2011–2012, 2013–2014 and 2015–2016, respectively. Liver transplantations for HCC were performed in 45, 51, 59 and 67 patients (20, 21, 22 and 25% of all transplantations) in the four consecutive 2-year periods ($p = 0.028$) [21]. Finally, information regarding recurrence or progression of HCC and eventual subsequent treatment is lacking.

4. Conclusion

In the course of the period 2009–2016, incidence of HCC diagnoses consistently increased, more often cancer treatment was given and survival improved. There were large regional differences in the use of various treatment options. Potential beneficial effects of centralisation of HCC treatment should be further explored.

Financial support statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contribution statement

Margot T.M. Reinders: Conceptualization, Methodology, Formal Analysis, Writing-Original draft, Writing - Review & Editing, Visualization.

Suzanne van Meer: Conceptualization, Methodology, Validation, Writing - Review & Editing.

Mark C. Burgmans: Resources, Validation, Writing - Review & Editing.

Koert P. de Jong: Resources, Validation, Writing - Review & Editing.

Heinz-Josef Klümpen: Resources, Validation, Writing - Review & Editing.

Robert A. de Man: Resources, Validation, Writing - Review & Editing.

Sandjai Ramsoekh: Resources, Validation, Writing - Review & Editing.

Dave Sprengers: Resources, Validation, Writing - Review & Editing.

Eric T.T.L. Tjwa: Resources, Validation, Writing - Review & Editing.

Judith de Vos-Geelen: Resources, Validation, Writing - Review & Editing.

Karel J. van Erpecum: Conceptualization, Methodology, Validation, Resources, Writing - Original draft, Writing - Review & Editing, Supervision.

Lydia G.M. van der Geest: Conceptualization, Methodology, Validation, Formal Analysis, Data curation, Writing - Review & Editing, Supervision, Visualization.

Netherlands Comprehensive Cancer Organisation (IKNL) in the NCR, Resources, Investigation, Data curation.

Conflict of interest statement

M.T.M.R. reports grants from Dutch Cancer Society (KWF Kankerbestrijding); received personal fees from Boston Scientific/BTG, United Kingdom; received other fees from Quirem Medical B.V.; received nonfinancial support from Quirem Medical B.V. and Terumo, outside the submitted work. M.C.B. reports grants from ZonMW Programma Translationeel Onderzoek/Top-sector LSH, Maag Lever Darm Stichting; reports receiving nonfinancial support from Quirem Medical for HORA EST HCC study; grants from Covidien for HORA EST HCC study, outside the submitted work. H.J.K. reports receiving personal fees from IPSEN and SIRTEX, outside the submitted work. J.d.V.-G. reports grants and nonfinancial support from Servier, outside the submitted work. K.J.v.E. reports grants from Dutch Cancer Society (KWF Kankerbestrijding), outside the submitted work. All other authors report no conflict of interest.

Acknowledgements

The authors would like to thank the Netherlands Cancer Registry data managers for collecting the patient data. Furthermore, the authors would like to thank the Dutch Organ Transplant Registry for sharing the data regarding liver transplantation with them.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2020.07.008.

References

[1] EASL. Corrigendum to "EASL clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2019/02/12: 182–236. ed2019.

[2] Heimbach JK, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology (Baltimore, Md) 2018;67: 358–80. https://doi.org/10.1002/hep.29086.

[3] Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378–90. https://doi.org/10.1056/NEJMoa0708857.

[4] Petrick JL, Florio AA, Znaor A, Ruggieri D, Laversanne M, Alvarez CS, et al. International trends in hepatocellular carcinoma incidence, 1978–2012. Int J Canc 15 Jul 2020;147(2): 317–30. https://doi.org/10.1002/ijc.32723. n/a.

[5] van Meer S, van Erpecum KJ, Schrier GH, Verhoef C, Verheij J, de Man RA, et al. Diagnostics and treatment of hepatocellular carcinoma: trends in The Netherlands in the period 2003-2011. Ned Tijdschr Geneeskd 2014;158:A7074.

[6] Witjes CD, Karim-Kos HE, Visser O, van den Akker SA, de Vries E, Ijzermans JN, et al. Hepatocellular carcinoma in a low-endemic area: rising incidence and improved survival. Eur J Gastroenterol Hepatol 2012;24:450–7. https://doi.org/10.1097/MEG.0b013e32835030ce.

[7] Eskens F, Van Erpecum K, De Jong K, van Delden O, Klumpen H, Verhoef C, et al. Hepatocellular carcinoma: Dutch guideline for surveillance, diagnosis and therapy. Neth J Med 2014;72:299–304.

[8] Schouten LJ, Hoppener P, van den Brandt PA, Knottnerus JA, Jager JJ. Completeness of cancer registration in Limburg, The Netherlands. Int J Epidemiol 1993;22:369–76.

[9] Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 2010;17:1471–4. https://doi.org/10.1245/s10434-010-0985-4.

[10] Young JJ, Roffers S, Ries L, Fritz A, Hurlbut A. SEER summary staging manual - 2000: codes and coding instructions. National Cancer Institute; 2001. NIH Pub. No. 01-4969.

[11] Crocetti E, Dyba T, Martos C, Randi G, Rooney R, Bettio M. The need for a rapid and comprehensive adoption of the revised European standard population in cancer incidence comparisons. Eur J Canc Prev 2017;26:447–52. https://doi.org/10.1097/cej.0000000000000250.

[12] Goutte N, Sogni P, Bendersky N, Barbare JC, Falissard B, Farges O. Geographical variations in incidence, management and survival of hepatocellular carcinoma in a Western country. J Hepatol 2017;66:537–44. https://doi.org/10.1016/j.jhep.2016.10.015.

[13] Cwinn M, Molinari M. Regional variations in treatment modalities for hepatocellular carcinoma in Canada. HPB 2016;18: e196–7. https://doi.org/10.1016/j.hpb.2016.02.478.

[14] DHCG. Dutch hepatocellular cholangiocarcinoma group (DHCG). 2020. https://www.dhcg.org/. [Accessed 14 April 2020].

[15] SONCOS. Stichting oncologische samenwerking. 2020. https://www.soncos.org. [Accessed 14 April 2020].

[16] Mokdad AA, Zhu H, Marrero JA, Mansour JC, Singal AG, Yopp AC. Hospital volume and survival after hepatocellular carcinoma diagnosis. Am J Gastroenterol 2016;111:967–75. https://doi.org/10.1038/ajg.2016.181.

[17] Holliday EB, Allen PK, Elhalawani H, Abdel-Rahman O. Treatment at a high-volume centre is associated with improved survival among patients with non-metastatic hepatocellular carcinoma. Liver Int: Off J Int Assoc Study Liver 2018;38:665–75. https://doi.org/10.1111/liv.13561.

[18] Chen TM, Chang TM, Huang PT, Tsai MH, Lin LF, Liu CC, et al. Management and patient survival in hepatocellular

carcinoma: does the physician's level of experience matter? J Gastroenterol Hepatol 2008;23:e179–88. https://doi.org/10.1111/j.1440-1746.2008.05341.x.

[19] Chapman BC, Paniccia A, Hosokawa PW, Henderson WG, Overbey DM, Messersmith W, et al. Impact of facility type and surgical volume on 10-year survival in patients undergoing hepatic resection for hepatocellular carcinoma. J Am Coll Surg 2017;224:362–72. https://doi.org/10.1016/j.jamcollsurg.2016.11.011.

[20] Rothman KJ. Epidemiology: an introduction. Oxford University Press; 2012.

[21] Eurotransplant. Eurotransplant Network information system (ENIS). 2020.