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Hepatocellular carcinoma in the Netherlands incidence, treatment and survival patterns

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Abstract

To examine recent trends of hepatocellular carcinoma (HCC) in an unselected patient population in the Western world, cancer registration data of HCC in the Netherlands were analysed. Trends in incidence, mortality, treatment and survival, according to gender, age, stage of disease and period of diagnosis were studied. Age-standardised incidence of HCC in the Netherlands did not rise from 1989 to 2000. In men older than 75 years, there was a significant increase. Mortality due to primary liver cancer increased from 1989 to 2000. There was no change in the treatment pattern (1989–1998), whereas 73% of patients with HCC received no cancer-related therapy during this period of analysis. Twelve percent of the patients underwent either a partial liver resection or orthotopic liver transplantation. This low percentage suggests that patients with HCC must be analysed and discussed in specialised centres to minimise the number of patients not receiving possible curative therapy.

Keywords: Hepatocellular carcinoma; Trends; Incidence; Treatment; Mortality; Survival

1. Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world and the third most common cause of cancer mortality. The estimated number of people who develop HCC is 564 000 cases/year worldwide [1]. In North America and several European countries, HCC is uncommon and the estimated death rate is less than 5/100 000 inhabitants/year [2,3]. However, the incidence has been increasing in low-endemic areas, as has been reported for the UK [4], France [5] and the US [6]. Most of the publications regarding incidence, treatment and prognosis of patients with HCC are derived from selected groups of patients [7–10]; because these may be of limited relevance, we performed a population-based study in the Netherlands including all patients with HCC diagnosed between 1989 and 2000. Trends in incidence, mortality, treatment and survival, according to gender, age, stage of disease and period of diagnosis were studied.

2. Patients and methods

2.1. Incidence, treatment and mortality

Incidence (1989–2000) and treatment (1989–1998) data regarding liver tumours were provided by the population-based Netherlands Cancer Registry, for which 9 regional cancer registries collect data. All liver malignancies diagnosed and treated from 1989 onwards in people living in the Netherlands, have been registered nationwide [11]. Upon notification by the pathological laboratories or the hospital medical records

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departments, the registration clerks actively collect data (diagnosis, staging and treatment) on all new patients. Data are collected from the medical records of the various hospitals, usually within 6 months of diagnosis. Primary liver cancer was classified as HCC, cholangiocarcinoma, angiosarcoma, other sarcomas or tumours not otherwise specified. Due to privacy regulations, death certificates cannot be used as an additional source of notification of cancer cases in the Netherlands. Despite the lack of this notification source, the infrastructure of the Netherlands health care system and the notification procedures used have made it possible to establish a cancer registry with high completeness (96.2%) [12,13]. In the case of multiple tumours, the same rules were applied as those recommended by the International Association of Cancer Registries [14].

We calculated age-specific and age-standardised incidence rates. For the age-standardised rates, the European population was used as a standard (European Standardised Rates, ESR). Treatment was scored as follows: surgery included partial liver resection or liver transplantation, chemotherapy was systemic or regional, other therapies included local ablation, systemic or local therapy (other than chemotherapy) and radiation. Statistics Netherlands provided mortality data. Trends in incidence and mortality were estimated by calculating the Estimated Annual Percentage Change (EAPC) [15]. Mortality data are based on all primary liver cancers. Due to different coding during the study period, it was impossible to examine the mortality trends for the histological subgroups. For calculating age-standardised incidence rates in European cancer registries between 1978 and 1997 we used data of the EUROCIM (European cancer incidence and mortality) database. Only registries with data since 1978 were included. Age-adjustment was performed by direct standardisation according to the European Standard Population (ESR: European Standardised Rate) [16].

2.2. Survival

Follow-up of cancer patients was completed in two regional cancer registries: the Amsterdam Cancer Registry, Comprehensive Cancer Centre Amsterdam (CCCA) and the Eindhoven Cancer Registry, Comprehensive Cancer Centre South (CCCS). Therefore, survival analyses were restricted to these registries. Together these covered an area of approximately 3.5 million inhabitants (±25% of the total population in the Netherlands at that time). In addition to passive follow-up in the hospitals, active follow-up was done, using regional municipal databases and the national bureau for genealogy. The database of the bureau for genealogy contains data of all people deceased in the Netherlands. Follow-up was complete at least until 1 January 1999. Survival was analysed according to gender, age, tumour stage and treatment. Patients were staged according to the Internationla Union Against Cancer (UICC) staging system [17]. We calculated Kaplan–Meier curves: to analyse differences between subgroups the log-rank test was used. To calculate variation in survival within Europe, data of the EUROCARE database (a concerted action among European cancer registries) were used [18]. Patients diagnosed with primary liver cancer between 1990 and 1994 in European population-based cancer registries were included. For international comparison and for comparison with clinical studies, cases incidentally discovered at autopsy were excluded, as were those known to registries from the death-certificate-only (DCO). In case of multiple metachronous tumours, only the first-diagnosed tumour was included in the survival analysis. In EUROCARE, relative survival rates are computed. Relative survival is an estimation of disease-specific survival. It is calculated as the ratio of the observed to the expected survival rates. Expected survival rates were calculated from life tables for regional male and female populations with the same 5-year age distribution. Since the age distribution of patients differs between countries, the survival rates were adjusted to a common age structure.

3. Results

3.1. Incidence

Between 1989 and 2000, 3048 primary liver cancers were recorded in the Netherlands. Liver cancer was approximately twice as common in males as in females. HCC was the predominant histology (64%) followed by cholangiocarcinoma (10%). In 16% of the cases the disease was not microscopically confirmed. The remaining 10% were angiosarcomas, other sarcomas, or tumours not otherwise specified. The percentages of the three largest groups, i.e. HCC, cholangiocarcinoma and tumours not microscopically confirmed, remained stable over time (1989–1998) (Fig. 1). Between 1989 and 2000, 1964 new patients with HCC were registered in the Netherlands. The male/female ratio was 2.4:1. The age-standardised incidence rate (ESR) did not show a significant trend in these 12 years (Fig. 2). In 2000, the ESR for males was 1.6/100 000 and for females 0.3/100 000. Figs. 3 and 4 show the age-specific trends of HCC incidence. Besides in males older than 75 years, there was no significant increase of incidence.

Mortality due to primary liver cancer increased (Fig. 5). This trend was present both in males and females (males EAPC = 3.1%, females EAPC = 4.6%) [19]. This was mainly caused by an increase in mortality in patients aged 60 years or older. The age distribution has remained relatively stable throughout the study period. Two percent of all HCCs were diagnosed under the age

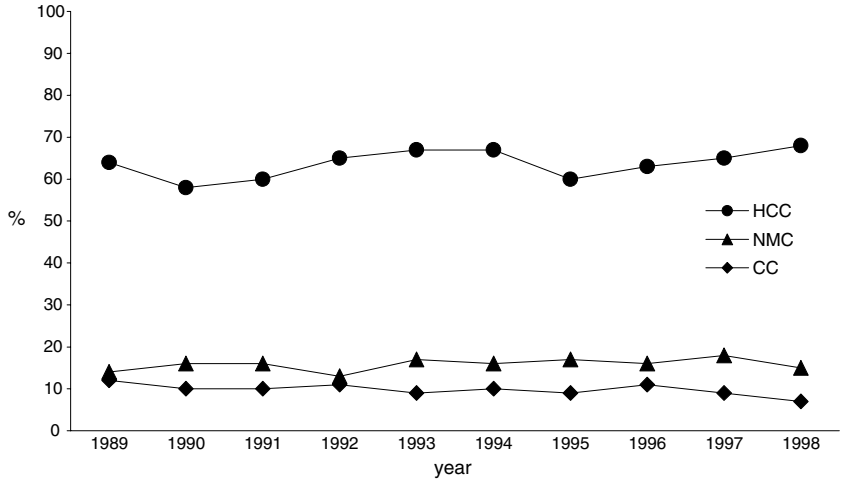

Fig. 1. Proportional distribution of the histological subtypes of primary liver cancer in the Netherlands (1989–1998). NMC: not microscopically confirmed; HCC: hepatocellular carcinoma; CC: cholangiocarcinoma.

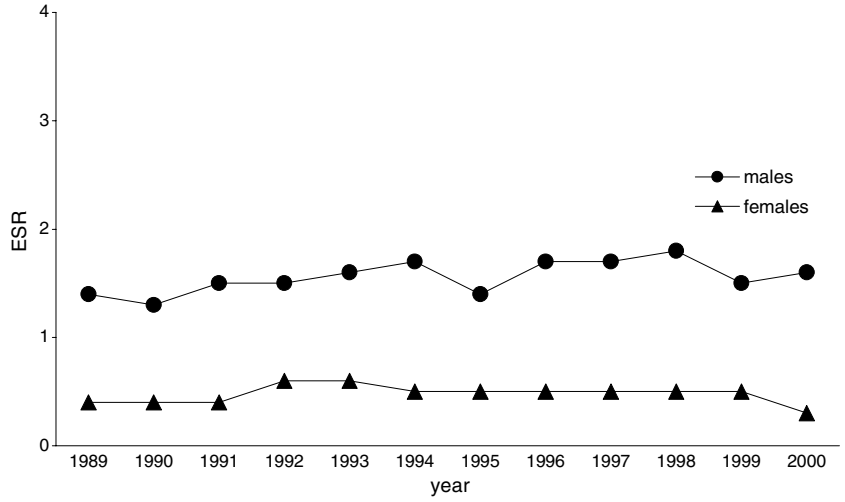

Fig. 2. The age-standardised incidence rate (patients/100 000/year) for HCC in the Netherlands (1989–2000). ESR: European standardised rates.

of 29 years, approximately 3 patients yearly. The incidence was highest for men older than 75 years (12/100 000/year). Despite the low incidence rate, there was a large variation in incidence within the Netherlands, especially among males. Among males, the age-standardised incidence rates were 2.5/100 000 in highly urbanised areas and only 0.7/100 000 in rural areas. These differences were only found for HCC and not for the other primary liver cancers. The incidence of HCC in several countries in Europe is given in Table 1. The incidence of HCC was relatively low in England, Norway and the Netherlands, and relatively high in France (North), Italy (Varese), Spain (Navarra) and Switzerland (Geneva).

3.2. Treatment

Between 1989 and 1998, twelve percent ($n = 197$) of the total HCC population underwent a partial liver resection or orthotopic liver transplantation (OLT) (Table 2). There was no difference in the resection rate between males and females. During the 10-year study period, the resection rate remained stable. Patients younger than 45 years of age ($n = 132$) had the highest resection rate (33%). Patients older than 75 years ($n = 416$) had the lowest resection rate (5%). Seventy-three percent did not get any form of cancer-related treatment; this did not change during the study period.

3.3. Survival

Table 3 gives the estimated 5-year survival rates according to Kaplan–Meier, stratified according to age and treatment. Survival was best for patients with a resected tumour. Survival of patients diagnosed during 1989–1993 was the same as the survival of patients diagnosed during 1994–1998 (data not shown). No difference in survival was found either in the untreated

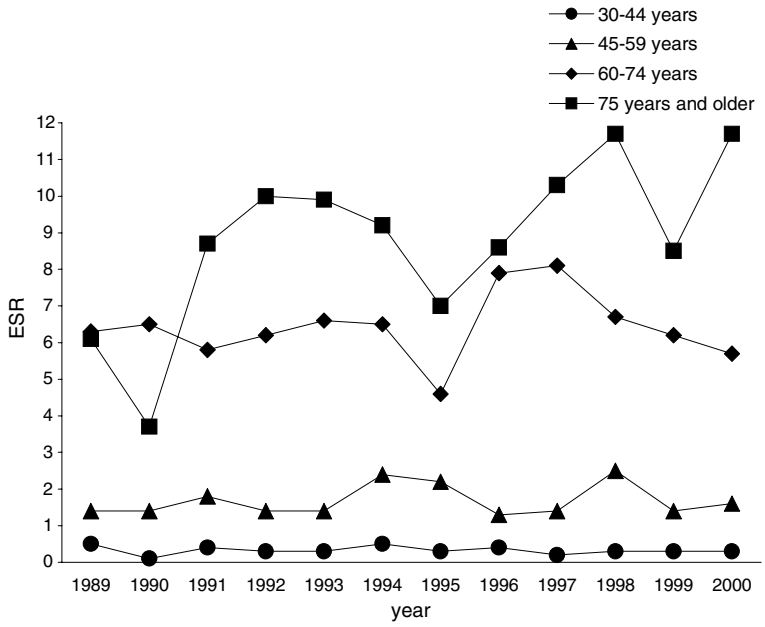

Fig. 3. HCC age-specific trends for males in the Netherlands (1989–2000). ESR: European standardised rates.

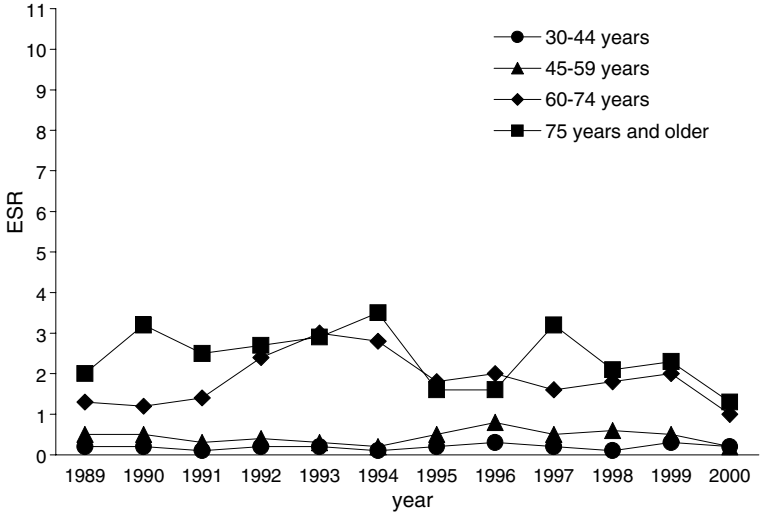

Fig. 4. HCC age-specific trends for females in the Netherlands (1989–2000). ESR: European standardised rates.

group or in the surgically treated group between these two time intervals.

There was no difference in a 5-year survival rate between males and females or between patients younger than 60 years and those older than 60 years. Five-year survival of patients with tumour stage I/II or III (13%) was significantly better than for those with tumour stage IV (1%). In the surgically treated group, there was also a difference in 5-year survival between tumour stage I/II and tumour stage III (48% and 24%, respectively, $P = 0.06$). In the group of patients who did not receive surgery or chemotherapy, patients with tumour stage I/II and III had a 2-year survival rate of 14% and 18%, respectively, and both groups had a 5-year survival rate of only 2%. Patients with tumour stage IV had the poorest survival (2-year survival-rate of 3% and no 5-year survivors). Relative 1- and 5-year survival of patients with HCC in the Netherlands was average compared with other European countries (Table 4).

4. Discussion

The results of this study show that the incidence of HCC in the Netherlands was stable during 1989–2000. This is in contrast with recent publications that described an increased incidence in other low-endemic areas [4–6,20]. An article of McGlynn *et al.* [21] about

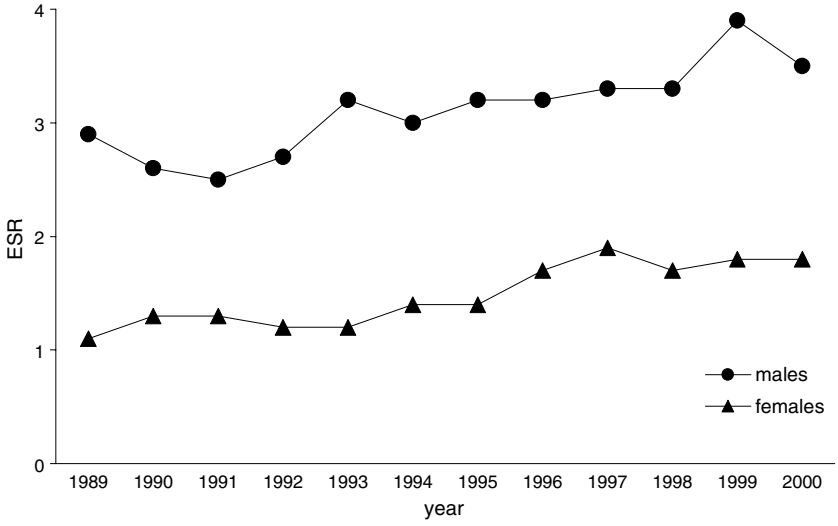

Fig. 5. Age-standardised mortality rates due to primary liver cancer in the Netherlands (1989–2000). ESR: European standardised rates.

Table 1
Incidence rates of HCC in Europe (patients/100 000/year); source: EUROCIM

	Male		Female	
	1988–992	1993–1997	1988–1992	1993–1997
Estonia	1.72	2.34	0.65	0.84
England	1.30	1.65	0.38	0.51
Finland	3.35	3.28	1.29	1.01
France-North	9.31	9.94	0.97	0.88
Germany-Saarland	1.86	3.30	0.50	0.84
Iceland	3.29	3.34	0.64	1.27
Italy-Varese	10.40	14.10	2.23	2.26
Norway	1.46	1.36	0.58	0.56
Slovenia	2.87	3.34	0.55	0.85
Spain-Navarra	4.82	7.66	0.66	1.42
Sweden	3.67	3.40	1.49	1.33
Switzerland-Geneva	11.32	8.89	1.16	1.61
Scotland	2.27	3.02	0.55	0.72
The Netherlands	1.54	1.70	0.50	0.52

HCC, hepatocellular carcinoma.

international trends and patterns of primary liver cancer suggested that developed countries have experienced an increase in primary liver cancer incidence, whereas developing countries have experienced a decline. The apparent changes in liver cancer rates as described worldwide are not fully understood. Possible explanations for the rise in low-endemic areas may be the rise of hepatitis C viral (HCV) infections, improved survival of cirrhotic patients, and a better diagnostic work-up [21–25]. Another possible explanation for the rise is the increased proportion of immigrants from high-endemic areas. The relatively high proportion of immigrants from high-risk areas in the world could explain the high rates in urbanised areas in our study. However, during our 12-year study period, the incidence of HCC in urbanised areas also remained stable (data not shown).

The geographical variation in different incidence rates within Europe strongly correlates with the prevalence of hepatitis infection and the prevalence of liver cirrhosis from any cause [3]. Therefore, the incidence rates in France, Italy, Switzerland and Spain are markedly higher than in the other European countries (Table 1).

Diagnostic work-up has changed over time. Computed tomography and high-resolution magnetic resonance imaging (MRI) of the liver have facilitated the diagnosis of liver malignancies. One may consider that if there is an increase for all primary liver cancers this reflects a better diagnostic work-up of liver malignancies. This could be an explanation for the increasing incidence for both intrahepatic cholangiocarcinoma and HCC in the US and the UK [4,6,26,27]. We did not find an increasing trend for HCC, cholangiocarcinoma or any other primary liver malignancies (Fig. 1). These data support the concept that a better diagnostic work-up for patients or the accuracy of registration probably did not influence the incidence rate in our study.

Table 2
Treatment patterns of patients with HCC in the Netherlands according to age and time of diagnosis

Age (years)	Treatment	1989–1993 *n* (%)	1994–1998 *n* (%)	1989–1998 *n* (%)
<45	Surgery	26 (37%)	17 (28%)	43 (33%)
	Chemotherapy	12 (17%)	11 (18%)	23 (17%)
	Other therapy	6 (8%)	7 (11%)	13 (10%)
	No therapy	27 (38%)	26 (43%)	53 (40%)
		71 (100%)	61 (100%)	132 (100%)
45–59	Surgery	20 (17%)	40 (23%)	60 (20%)
	Chemotherapy	9 (7%)	18 (10%)	27 (9%)
	Other therapy	16 (13%)	15 (8%)	31 (10%)
	No therapy	77 (63%)	103 (59%)	180 (60%)
		122 (100%)	176 (100%)	298 (100%)
60–74	Surgery	28 (8%)	46 (11%)	74 (10%)
	Chemotherapy	19 (5%)	15 (4%)	34 (4%)
	Other therapy	28 (8%)	46 (11%)	74 (10%)
	No therapy	278 (79%)	309 (74%)	587 (76%)
		353 (100%)	416 (100%)	769 (100%)
>75	Surgery	8 (4%)	12 (5%)	20 (5%)
	Chemotherapy	2 (1%)	3 (1%)	5 (1%)
	Other therapy	12 (6%)	19 (9%)	31 (7%)
	No therapy	172 (89%)	188 (85%)	360 (87%)
		194 (100%)	222 (100%)	416 (100%)
Total	Surgery	82 (11%)	115 (13%)	197 (12%)
	Chemotherapy	42 (6%)	47 (5%)	89 (6%)
	Other therapy	62 (8%)	87 (10%)	149 (9%)
	No therapy	554 (75%)	626 (72%)	1180 (73%)
		740 (100%)	875 (100%)	1615 (100%)

n, number of patients.

Table 3
Survival patterns according to age and treatment in CCCS (comprehensive cancer centre south) and CCCA (comprehensive cancer centre amsterdam) of patients diagnosed with HCC between 1989 and 1998

Treatment	5-year survival age <60 years (%)	5-year survival age >60 years (%)	5-year survival total population (%)
Surgery	31	25	29
Chemotherapy	5	6	6
Other therapy	0	0	0
No therapy	2	2	2
Overall	5	5	5

The terms HCC and primary liver cancer are often used interchangeably. In Japan, 94% of all primary liver cancers were HCC [25], compared with 64% in our study and 74% in the USA [6]. Therefore, it is more accurate to describe the primary liver cancers separately if the population is based on Western-world standards. Differences in study design might explain the difference between our results and studies reporting an increase of HCC [4–6,20,22,28].

The study of El-Serag *et al*. [6] used data on incidence from the Surveillance, Epidemiology and End Results (SEER) Program of the National Cancer Institute and found a rising incidence. Since this database accounts for 14% of the American population, it may not reflect the USA as a whole (SEER regions are more urban and have a higher proportion of foreign-born persons than the general US population) [6,29]. El-Serag and Mason [6] analysed mortality and data on hospitalisation. The results of these two measures were similar to the observed increasing incidence rate of HCC. This strengthens the internal validity of the observed increasing incidence trend. However, it has been stated that analyses on mortality data are not very reliable if one analyses a subgroup of cancer [22] and the data on hospitalisation were of a specific subgroup of the population; i.e. US veterans, mainly men. We found a significant rise of mortality due to primary liver cancer. This is in contrast to the stable incidence rate of the primary liver cancers during the same period (Fig. 5). An increasing incidence in the period before this study with long-time survivors is a very unlikely explanation in this usually rapidly fatal disease. In a recent update of the study of El-Serag *et al*. [29], the incidence of HCC continues to increase in the US, with rates increasing the fastest in white men 45–54 years of age. If age-adjusted rates are analysed, age-specific trends can be diverse. Therefore, we analysed our data according to specific age groups in both sexes (Figs. 3 and 4). In males older than 75 years, there was a significant increase. We do not have a conclusive explanation for this phenomenon. An aging population is an unlikely explanation for this

Table 4
Survival rates in Europe (1990–1994); source: EUROCARE

	Cov. (%)	Male		Female		Overall	
		No. of cases	Surv. (%)	No. of cases	Surv. (%)	No. of cases	Surv. (%)
Estonia	100	138	11–3	107	12–1	245	12–2
England	59	2222	16–6	1370	16–8	3592	16–7
Finland	100	613	14–4	597	16–4	1210	18–4
France-North	4	628	33–7	145	24–9	773	31–7
Germany	2	133	16–5	77	15–6	210	16–5
Italy	14	4004	29–7	1825	27–8	5829	28–7
Norway	100	247	20–3	190	18–4	437	19–3
Slovenia	100	162	19–6	78	26–4	240	22–5
Spain	6	881	27–10	349	24–10	1230	26–10
Sweden	100	1215	14–3	967	13–3	2182	14–3
Switzerland	13	137	30–6	43	27–0	180	29–5
Scotland	100	515	17–4	321	17–5	836	17–4
The Netherlands	23	179	22–7	83	23–6	262	22–7

COV: coverage of the country; Surv.: 1- and 5-year relative survival rate.

increase in HCC since it was not observed for females as well. The most likely explanation is that the increase of HCC incidence in males older than 75 years is due to confounding by the small numbers of patients (323 patients in 12 years). It may also reflect an influx of male immigrants in recent decades. An increase in HCV infection during the 1970s is another suggestion. However, this does not explain the sex difference. After HCV infection it takes approximately 25 years to develop liver cirrhosis. Afterwards, there is an incidence of 1 or 2 percent annually to develop HCC.

In our study, a high proportion of patients with HCC (73%) did not receive cancer-related treatment. In the USA, e.g., 51% of the HCC patients received no treatment [10]. To our knowledge, there are no other Western data on the percentage of patients who received treatment without any referral bias. In view of the promising local ablation methods [30] and the upcoming living related liver transplantation programme [31], the percentage of patients receiving no treatment may decline in the near future. However, in our series, there was no trend towards this phenomenon. Of all patients, 12% were treated by partial liver resection or OLT. This is interesting because this percentage is in the absence of any referral bias. In experienced centres, the reported resection rates (*not* including OLT) are, e.g., 37% [8], 49% [32] and even 67% [33]. Resection rates of patients with HCC without referral bias are scarce in the literature. Cance *et al.* [10] (data representing approximately 14% of the estimated cases of carcinomas of the liver and biliary tract diagnosed in the USA) found a resection rate of 17%, excluding the patients who underwent OLT. We have the impression that our percentage (12%) with either partial liver resection or OLT is low. Reasons for this low percentage need to be explored. The underlying liver disease (60–95%) [34–36], the older age of patients (75% older than 60 years in this study) and the usually large tumour diameter of patients without underlying liver cirrhosis (mean 9 and 10 cm) [37,38] are known drawbacks for resection. However, liver cirrhosis is nowadays not an absolute contra-indication for even major liver resections in specialised centres [39]. Liver resection in the elderly patients with HCC has short- and long-term results comparable to those of younger patients, if they well selected and receive specialised postoperative care [40,41]. Despite the usually large tumour diameter in the non-cirrhotic liver, 5-year survival rates of 40% after partial liver resection have been reported [37,38]. To minimise the number of patients not receiving possible curative therapy, we suggest that all patients with HCC must at least be discussed in specialised centres offering a consultation service.

The 5-year survival rate of 29% after resection/OLT is rather low compared with the 5-year survival rates found in the literature. It is difficult to explain this difference since the survival after resection or OLT is highly influenced by the underlying liver disease, vascular invasion, size and number of the tumour nodules. This is exactly the reason why the TNM classification [17] does not have prognostic power in patients with HCC [42]. However, the survival rate in our study is interesting because, in contrast to previous studies, it is without any referral bias. Previous reports have demonstrated that women appear to have better survival outcomes from HCC than men [10,43]. In the current report, enhanced survival among women was not observed; this was seen in all treatment modalities and the untreated group. Cance *et al.* [10] suggested that especially women with tumour stages II and III had a better survival than men, however, even in this subgroup we did not find better survival rates for females. Table 4 gives the relative survival rates at 1- and 5 years among several European countries between 1990 and 1994 (EUROCARE III). There are small intercountry differ-

ences in survival. Survival rates were slightly higher in England, Italy, Spain and France than in the other countries. It is unclear if the intercountry differences are a result of differences in the stage at diagnosis and/or more aggressive therapeutic approaches, or a methodological difference (completeness) [44].

In conclusion to our knowledge, this is the first study that reports on incidence data and treatment patterns for a whole country. In contrast to previous reports of sub-populations in non-endemic areas, we found no age-standardised rising incidence of HCC in the Netherlands between 1989 and 2000. There was no change in the treatment pattern overtime. Seventy-three percent of patients with HCC received no therapy and only 12% of the patients underwent either partial liver resection or OLT. This low percentage suggests that patients with HCC must be analysed and discussed in specialised centres to minimise the number of patients not receiving possible curative therapy.

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