Treatment trends and outcomes of hepatocellular carcinoma in a single center during 35 years.

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Abstract

Background: Hepatocellular carcinoma (HCC) is one leading cause of cancer mortality. The aim of this study was to examine the trends of HCC treatment and outcomes in a single tertiary center during 35 years.

Methods: Some 273 consecutive HCC patients between 1983-2018 were identified from Oulu University Hospital records. Primary outcomes of the study were postoperative complications within 30 days after the operation, and short- (30- and 90-day) and long-term (1, 3 and 5-year) survival.

Results: Of 273 patients, 49 underwent surgical resection, 25 local ablation, 48 angiological treatment and 151 had palliative treatment. The rate of surgery declined over time, while other invasive treatments increased. Major complications occurred in 14 (28.6%) patients after surgical resection, in 2 (8.0%) patients after local ablation and 13 (27.1%) patients after angiological treatment ($p=0.022$). Recurrence and local recidives were observed more often in local ablation group and in angiological treatment group ($p<0.001$). Overall survival rates in surgical resection group were at 30 and 90 days, 1-,3 and 5-years 95.9%, 95.9%, 85.1%, 59.0% and 51.2%. In local ablation group, respective overall survival rates were 100.0%, 100.0%, 86.1%, 43.1% and 18.8%, and in angiological group 95.8%, 93.6%, 56.1%, 26.3% and 6.6%. In cox regression model adjusted for confounding factors, mortality hazard was lowest after surgical resection. Prognosis was poor in palliative group.

Conclusions: Based on this Northern Finland population, the surgical resection of HCC has acceptable complication rate compared to other treatments and yields the best long-term survival. Overall prognosis of HCC remains poor.

Key words: Hepatocellular carcinoma, surgery, local ablation, TACE.

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide and it is the fourth most common cause of cancer mortality (1) Globally, hepatitis B and C viral infections are the most common underlying causes of HCC, especially in eastern countries.(2) In western countries, heavy alcohol consumption is a major cause of liver disease, which can lead to cirrhosis and HCC.(3)(4) Surgical resection is the first-line therapy for single HCC of any size, when hepatic function is preserved, and sufficient remnant liver volume is maintained. (5) Only 20-30% of the HCC are resectable. (6) Liver transplantation is considered as the first-line therapy for HCC within Milan Criteria unsuitable for resection (5), but the availability of transplantation is limited. (6) Radiofrequency ablation (RF) in single tumors 2 to 3 cm is an alternative to surgical resection based on technical factors (location of the tumor), hepatic and extrahepatic conditions. (5) Percutaneous ethanol injection (PEI) is an option in some cases where RF is not technically feasible due to localization of the tumor. (5) Other options for non-resectable HCC are transarterial chemoembolization (TACE) and molecular targeted therapies. (5) In resections, < 30% morbidity and < 3% mortality rates have been reported. (5) Morbidity and mortality rates are higher in patients with cirrhotic liver. (7) In RF, complication rates vary from 0 to 6.1% (8) and perioperative mortality rates ranges from 0 to 1.8%. (9) In TACE, complication rates vary from 25 to 45% (10) and overall mortality rates are around 0.6%. (11) The aim of this study was to examine the treatment trends and outcomes of HCC in Northern Finland, where alcohol plays a major role in the etiology. Results of different treatments were compared with aim to find places for improvements.

Materials and methods

Study design

This study was a retrospective cohort study in a single institution tertiary care hospital in Northern Finland. The study population consists of 273 consecutive patients with hepatocellular carcinoma diagnosed in Oulu University Hospital between January 1, 1983 and March 12, 2018.

Data collection

The patients were identified from archives using ICD-10 code C22.0& (hepatocellular carcinoma). All diagnoses were confirmed with histological examination. The clinical data was collected from Oulu University Hospital patient records. Four groups were formed: 1) surgical resection, 2) local ablation (RF or PEI), 3) angiological group (TACE, TAE, SIRT) and 4) palliative treatment (chemotherapy or best supportive care). Study groups were formed according to the most radical treatment, for example, if HCC was surgically resected and the patient received also RF, patient was included in surgical resection group. Charlson comorbidity index (CCI) was used to measure comorbidity (12). The complications were classified primarily with Accordion Severity Grading System (13) and secondarily with Clavien-Dindo classification system. The 8th edition of TNM classification was used in staging. A gastrointestinal pathologist (V-M. P) re-evaluated and confirmed the diagnoses of all included patients. All cases were also re-graded for histological grade of differentiation by a gastrointestinal pathologist (V-M. P.).

Outcomes

Primary outcomes of the study were postoperative complications within 30 days after the operation, and short- (30- and 90-day) and long-term (1, 3 and 5-year) survival.

Statistical analysis

Mann-Whitney U-test was used to compare differences between two independent groups with continuous variable. For categorical data-analysis $\chi 2$-test and Fisher-test were used. The threshold for significance was set at $P < 0.05$. In all continuous variables, median and interquartile range was presented. For survival data, Kaplan-Meier with log-rank test was used. Cox-regression analysis was used to analyze survival in three treatment groups adjusting with the following covariates: sex (female/male), age (continuous), Charlson comorbidity index (0-1, 2 or higher), cirrhosis (no/yes), Child-Pugh index (A,B,C), ASA status (1,2,3,4 or more), year of operation (1983-2005, 2006-2018), and stage (1,2,3,4). Complications were classified as minor and major based on Clavien-Dindo classification system (14) and Accordion Severity Grading System. (13) Follow-up times were calculated using life-table method. For comparison of survival trends over time, patients were divided into equal sized groups (old and new cohort). Statistical analysis was performed with IBM SPSS statistics 24.0 (IBM Corp., Armonk, NY).

Results

Patients

Of 298 HCC patients, 49 underwent surgical resection, 25 RF, laser ablation or PEI, 48 were treated with TACE, TAE or SIRT and 151 were treated with palliative treatment or best supportive care. Some patients received more than one treatment presented in Figure 1. Twenty-five patients were excluded from the study due to

lack of information from the patient files. A total of 273 patients diagnosed with HCC were included in the study, resulting with mean 8.5 patients per year. Mean number increased during the study from 3.0 to 12.9 (1983-2000 and 2001-2018). Since introduction of ethanol injections (year 1997), TACE (year 2000) and RF (year 2006) the rate of surgery has declined with corresponding rise in local ablation and other invasive treatments (Figure 2). The median follow-up time in surgical patients was 2.3 years, interquartile range (IQR) (1.2-7.3). In local ablation group 2.2 years (IQR 0.9-3.3), in angiological group 1.0 years (IQR 0.5-2.7), and in palliative group 0.4 years (IQR 0.1-1.0).

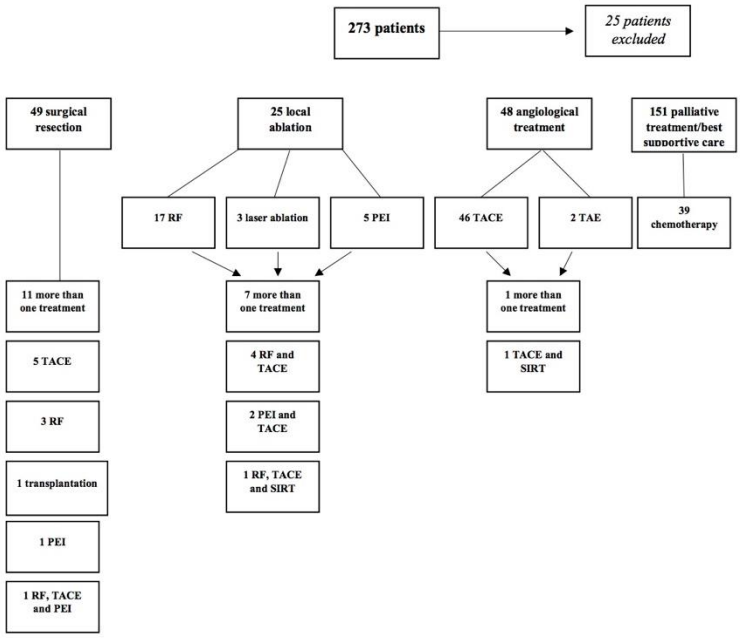

Fig. 1. Flow-chart presenting the given treatment in the four groups of patients with hepatocellular carcinoma.

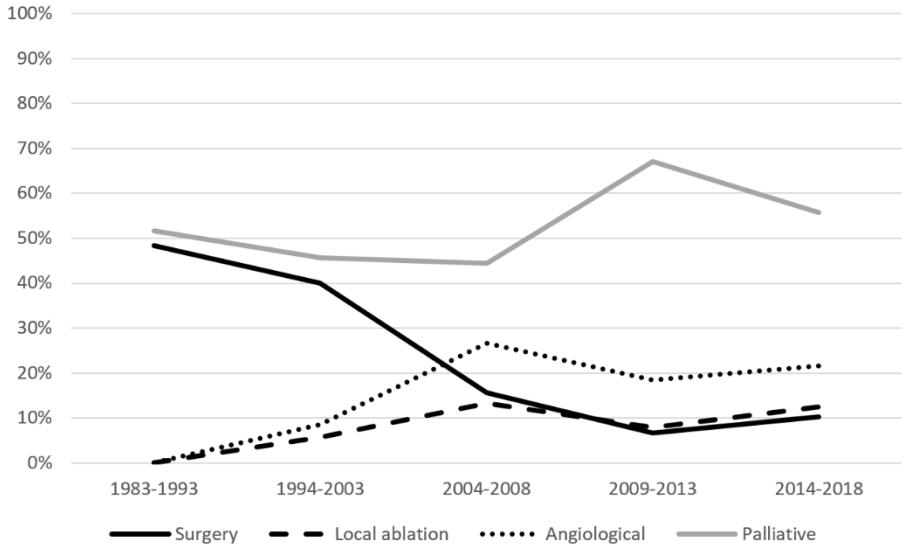

Fig. 2. Trends in treatment modalities of hepatocellular carcinoma.

Preoperative features of the study groups

Baseline characteristics of the study groups are presented in Table 1. Median age of patients who underwent surgical resection was 66.7 years (IQR 60.2-70.6). In other groups, patients were older (Table 1.) Male dominance was observed in all groups. Liver cirrhosis was present in high percentage of patients (Table 1.). According to Child Pugh Classification, class A was the most common in all groups. In patients treated with surgery, the most patients had Charlson Comorbidity Index (CCI) score 1 (42.9%), in local ablation and angiological treatment group, the most common CCI score was 2 (20.0% and 47.9%). In palliative group, the most patients had CCI score 1 (29.1%) (Table 1.)

Table 1. Baseline characteristics.

Characteristics	Surgical resection (=49)	Local ablation (=25)	Angiological (=48)	Palliative (=151)
Age, median (IQR) [a,b,c]	66.7 (60.2-70.6)	73.6 (68.3-83.8)	73.0 (68.8-78.8)	72.4 (64.7-79.9)
BMI kg/m^2 (median, IQR) [a,e]	26.0 (23.4-29.0)	29.1 (26.2-33.6)	27.5 (24.8-30.0)	26.1 (23.3-29.7)
Male, n (%) [b]	29 (59.2%)	20 (80.0%)	38 (79.2%)	105 (69.5)
Alcohol use [a,b,c]				
History of alcohol use	5 (10.2%)	12 (48.0%)	14 (29.2%)	49 (32.5%)
No/Missing	44 (88.0%)	13 (52.0%)	34 (70.8%)	102 (67.5%)
Liver cirrhosis [e]	16 (32.7%)	14 (56.0%)	19 (39.6%)	50 (33.1%)
Charlson Comorbidity Index [c,f]				
0	12 (24.5%)	2 (8.0%)	1 (2.1%)	19 (12.6%)
1	21 (42.9%)	4 (16.0%)	13 (27.1%)	44 (29.1%)
2	12 (24.5%)	5 (20.0%)	23 (47.9%)	40 (26.5%)
3	4 (8.2%)	9 (36.0%)	9 (18.8%)	24 (15.9%)
4 or more	0 (0.0%)	5 (20.0%)	2 (4.2%)	23 (15.2%)
Child-Pugh classification				
Child-Pugh A	43 (87.8%)	20 (80.0%)	45 (93.8%)	97 (64.2%)

Child-Pugh B	6 (12.2%)	5 (20.0%)	3 (6.3%)	42 (27.8%)
Child Pugh C	0 (0.0%)	0 (0.0%)	0 (0.0%)	12 (7.9%)
ASA status, n (%) [c]				
Grade I	9 (18.4%)	0 (0.0%)	0 (0.0%)	4 (2.6%)
Grade II	11 (22.4%)	4 (16.0%)	9 (18.8%)	25 (16.6%)
Grade III	29 (59.2%)	20 (80.0%)	31 (64.6%)	101 (66.9%)
Grade IV or more	0 (0.0%)	1 (4.0%)	8 (16.7%)	21 (13.9%)
WHO performance status [c]				
Grade 1	31 (63.3%)	4 (16.0%)	13 (27.1%)	27 (17.9%)
Grade 2	13 (26.5%)	11 (44.0%)	22 (45.8%)	52 (34.4%)
Grade 3	5 (10.2%)	8 (32.0%)	11 (22.9%)	54 (35.8%)
Grade 4 or more	0 (0.0%)	2 (8.0%)	2 (4.2%)	18 (11.9%)
AFP, median (IQR) [e]	6.0 (3.0-191.0)	6.0 (3.0-9.0)	9.0 (3.5-261.0)	15.0 (4.7-326.5)

a= Significant difference between resection group and local ablation group

b= Significant difference between resection group and angiological group

c= Significant difference between resection group and palliative group

d= Significant difference between local ablation group and angiological group

e= Significant difference between local ablation group and palliative group

f= Significant difference between angiological group and palliative group

Significant difference = P<0.050

Tumor features

Tumor stage I was the most common in the active treatment groups (surgical resection/local ablation/angiological) (Table 2.) In palliative group 58.3% had tumor stage III or IV. Tumor grade II was the most common in all four groups. Significant difference between groups were observed (resection group vs local ablation, $p=0.001$, resection group vs angiological group, $p<0.001$, resection group vs palliative group, $p=0.013$, angiological group vs palliative group, $p=0.044$) (Table 2.). Tumor size was bigger in resection group than in local ablation group (median 50 mm vs 30 mm, $p<0.001$). For other parameters and between group comparisons, see Table 2.

Postoperative features

In surgical resection group, overall resection rate during the study period was 17.9%, twenty (40.8%) patients underwent major liver resection (≥ 3 segments), 29 (59.2%) minor resection (≤ 2 segments). Twenty (40.8%) patients were treated with additional postoperative chemotherapy or radiotherapy. One patient was treated with further liver transplantation. Median time spent in hospital after operation was 11 days (IQR 8.0-19.5) and median time spent in ICU was 1 day (IQR 0.0-2.0). Readmission in 30 days occurred with 6 (12.2%) patients. Postoperative features are presented in Table 2.

In local ablation group the most common treatment was RF with 17 (68.0%) patients. Three (12.0%) patients underwent laser ablation and 5 (20.0%) patients PEI. One (4.0%) patient of local ablation group had postoperative chemotherapy. The median time spent in hospital was 3 days (IQR 2-5). Two (8.0%) patients had readmission in 30 days. In angiologically treated group, 9 (18.8%) patients had

postoperative chemotherapy. The median time spent in hospital was 5.5 days (IQR 3-9). Eight (16.7%) patients had readmission in 30 days. Postoperative features are presented in Table 2.

Postoperative complications

Overall complications occurred more frequently in surgical resection group than in local ablation group (71.5% vs 32.0%, $p<0.001$). Significant difference between local ablation group and angiological group was observed in overall complications (32.0% vs 58.3%, $p=0.033$) (Table 2 and 3).

In surgical resection group, 14 (28.6%) patients suffered a major complication (ASG III or more), and minor complications (ASG grade I-II) occurred in 21 (42.9%) patients. Respective numbers in local ablation group were 2 (8.0%) and 6 (24.0%), in angiological group 13 (27.1%) and 15 (31.3%). The type and severity of complications according to ASG-criteria are presented in Table 3.

Table 2. Patient characteristics.

Characteristics	Surgical resection (=49)	Local ablation (=25)	Angiological (=48)	Palliative (=151)
Major resection	20 (40.8%)	-	-	-
Minor resection	29 (59.2%)	-	-	-
Resection margin				
R0	38 (77.6%)	-	-	-
R1	3 (6.1%)	-	-	-
R2	2 (4.1%)	-	-	-
Postoperative chemo or radiotherapy [a,b,e]	20 (40.8%)	1 (4.0%)	9 (18.8%)	39 (25.8%)
Stage [c,e,f]				
Stage I	28 (57.1%)	19 (76.0%)	23 (47.9%)	45 (29.8%)
Stage II	16 (32.7%)	6 (24.0%)	12 (25.0%)	15 (9.9%)
Stage III	3 (6.1%)	0 (0.0%)	8 (16.7%)	55 (36.4%)
Stage IV	2 (4.1%)	0 (0.0%)	5 (10.4%)	34 (21.9%)
Tumor localization [c,e,f]				
Right lobe	30 (61.2%)	16 (64.0%)	28 (58.3%)	59 (39.1%)
Left lobe	14 (28.6%)	7 (28.0%)	9 (18.8%)	15 (9.9%)

Both lobes	5 (10.2%)	2 (8.0%)	11 (22.9%)	76 (50.3%)
Unifocal tumor [b,c,e]	41 (83.7%)	19 (76.0%)	26 (54.2%)	58 (38.4%)
Tumor grade [a,b,c,f]				
Grade I	4 (8.2%)	10 (40.0%)	15 (31.3%)	39 (25.8%)
Grade II	28 (57.1%)	13 (52.0%)	28 (58.3%)	79 (52.3%)
Grade III	14 (28.6%)	1 (4.0%)	1 (2.1%)	24 (15.9%)
Missing	3 (6.1%)	1 (4.0%)	4 (8.3%)	9 (6.0%)
Tumor size, median, (IQR) [a,c,d,e,f]	50.0 (35.0-100.0)	30.0 (25.0-38.5)	55.5 (41.3-89.5)	83.0 (53.5-130.0)
ASG [a,c,f]				
No complication	14 (28.6%)	17 (68.0%)	20 (41.7%)	142 (94.0%)
Minor complication	21 (42.9%)	6 (24.0%)	15 (31.3%)	3 (2.0%)
Major complication	14 (28.6%)	2 (8.0%)	13 (27.1%)	6 (4.0%)
Time spent in hospital, median (IQR) [a,b,c,d,f]	11.0 (8.0-19.5)	3.0 (2.0-4.5)	5.5 (3.0-9.0)	2.0 (2.0-6.0)
Readmission in 30 days [f]				
Yes	6 (12.2%)	2 (8.0%)	8 (16.7%)	4 (2.6%)
No	42 (85.7%)	23 (92.0%)	40 (83.3%)	147 (97.4%)
Recurrence [b]				
Treated but vital tumor tissue observable or poor result	3 (6.1%)	2 (8.0%)	9 (18.8%)	-

Good preliminary outcome, recurrence detected in follow-up	0 (0.0%)	2 (8.0%)	7 (14.6%)	-
Treated but cancer recurs in a new area of the liver	20 (40.8%)	7 (28.0%)	10 (20.8%)	-
Treated but cancer metastasizes in a new site of the body	4 (8.2%)	4 (16.0%)	12 (25.0%)	-
Treated, no sign of recurrence	20 (40.8%)	7 (28.0%)	3 (6.3%)	-
Local recidive [a,b,d]				-
No	47 (95.9%)	14 (46.0%)	12 (25.0%)	-
Yes	2 (4.1%)	8 (32.0%)	25 (52.1%)	-
Emergency patient	0 (0.0%)	0 (0.0%)	3 (6.3%)	5 (3.3%)

a= Significant difference between resection group and local ablation group

b= Significant difference between resection group and angiological group

c= Significant difference between resection group and palliative group

d= Significant difference between local ablation group and angiological group

e= Significant difference between local ablation group and palliative group

f= Significant difference between angiological group and palliative group

Significant difference = $P<0.050$

Table 3. Accordion Severity Grading System -based postoperative complications in patients with hepatocellular carcinoma after surgical resection, local ablation including RF, laser ablation and PEI and angiological group including TACE, TAE and SIRT. The numbers of resection, local ablation group and angiological group are presented in the same table with local ablation group in parentheses and angiological group in square brackets.

Characteristics	Frequency of all complications		Accordion Severity Grade							Frequency of highest grade complications	
Complication	n	%	NHG	1	2	3	4	5	6	n	%
Bleeding/Transfusion	11	22.4	8	0	3	0	0	0	0	3	8.6
	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	[2]	[4.2]	[2]	[0]	[0]	[0]	[0]	[0]	[0]	[0]	[0]
Superficial incisional SSI	2	4.1	1	1	0	0	0	0	0	1	2.9
	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	[2]	[4.2]	[1]	[0]	[1]	[0]	[0]	[0]	[0]	[1]	[3.4]
Organ space SSI	12	24.5	3	0	4	4	0	10	0	9	25.7
	(1)	(4.0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(1)	(12.5)
	[14]	[29.2]	[2]	[1]	[8]	[2]	[1]	[0]	[0]	[12]	[41.4]
Sepsis	2	4.1	2	0	0	0	0	0	0	0	0.0
	(1)	(4.0)	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(1)	(12.5)
	[6]	[12.5]	[2]	[0]	[2]	[1]	[1]	[0]	[0]	[4]	[13.8]

Urinary tract infection	1 (0) [0]	2.0 (0) [0]	1 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0.0 (0) [0]
Pneumonia	6 (1) [2]	12.2 (4.0) [4.2]	3 (0) [0]	0 (0) [0]	3 (1) [0]	0 (0) [0]	0 (0) [2]	0 (0) [0]	0 (0) [0]	3 (1) [2]	8.6 (12.5) [6.9]
On ventilator >48h	1 (0) [0]	2.0 (0) [0]	1 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]
Septic shock	2 (0) [1]	4.1 (0) [2.1]	2 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [1]	0 (0) [0]	0 (1) [1]	0 (3.4)
Unplanned intubation	1 (1) [0]	2.0 (4.0) [0]	1 (1) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]
Deep venous thrombosis	0 (0) [1]	0 (0) [2.1]	0 (0) [1]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]
Deep incisional SSI	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]

Wound disruption	1	2.0	0	0	0	0	1	0	0	1	2.9
	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	[0]	[0]	[0]	[0]	[0]	[0]	[0]	[0]	[0]	[0]	[0]
Death	2	4.1	0	0	0	0	0	0	2	2	5.7
	(1)	(4.0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(1)	(12.5)
	[3]	[6.3]	[0]	[0]	[0]	[0]	[0]	[0]	[3]	[3]	[10.3]
Acute renal failure	1	2.0	1	0	0	0	0	0	0	0	0
	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	[2]	[4.2]	[1]	[0]	[0]	[0]	[1]	[0]	[0]	[1]	[3.4]
Myocardial infarction	1	2.0	1	0	0	0	0	0	0	0	0
	(1)	(2.1)	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	[0]	[0]	[0]	[0]	[0]	[0]	[0]	[0]	[0]	[0]	[0]
Pulmonary embolism	1	2.0	0	0	1	0	0	0	0	1	2.9
	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	[2]	[4.2]	[1]	[0]	[1]	[0]	[0]	[0]	[0]	[1]	[3.4]
Cardiac arrest requiring CPR	1	2.0	0	0	0	0	0	1	0	1	2.9
	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	[0]	[0]	[0]	[0]	[0]	[0]	[0]	[0]	[0]	[0]	[0]
Progressive renal insufficiency	1	2.0	1	0	0	0	0	0	0	0	0
	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	[2]	[4.2]	[2]	[0]	[0]	[0]	[0]	[0]	[0]	[0]	[0]

Other occurrence	20	40.8	9	6	2	1	2	0	0	11	31.4
	(6)	(24.0)	(2)	(3)	(1)	(0)	(0)	(0)	(0)	(4)	(50.0)
	[9]	[18.8]	[6]	[1]	[2]	[0]	[0]	[0]	[0]	[3]	[10.3]
Stroke/CVA	1	2.0	0	0	0	0	0	1	0	1	2.9
	(1)	(4.0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	[1]	[2.1]	[0]	[0]	[0]	[0]	[0]	[1]	[0]	[1]	[3.4]
Coma	1	2.0	0	0	0	0	1	0	0	1	2.9
	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	[0]	[0]	[0]	[0]	[0]	[0]	[0]	[0]	[0]	[0]	[0]
Peripheral nerve injury	1	0	0	0	1	0	0	0	0	1	2.9
	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	[0]	[0]	[0]	[0]	[0]	[0]	[0]	[0]	[0]	[0]	[0]
All complications	69		34	7	14	5	4	3	2	35	100.0
	(13)		(5)	(3)	(3)	(0)	(1)	(0)	(1)	(8)	(100.0)
	[47]		[18]	[2]	[14]	[3]	[5]	[2]	[3]	[29]	[100.0]

Short- and long-term outcomes

In surgical resection group 27 (55.1%) patients had tumor recurrence during follow-up, of which 2 (4.1%) patients had local recidive. In local ablation group, 15 (60.0%) patients were diagnosed with tumor recurrence, of which local recidive occurred with 8 (32.0%) patients, of which five patients were treated with RF and three with PEI. In angiological group, 38 (79.2%) patients were diagnosed with tumor recurrence, of which local recidive occurred with 25 (52.1%) patients (Table 2).

Disease-specific survival

In disease-specific survival postoperative mortality was included. Disease-specific survival rates are presented in Table 4. Disease-specific survival curves are presented in Figure 3. At 5-years, statistically significant difference was observed between resection and angiological group ($p=0.010$), resection and palliative treatment ($p<0.001$), local ablation and palliative treatment ($p<0.001$), and angiological group and palliative treatment ($p<0.001$).

Table 4. Disease-specific survival of respective groups.

Groups	30 days	90 days	1 year	3 years	5 years	Median survival (years (IQR))
Surgical resection group	95.9%	95.9%	85.1%	63.7%	58.2%	7.7 (IQR 1.6-non est)
Local ablation group	100.0%	100.0%	90.2%	67.4%	36.8%	3.4 (IQR 2.7-non est)
Angiological group	95.8%	93.6%	61.8%	47.2%	15.7%	2.7 (IQR 0.7-4.7)
Palliative group	85.9%	65.9%	33.9%	7.8%	0.0%	0.5 (IQR 0.2-4.1)

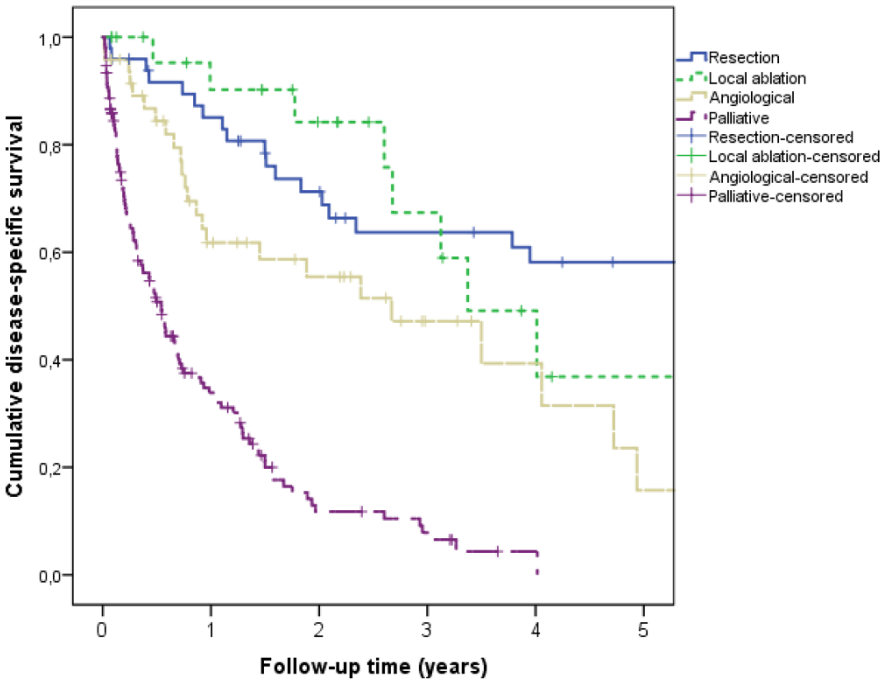

Fig. 3. Disease-specific survival of hepatocellular carcinoma stratified by treatment modality.

Overall survival

Overall survival rates are presented in Table 5. Overall survival curves are presented in Figure 4. At 5-years, statistically significant difference was observed between resection and angiological group ($p<0.001$), resection and palliative treatment ($p<0.001$), local ablation and palliative treatment ($p<0.001$), and angiological group and palliative treatment ($p<0.001$).

When palliative group was stratified between patients receiving oncological treatment (n=39) and only best supportive treatment (n=112), overall survival rates at 30 and 90 days, 1-, 3- and 5- years were 100%, 84.2%, 36.8%, 3.7% and 0%,

median 0.6 years (IQR 0.4-1.4) in oncological treatment group. In those who received only palliative treatment rates were 74.9%, 52.4%, 22.2%, 5.2% and 0%, median 0.3 years (IQR 0.1-0.8), p=0.050 between groups at 5-years.

In cox regression analysis adjusted for confounding factors, local ablation (HR 2.56, 95% CI 1.10-5.97) and angiological treatment (HR 3.42, 95% CI 1.61-7.27) were associated with increased risk for long-term mortality compared to resection group (Table 6).

Table 5. Overall survival of respective groups.

Groups	30 days	90 days	1 year	3 years	5 years	Median survival (years)
Surgical resection group	95.9%	95.9%	85.1%	59.0%	51.2%	5.9 (IQR 1.6-9.7)
Local ablation group	100.0%	100.0%	86.1%	43.1%	18.8%	2.6 (IQR 2.0-4.0)
Angiological group	95.8%	93.6%	56.1%	26.3%	6.6%	1.5 (IQR 0.7-3.3)
Palliative group	81.4%	60.7%	26.0%	4.9%	0.0%	0.4 (IQR 0.1-1.1)

Table 6. Hazard ratios (HR) with 95% confidence intervals (CI) of mortality comparing patients with hepatocellular carcinoma undergoing surgical resection, local ablation (RF, laser ablation, PEI), and angiological treatment (TACE, TAE, SIRT) in Oulu University Hospital 1983-2018. Follow-up ended December 31, 2017. In patients operated 2018, follow up ended 30 days after operation.

Mortalities	Surgical resection (n=49) HR (95% CI)	Local ablation (n=25) HR (95% CI)	Angiological (n=48) HR (95% CI)
1-year mortality			
Crude	1 (reference)	0.88 (0.23-3.41)	3.25 (1.36-7.73)
Adjusted[a]	1 (reference)	3.18 (0.50-20.40)	11.01 (2.31-52.61)
3-year mortality			
Crude	1 (reference)	1.30 (6.15-2.76)	2.32 (1.29-4.18)
Adjusted[a]	1 (reference)	1.58 (0.61-4.08)	2.40 (1.04-5.54)
5-year mortality			
Crude	1 (reference)	1.88 (0.96-3.68)	3.02 (1.74-5.25)
Adjusted[a]	1 (reference)	2.56 (1.10-5.97)	3.42 (1.61-7.27)

[a] Adjustment for age (continuous), sex (female/male), Charlson comorbidity index (0-1, 2 or higher), stage (1, 2, 3, 4), cirrhosis (no / yes), ASA status (1, 2, 3, 4 or more), year of surgery/diagnosis (1983-2005, 2006-2018), Child-Pugh index (A,B,C), Tumor Grade (1,2,3)

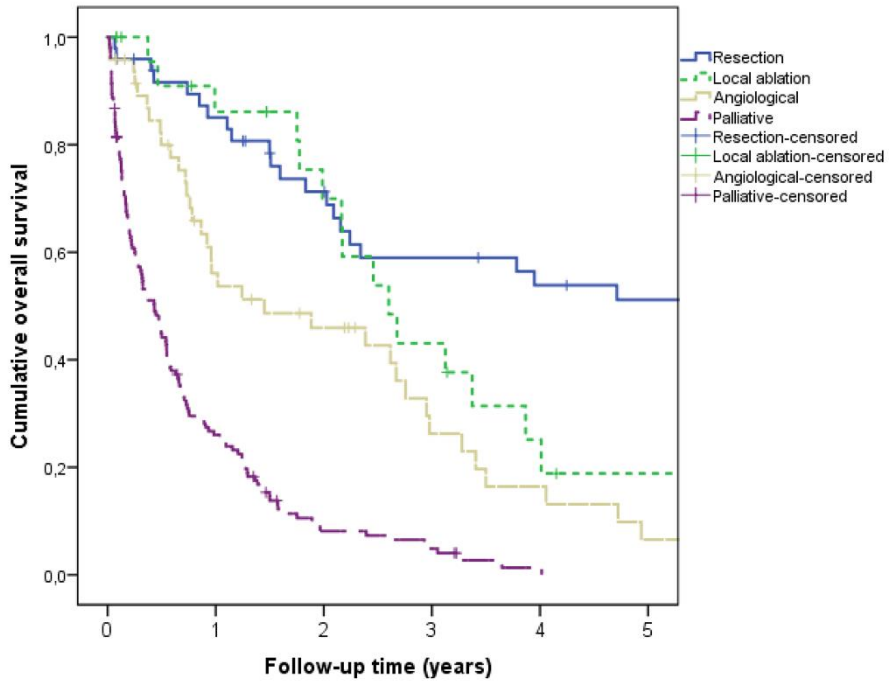

Fig. 4. Overall survival of hepatocellular carcinoma stratified by treatment modality

Survival trends over time

To analyse survival trends over time, we divided groups (surgical resection, local ablation, angiological, palliative) into further two equal sized cohorts based on year of operation. Cut-off years were 2000 for resection, 2012 for local ablation, 2011 for angiological and 2011 for palliative group. We observed no statistically significant differences over time inside any of the groups separately. If treatment groups were combined, disease-specific survival in old cohort at 1-, 3- and 5- years were 50.8%, 27.6% and 16.5%. Respective survival rates in new cohort were 58.0%, 40.6% and 37.2% (p=0.035 between groups at 5-years).

Discussion and conclusions

In Northern Finland population, major changes in HCC treatment have occurred over time. Still, surgical resection provides acceptable complication rates and best long-term survival when compared to other treatment methods. Survival has improved over time. Based on resection rate and baseline characteristics, more patients could be treated with surgery in Northern Finland.

The strengths of the current study are long time period of 35 years including all HCC patients diagnosed and treated in Oulu University Hospital. Study patients come from a single geographical area with homogenous study population where the diagnosis and treatment occurred in same hospital without selection bias. Many patients possibly eligible for surgery have been treated with local ablation or angiological therapy, therefore making the comparison between modalities possible. With complete follow-up information on diagnosis, treatment, complications and long-term survival, we were able to provide reliable comparison of treatment modalities. Limitations include retrospective nature and small study population, leading to low power in the analysis of short-term survival. However, our aim was to describe changes and results of HCC treatment, and compare the number and profile of perioperative complications and long-term survival, where the number of patients is sufficient. Laparotomy was the standard surgical approach in our center. In guidelines hepatic resection is recommended to be performed via laparoscopic/minimally invasive approaches when possible. (5) Approach can cause confounding when comparing complication profiles to recent reports.

In surgically resected group, overall survival rates at 1-, 3 and 5-years were 85.1%, 59.0% and 51.2%. In previous studies, better survival rates has been reported in small (< 5cm) HCC.(16–21). In these studies, the overall survival rates varied at 1-,3 and 5-years from 91.3% to 100.0%, from 73.4% to 92.2% and from 61.5% to

75.7%.(16–21) Lower overall survival rates have been reported in patients with cirrhosis varying from 41.0 to 79.0% at 5-years.(7,22,23) It is notable that in our study, the median tumor size in surgically resected group was 5.0 cm (IQR 3.5-10.0), with cirrhotic liver in one third of patients. Hepatic recurrence rates after surgical resection from 16.7% to 78.8% have been reported.(17,24) In our study, local recidive at surgical site was detected in two (4.1%) patients and hepatic recurrence in other site in 27 (55.1%) patients. Results of patients undergoing surgical resection in our center were therefore comparable to previous studies. However, our resection rate was 17.9% which is significantly lower compared to overall resection rate of 29.6% in systematic review.(25)

Several studies have reported decent overall survival rates in HCC patients treated with RF (26–31). In the current study, local ablation group consisted of patients treated with RF, laser ablation and PEI with overall survival rates at 1-, 3- and 5-years 86.1%, 43.1% and 18.8%. Previously, overall survival rates at 1-, 3 and 5-years from 90.0% to 100.0%, from 60.0% to 89.0% and from 40.0% to 72.0% have been reported.(17–21,26–34) with overall recurrence rates from 27.5% to 53.9% and local recurrence rates from 0.9% to 11.5% after RF. (17,26,28,29,33,34) In our study, local recurrence at treatment site occurred in 32.0% and hepatic recurrence in other site in 60.0% of patients treated with local ablation. Inclusion of PEI and also larger tumors can have effect on our outcomes, since previous studies have favored RF over PEI.(5)

TACE is the most widely used primary treatment for inoperable HCC, in previous guidelines, it was recommended first-line therapy for patients with intermediate-stage.(5) In previous studies comparing RF and TACE within Milan criteria, RF led to better long-term results in univariate analysis, but RF was not an independent favorable prognostic factor in adjusted Cox model.(31) At 1-, 3- and 5 years survival rates from 29.0% to 95.0%, from 29.0% to 61.7% and from 12.8% to 38.3%

have been reported after TACE,(11,35–38) being slightly superior to the results of this study: 56.1%, 26.3% and 6.6% at 1-, 3- and 5 years, respectively.

Patients with untreatable tumor in our study had dismal prognosis. Previous studies reported overall survivals in untreated patients with intermediate HCC at 1 and 3-years from 54.0% to 63.0% and from 17.0% to 28.0%.(35,39)

In surgically treated group, we reported 14 (28.6%) major complications and 21 (42.9%) minor complications, and two (4.1%) postoperative deaths. Liver resection remains a complex surgical procedure with reported major complication rates from 27.8% to 55.5% and mortality rates from 0.0% to 11.0%. (7,18,19,40) Cirrhosis and weak liver function associate to high mortality rates.(7) Perioperative mortality in cirrhotic patients should be less than 3% (5) and major morbidity less than 30%. (5,24) The complication profile in referenced studies in major complications was similar to our study, with surgical site infection being the most common complication. In our study, less ascites-, bile leakage -and pleural effusion-related complications were observed.(7,18,19) Complications in our study were more common after surgical resection when compared to RF, but no difference was observed between resection and angiological treatment, advocating the use of surgical treatment. In literature, major complications in RF treated patients have been reported from 0.9% to 4.3% (19,26–30,34,41,42) and mortality rates from 0.0% to 1.6%. (27,28,34,41,42) Reported complications rates following TACE are high (25-45%), with the majority being reversible elevations of hepatic transaminases and serum bilirubin.(10) In our study, overall complications occurred in 28 (58.4%) patients. We did not observe any tumor needle seeding complications, which was reported in several studies.(26–28,30,34) The most common complications after TACE in our study were pain problems, organ site infection and sepsis, which were also detected in several referenced studies.(10) The length of hospital stay after surgical resection and other less invasive treatments was similar compared to previous reports.(7,18,19,40,43)

We observed a significant rise in other treatment modalities than surgery, which can be due to multiple factors, for example the development of new therapies, histological and radiological examination and patient evaluation. In Finland, alcohol plays a critical role in etiology of cirrhosis and HCC, which is a known risk factor of surgery. (7,44) Other reasons might be the long distances in Northern Finland, patient material, time delay in seeking medical treatment and unwillingness to surgical treatment. Even after adjustment, underlying disease may be a more important determinant of outcome than the treatment patients received. However, there was no significant differences between the actively treated patient groups in tumor stage and Child-Pugh classification, and despite the cirrhosis and physical status, more patients could possibly be treated with surgery. With standardized reporting of complications and long-term survival, critical evaluation of results can be performed with possibility to improve treatment of our patients.(45) Based on our study on Northern Finland population, the surgical resection of HCC could be more used and is the most effective treatment considering long-term survival and tumor recurrence after adjustment for confounding factors. Despite improvements, overall prognosis of patients diagnosed with HCC remain poor.

Ethics declarations

Ethics approval and consent to participate

The study was approved by the Oulu University Hospital Ethics Committee and the hospital district (committee's reference number 81/2008). The need to obtain informed consent from the study patients was waived by the Finnish National Authority for Medicolegal Affairs (VALVIRA, reference number 10832/06.01.03.01/2014). The study was performed in accordance with the declaration of Helsinki.

Consent for publication

The manuscript is approved for publication by all the authors.

Availability of data and materials

Anonymized data is available from the corresponding author upon request. Sharing the data will require additional ethical approval.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

V.K., H.H. and O.H. conceived and designed the study; V.K., M.K., H.H. and O.H. acquired the data; V.K, H.H. and O.H. performed the experiments; V.K., H.H., V-M.P., J.S., J.N., and O.H. analyzed the data; V.K. and O.H. drafted the manuscript; all authors critically reviewed, edited and approved the manuscript. O.H. provided funding, supervised the study and is the guarantor of the study.

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