Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Comparison of short- and long-term outcomes of patients with hepatocellular carcinoma undergoing surgical resection, local ablation, angiological treatment or palliation: Single center results over 35 years

Valtteri Kairaluoma (valtteri.kairaluoma@oulu.fi)
Oulun yliopistollinen sairaala https://orcid.org/0000-0003-2399-3722
Mira Karjalainen
Oulun yliopistollinen sairaala
Juha Saarnio
Oulun yliopistollinen sairaala
Jarmo Niemelä
Oulun yliopistollinen sairaala
Heikki Huhta
Oulun yliopistollinen sairaala
Olli Helminen
Keski-Suomen keskussairaala

Research article

Keywords:

Posted Date: August 13th, 2019

DOI: https://doi.org/10.21203/rs.2.12755/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Abstract

Background Hepatocellular carcinoma (HCC) is one leading cause of cancer mortality often presenting at inoperable stage. The aim of this study was to examine and compare surgically resected, locally ablated, angiologically treated and palliatively treated HCC patients' short- and long-term outcomes in a single center over 35 year period. Methods All HCC diagnosed in Oulu University Hospital between 1983-2018 were identified from hospital records (n=273). Patients underwent hepatic resection (n=49), local ablation (RF, laser ablation or PEI; n=25), angiological treatments (TACE, TAE and SIRT; n=48) or palliative treatment (chemotherapy, best supportive care; n=151). 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 were adjusted with sex, age, comorbidities, cirrhosis, Child-Pugh index points, ASA status, year of operation and stage. Results Surgically resected patients were younger than patients in other groups. Recurrence and local recidives occurred more often in local ablation group and in angiological treatment group (p<0.001). Surgical resection rate was 17.9%. Overall complication rates in surgical resection, local ablation and angiological group were 71.5%, 32.0% and 58.3%, (p<0.001). Major complications in respective groups occurred in 28.6%, 8.0% and 27.1%. 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, local ablation and angiological treatment were significant risk factors for mortality. Prognosis was poor in palliatively treated patients. Conclusions Based on our study on Northern Finland population, the surgical resection of HCC seems to be the most effective treatment considering long-term survival and tumor recurrence after adjustment for confounding factors.

Background

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 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 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 and compare results of surgical resection, local ablation (RF and PEI), angiological treatment (TACE, transarterial embolization (TAE), selective internal radiation therapy (SIRT)) and palliative treatment in HCC regarding complication rates, and short- and long-term outcomes. The study population consisted of Northern Finland population, where alcohol plays a major role behind the etiology of HCC. All patients were treated in Oulu University Hospital.

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 patients with hepatocellular carcinoma diagnosed in Oulu University Hospital between January 1983 and March 12, 2018.

Data collection

The patients were identified from archives using ICD-10 code C22.0& (hepatocellular carcinoma). Inclusion criteria was histological verification of HCC. All diagnoses were confirmed with histological examination either from surgical resecate or biopsy sample. The clinical data was collected from Oulu University Hospital patient records. Of 273 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 or because of the indefinite diagnosis. 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 received also RF, patient was included in surgical resection group. The complications were classified primarily with Accordion Severity Grading System[12] and secondarily with Clavien-Dindo classification system[13].

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 we used $\chi 2$-test and Fisher-tests. The threshold for significance was set at $P < 0.05$. In all continuous variables, median and interquartile range is 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, age, comorbidities, cirrhosis Child-Pugh index, ASA status, year of operation and stage. Complications were classified as minor and major based on Clavien-Dindo classification system [13] and Accordion Severity Grading System [12]. Follow-up times were calculated for survivors. 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

A total of 273 patients diagnosed with HCC were included in the study, resulting with mean 7.8 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). Respective follow-up times calculated only for survivors were 3.4 years (IQR 1.3-6.2), 1.4 years (IQR 0.1-3.6), 0.8 years (IQR 0.2-2.2) and 0.6 years (IQR 0.3-1.4).

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 local ablation, angiological treatment and palliative group respective median ages were 73.6, 73.0 and 72.4 years. Male dominance was observed in all groups. Median Charlson Comorbidity Index in the four groups was 1, 3, 2 and 1, respectively. Liver cirrhosis was present in 33%, 56%, 40% and 33%. According to Child Pugh Classification, class B/C was present in surgical resection group in 4.1%, in local ablation group 20%, in other invasive treatment group 4.2% and in palliative group 29.8%. Most common ASA status in all four groups was grade III, including

59% in the resection group, 80% in local ablation group, 65% in angiological group and 67% in palliative group.

Tumor features

Tumor stage I was the most common in the first three groups, including 79.6% in the resection group, 76.0% in local ablation group and 47.9% in angiological group. In palliative group 58.3% had tumor stage III or IV. Tumor size was bigger in resection group than in local ablation group (median 50 mm vs 30 mm, p<0.001). No difference in size was observed between resection and angiological group. 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 intraoperative bleeding was 1350 ml (IQR 575-2700) and 22 (44.9%) patients were given red blood cell transfusion intraoperatively. Postoperatively 10 (20.4%) patients needed red blood cell transfusion. 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 had postoperative chemotherapy. The median time spent in hospital was 3 days (IQR 2-5). Two (8.0%) patients had readmission in 30 days. Postoperative features are presented in Table 2. 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 resection group than in local ablation group (71.5% vs 32.0%, p<0.001). There was no significant difference between resection group and angiological group in number of complications (71.5% vs 58.3%, p=0.116). Significant difference between local ablation group and angiological group was noted 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.

Short- and long-term outcomes

In 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. In surgical resection group disease-specific 30 and 90-day survival rates were 95.9% and 95.9%. The 1-, 3 and 5-year disease-specific survival rates were 85.1%, 63.7% and 58.2%. The median survival was 7.7 years, (IQR 1.6-non est.). The respective disease-specific survival rates in local ablation group were 100%, 100%, 90.2%, 67.4% and 36.8%, with a median survival of 3.4 years (IQR 2.7-non est). In angiological group 95.8%, 93.6%, 61.8%, 47.2% and 15.7%, median 2.7 years (IQR 0.7-4.7). In palliative group rates were 85.9%, 65.9%, 33.9%, 7.8% and 0%, median 0.5 years (IQR 0.2-4.1). Disease-specific survivals 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 ($p<0.001$).

Overall survival

In surgical resection group, overall 30 and 90-day survival rates were 95.9% and 95.9%. The 1-, 3 and 5-year overall survival rates were 85.1%, 59.0% and 51.2%. The median survival was 5.9 years, (IQR 1.6-9.7). The respective overall survival rates in local ablation group were 100%, 100%, 86.1%, 43.1% and 18.8%, with a median survival of 2.6 years (IQR 2.0-4.0). In angiological group 95.8%, 93.6%, 56.1%, 26.3% and 6.6%, median 1.5 years (IQR 0.7-3.3). In palliative group rates were 81.4%, 60.7%, 26.0%, 4.9% and 0%, median 0.4 years (IQR 0.1-1.1). Overall survivals 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 palliative 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 3.79, 95% CI 1.64-8.77) and angiological treatment (HR 3.76, 95% CI 1.74-8.13) were associated with increased risk for long-term mortality compared to resection group (Table 4).

Survival trends over time

To analyse survival trends over time, we divided groups (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

We observed preferable long-term survival after surgical treatment of HCC when compared to other treatment modalities also after adjusting for confounding factors. Improvement in survival was observed over time. Based on resection rate and baseline characteristics, more patients might 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 from a single geographical area with homogenous study population. Number of 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, affecting especially short-term survival. However, our aim was to compare the number and profile of post-operative 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.[14–19]. 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%.[14–19] Lower overall survival rates have been reported in patients with cirrhosis varying from 41.0 to 79.0% at 5-years.[7,20,21] 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.[15,22] In our study, local recidive at surgical site was detected altogether 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.[23]

Several studies have reported decent overall survival rates in HCC patients treated with RF [24–29]. 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-year 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.[15,16,29–32,17–19,24–28] with overall recurrence rates from 27.5% to 53.9% and local recurrence rates from 0.9% to 11.5% after RF. [15,24,26,27,31,32] 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.[29] 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,[11,33–36] being slightly superior to our results of 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%.[33,37]

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 rated from 0.0% to 11.0%. [7,16,17,38] 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%[522]. The complication profile in referenced studies in major complications was mainly similar to our study, with surgical site infection being the most common. In our study less ascites-, bile leakage -and pleural effusion-related complications were observed.[7,16,17] 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%. [17,24–28,32,39,40] and mortality rates from 0.0% to 1.6%. [25,26,32,39,40] 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.[24–26,28,32] The most common complications after TACE in our study was 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.[7,16,17,38,41]

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. [7,42] 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 more important determiner of outcome than the treatment patients received. However, despite differences in tumor stage, 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.[43]

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.

References

1. Global Burden of Disease Cancer Collaboration GB of DC, Fitzmaurice C, Allen C, et al. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study. *JAMA Oncol*. 2017;3(4):524-548. doi:10.1001/jamaoncol.2016.5688
2. El-Serag HB, Rudolph KL. Hepatocellular Carcinoma: Epidemiology and Molecular Carcinogenesis. *Gastroenterology*. 2007;132(7):2557-2576. doi:10.1053/j.gastro.2007.04.061
3. Gao B, Bataller R. Alcoholic liver disease: Pathogenesis and new therapeutic targets. *Gastroenterology*. 2011;141(5):1572-1585. doi:10.1053/j.gastro.2011.09.002
4. Morgan TR, Mandayam S, Jamal MM. Alcohol and hepatocellular carcinoma. *Gastroenterology*. 2004;127(5):S87-S96. doi:10.1053/j.gastro.2004.09.020
5. Galle PR, Forner A, Llovet JM, et al. *EASL Clinical Practice Guidelines: Management of Hepatocellular Carcinoma Q*. Vol 69.; 2018. doi:10.1016/j.jhep.2018.03.019
6. She WH, Chok KSH. Strategies to increase the resectability of hepatocellular carcinoma. *World J Hepatol*. 2015;7(18):2147-2154. doi:10.4254/wjh.v7.i18.2147
7. Wu C-C, Cheng S-B, Ho W-M, Chen the late J-T, Liu T-J, P'eng F-K. Liver resection for hepatocellular carcinoma in patients with cirrhosis. *Br J Surg*. 2005;92(3):348-355. doi:10.1002/bjs.4838
8. Shiina S, Tateishi R, Arano T, et al. Radiofrequency ablation for hepatocellular carcinoma: 10-Year outcome and prognostic factors. *Am J Gastroenterol*. 2012;107(4):569-577. doi:10.1038/ajg.2011.425
9. Sato M, Tateishi R, Yasunaga H, et al. Association between hospital volume and in-hospital mortality following radiofrequency ablation for hepatocellular carcinoma. *BJS Open*. 2017;1(2):50-54. doi:10.1002/bjs5.9
10. Garwood ER, Fidelman N, Hoch SE, Kerlan RK, Yao FY. Morbidity and mortality following transarterial liver chemoembolization in patients with hepatocellular carcinoma and synthetic hepatic dysfunction. *Liver Transplant*. 2013;19(2):164-173. doi:10.1002/lt.23552
11. Lencioni R, de Baere T, Soulen MC, Rilling WS, Geschwind J-FH. Lipiodol transarterial chemoembolization for hepatocellular carcinoma: A systematic review of efficacy and safety data. *Hepatology*. 2016;64(1):106-116. doi:10.1002/hep.28453
12. Strasberg SM, Linehan DC, Hawkins WG. The Accordion Severity Grading System of Surgical Complications. *Ann Surg*. 2009;250(2):177-186. doi:10.1097/SLA.0b013e3181afde41
13. Dindo D, Demartines N, Clavien P-A. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240(2):205-213. doi:10.1097/01.SLA.0000133083.54934.AE

14. Yamamoto J, Okada S, Shimada K, et al. Treatment strategy for small hepatocellular carcinoma: Comparison of long-term results after percutaneous ethanol injection therapy and surgical resection. *Hepatology*. 2001;34(4):707-713. doi:10.1053/jhep.2001.27950
15. Lü M, Kuang M, Liang L, et al. [Surgical resection versus percutaneous thermal ablation for early-stage hepatocellular carcinoma: a randomized clinical trial]. *Zhonghua Yi Xue Za Zhi*. 2006;86(12):801-805. http://www.ncbi.nlm.nih.gov/pubmed/16681964. Accessed November 23, 2018.
16. Chen M-S, Li J-Q, Zheng Y, et al. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. *Ann Surg*. 2006;243(3):321-328. doi:10.1097/01.sla.0000201480.65519.b8
17. Jiwei Huang LYZCHWLDJWYXYZ. A Randomized Trial Comparing Radiofrequency Ablation and Surgical Resection for Hcc Conforming to the Milan Criteria. *Ann Surg*. 2010;252(6):903-912. doi:10.1097/sla.0b013e3181efc656
18. Hasegawa K, Makuuchi M, Takayama T, et al. Surgical resection vs. percutaneous ablation for hepatocellular carcinoma: A preliminary report of the Japanese nationwide survey. *J Hepatol*. 2008;49(4):589-594. doi:10.1016/J.JHEP.2008.05.018
19. Hasegawa K, Kokudo N, Makuuchi M, et al. Comparison of resection and ablation for hepatocellular carcinoma: A cohort study based on a Japanese nationwide survey. *J Hepatol*. 2013;58(4):724-729. doi:10.1016/J.JHEP.2012.11.009
20. Livraghi T, Bolondi L, Buscarini L, et al. No treatment, resection and ethanol injection in hepatocellular carcinoma: a retrospective analysis of survival in 391 patients with cirrhosis. *J Hepatol*. 1995;22(5):522-526. doi:10.1016/0168-8278(95)80445-5
21. Castells A, Bruix J, Bru C, et al. Treatment of small hepatocellular carcinoma in cirrhotic patients: A cohort study comparing surgical resection and percutaneous ethanol injection. *Hepatology*. 1993;18(5):1121-1126. doi:10.1002/hep.1840180517
22. Fan ST, Mau Lo C, Poon RTP, et al. Continuous Improvement of Survival Outcomes of Resection of Hepatocellular Carcinoma. *Ann Surg*. 2011;253(4):745-758. doi:10.1097/SLA.0b013e3182111195
23. Sotiropoulos GC, Lang H, Frilling A, et al. Resectability of hepatocellular carcinoma: evaluation of 333 consecutive cases at a single hepatobiliary specialty center and systematic review of the literature. *Hepatogastroenterology*. 53(69):322-329. http://www.ncbi.nlm.nih.gov/pubmed/16795964. Accessed January 15, 2019.
24. Tateishi R, Shiina S, Teratani T, et al. Percutaneous radiofrequency ablation for hepatocellular carcinoma. *Cancer*. 2005;103(6):1201-1209. doi:10.1002/cncr.20892
25. Choi D, Lim HK, Rhim H, et al. Percutaneous radiofrequency ablation for early-stage hepatocellular carcinoma as a first-line treatment: long-term results and prognostic factors in a large single-institution series. *Eur Radiol*. 2007;17(3):684-692. doi:10.1007/s00330-006-0461-5
26. Yang W, Yan K, Goldberg SN, et al. Ten-year survival of hepatocellular carcinoma patients undergoing radiofrequency ablation as a first-line treatment. *World J Gastroenterol*. 2016;22(10):2993-3005.

doi:10.3748/wjg.v22.i10.2993

27. Livraghi T, Meloni F, Di Stasi M, et al. Sustained complete response and complications rates after radiofrequency ablation of very early hepatocellular carcinoma in cirrhosis: Is resection still the treatment of choice? *Hepatology*. 2007;47(1):82-89. doi:10.1002/hep.21933
28. Lee DH, Lee JM, Lee JY, et al. Radiofrequency Ablation of Hepatocellular Carcinoma as First-Line Treatment: Long-term Results and Prognostic Factors in 162 Patients with Cirrhosis. *Radiology*. 2014;270(3):900-909. doi:10.1148/radiol.13130940
29. Hsu C-Y, Huang Y-H, Chiou Y-Y, et al. Comparison of Radiofrequency Ablation and Transarterial Chemoembolization for Hepatocellular Carcinoma Within the Milan Criteria: A Propensity Score Analysis. *Liver Transpl*. 2011;17:556-566. doi:10.1002/lt.22273
30. Lencioni RA, Allgaier H-P, Cioni D, et al. Small Hepatocellular Carcinoma in Cirrhosis: Randomized Comparison of Radio-frequency Thermal Ablation versus Percutaneous Ethanol Injection. *Radiology*. 2003;228(1):235-240. doi:10.1148/radiol.2281020718
31. Lencioni R, Cioni D, Crocetti L, et al. Early-Stage Hepatocellular Carcinoma in Patients with Cirrhosis: Long-term Results of Percutaneous Image-guided Radiofrequency Ablation. *Radiology*. 2005;234(3):961-967. doi:10.1148/radiol.2343040350
32. N'Kontchou G, Mahamoudi A, Aout M, et al. Radiofrequency ablation of hepatocellular carcinoma: Long-term results and prognostic factors in 235 Western patients with cirrhosis. *Hepatology*. 2009;50(5):1475-1483. doi:10.1002/hep.23181
33. Llovet JM, Real MI, Montaña X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet*. 2002;359(9319):1734-1739. doi:10.1016/S0140-6736(02)08649-X
34. Terzi E, Golfieri R, Piscaglia F, et al. Response rate and clinical outcome of HCC after first and repeated cTACE performed "on demand." *J Hepatol*. 2012;57(6):1258-1267. doi:10.1016/J.JHEP.2012.07.025
35. Burrel M, Reig M, Forner A, et al. Survival of patients with hepatocellular carcinoma treated by transarterial chemoembolisation (TACE) using Drug Eluting Beads. Implications for clinical practice and trial design. *J Hepatol*. 2012;56(6):1330-1335. doi:10.1016/J.JHEP.2012.01.008
36. Malagari K, Pomoni M, Moschouris H, et al. Chemoembolization With Doxorubicin-Eluting Beads for Unresectable Hepatocellular Carcinoma: Five-Year Survival Analysis. *Cardiovasc Intervent Radiol*. 2012;35(5):1119-1128. doi:10.1007/s00270-012-0394-0
37. Llovet JM, Bustamante J, Castells A, et al. Natural history of untreated nonsurgical hepatocellular carcinoma: Rationale for the design and evaluation of therapeutic trials. *Hepatology*. 1999;29(1):62-67. doi:10.1002/hep.510290145
38. Poon RTP, Fan ST, Lo CM, et al. Extended hepatic resection for hepatocellular carcinoma in patients with cirrhosis: is it justified? *Ann Surg*. 2002;236(5):602-611. doi:10.1097/01.SLA.0000033038.38956.5E

39. Rhim H, Yoon K-H, Lee JM, et al. Major Complications after Radio-frequency Thermal Ablation of Hepatic Tumors: Spectrum of Imaging Findings. *RadioGraphics*. 2003;23(1):123-134. doi:10.1148/rg.231025054
40. Livraghi T, Solbiati L, Meloni MF, Gazelle GS, Halpern EF, Goldberg SN. Treatment of Focal Liver Tumors with Percutaneous Radio-frequency Ablation: Complications Encountered in a Multicenter Study. *Radiology*. 2003;226(2):441-451. doi:10.1148/radiol.2262012198
41. Duan C, Liu M, Zhang Z, Ma K, Bie P. Radiofrequency ablation versus hepatic resection for the treatment of early-stage hepatocellular carcinoma meeting Milan criteria: A systematic review and meta-analysis. *World J Surg Oncol*. 2013;11(1):1. doi:10.1186/1477-7819-11-190
42. Leon DA, McCambridge J. Liver cirrhosis mortality rates in Britain from 1950 to 2002: an analysis of routine data. *Lancet*. 2006;367(9504):52-56. doi:10.1016/S0140-6736(06)67924-5
43. Staiger RD, Schwandt H, Puhan MA, Clavien P-A. Improving surgical outcomes through benchmarking. *Br J Surg*. November 2018. doi:10.1002/bjs.10976

Declarations

Ethics declarations

Ethics approval and consent to participate

The patient survival data was acquired from Statistics Finland. The use of patient data was approved by the Oulu University Hospital Ethics Committee and by the National Authority for Medicolegal Affairs (VALVIRA).

Consent for publication

The manuscript is approved for publication by all the authors.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This work was supported by Instrumentarium Science Foundation and Finnish State Research Funding (VTR) and The Finnish Medical Foundation.

Authors' contributions

VK was the main contributor to writing the manuscript and analyzing the data, MK was involved collecting the data. OH and HH were involved in the design of the study and OH contributed analyzing the data. JS and JN critically revised the manuscript.

Acknowledgements

Not applicable.

Tables

Table 1. Baseline characteristics.

	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 [c,d,f]				
Child-Pugh A	29 (59.2%)	18 (72.0%)	42 (87.5%)	71 (47.0%)
Child-Pugh B	2 (4.1%)	5 (20.0%)	2 (4.2%)	34 (22.5%)
Child Pugh C	0 (0.0%)	0 (0.0%)	0 (0.0%)	11 (7.3%)
Missing	18	2	4	35

	(36.7%)	(8.0%)	(8.3%)	(23.2%)
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 [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

Table 2. Patient characteristics, Baseline 2.

	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 [b,c,e,f]				
Stage I	39 (79.6%)	19 (76.0%)	23 (47.9%)	45 (29.8%)
Stage II	6 (12.2%)	6 (24.0%)	12 (25.0%)	15 (9.9%)
Stage III	2 (4.1%)	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%)
Tumor segment				
1	0	0	1	1

	(0.0%)	(0.0%)	(2.1%)	(0.7%)
2	6 (12.2%)	1 (4.0%)	6 (12.5%)	11 (7.3%)
3	8 (16.3%)	2 (8.0%)	2 (4.2%)	7 (4.6%)
4	7 (14.3%)	4 (16.0%)	9 (18.8%)	26 (17.2%)
5	10 (20.4%)	6 (24.0%)	10 (20.8%)	28 (18.5%)
6	7 (14.3%)	6 (24.0%)	4 (8.3%)	33 (21.9%)
7	3 (6.1%)	1 (4.0%)	6 (12.5%)	12 (7.9%)
8	8 (16.3%)	4 (16.0%)	8 (16.7%)	25 (16.6%)
Unifocal tumor [b,c,e]	41 (83.7%)	19 (76.0%)	26 (54.2%)	58 (38.4%)
Gradus				
Well differentiated	15 (30.6%)	9 (36.0%)	15 (31.3%)	44 (29.1%)
Moderately differentiated	13 (26.5%)	4 (16.0%)	10 (20.8%)	36 (23.8%)
Poorly differentiated	5 (10.2%)	1 (4.0%)	2 (4.2%)	20 (13.2%)
Missing	16 (32.7%)	11 (44.0%)	21 (43.8%)	51 (33.8%)
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.

	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 (0) [2]	22.4 (0) [4.2]	8 (0) [2]	0 (0) [0]	3 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	3 (0) [0]	8.6 (0) [0]
Superficial incisional SSI	2 (0) [2]	4.1 (0) [4.2]	1 (0) [1]	1 (0) [0]	0 (0) [1]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	1 (0) [1]	2.9 (0) [3.4]
Organ space SSI	12 (1) [14]	24.5 (4.0) [29.2]	3 (0) [2]	0 (0) [1]	4 (1) [8]	4 (0) [2]	0 (0) [1]	10 (0) [0]	0 (0) [0]	9 (1) [12]	25.7 (12.5) [41.4]
Sepsis	2 (1) [6]	4.1 (4.0) [12.5]	2 (0) [2]	0 (0) [0]	0 (0) [2]	0 (0) [1]	0 (1) [1]	0 (0) [0]	0 (0) [0]	0 (1) [4]	0.0 (12.5) [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 (0) [1]	0 (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)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

	[1]	[2.1]	[1]	[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 (0) [0]	2.0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	1 (0) [0]	0 (0) [0]	0 (0) [0]	1 (0) [0]	2.9 (0) [0]
Death	2 (1) [3]	4.1 (4.0) [6.3]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	2 (1) [3]	2 (1) [3]	5.7 (12.5) [10.3]
Acute renal failure	1 (0) [2]	2.0 (0) [4.2]	1 (0) [1]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [1]	0 (0) [0]	0 (0) [0]	0 (0) [1]	0 (0) [3.4]
Myocardial infarction	1 (1) [0]	2.0 (2.1) [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]
Pulmonary embolism	1 (0) [2]	2.0 (0) [4.2]	0 (0) [1]	0 (0) [0]	1 (0) [1]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	1 (0) [1]	2.9 (0) [3.4]
Cardiac arrest requiring CPR	1 (0) [0]	2.0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	1 (0) [0]	0 (0) [0]	1 (0) [0]	2.9 (0) [0]
Progressive renal insufficiency	1 (0) [2]	2.0 (0) [4.2]	1 (0) [2]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]
Other occurrence	20 (6) [9]	40.8 (24.0) [18.8]	9 (2) [6]	6 (3) [1]	2 (1) [2]	1 (0) [0]	2 (0) [0]	0 (0) [0]	0 (0) [0]	11 (4) [3]	31.4 (50.0) [10.3]
Stroke/CVA	1 (1) [1]	2.0 (4.0) [2.1]	0 (1) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	1 (0) [1]	0 (0) [0]	1 (0) [1]	2.9 (0) [3.4]
Coma	1 (0) [0]	2.0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	1 (0) [0]	0 (0) [0]	0 (0) [0]	1 (0) [0]	2.9 (0) [0]
Peripheral nerve injury	1 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	2.9 (0)

	[0]	[0]	[0]	[0]	[0]	[0]	[0]	[0]	[0]	[0]	[0]
Craft prothesis/flap failure	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]
All complications	69 (13) [47]		34 (5) [18]	7 (3) [2]	14 (3) [14]	5 (0) [3]	4 (1) [5]	3 (0) [2]	2 (1) [3]	35 (8) [29]	100.0 (100.0) [100.0]

Table 4. 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.

	Surgery (n=49) HR (95% CI)	Local ablation (n=25) HR (95% CI)	Angiological (n=48) HR (95% CI)	Palliative (n=151) HR (95% CI)
1-year mortality				
Crude	1 (reference)	0.88 (0.23-3.41)	3.25 (1.36-7.73)	8.81 (4.09-19.0)
Adjusted[a]	1 (reference)	3.12 (0.50-19.5)	6.51 (1.40-30.1)	13.2 (2.96-58.6)
3-year mortality				
Crude	1 (reference)	1.30 (6.15-2.76)	2.32 (1.29-4.18)	6.72 (4.07-11.1)
Adjusted[a]	1 (reference)	2.49 (0.97-6.39)	2.77 (1.19-6.45)	6.76 (3.00-15.2)
5-year mortality				
Crude	1 (reference)	1.88 (0.96-3.68)	3.02 (1.74-5.25)	8.51 (5.18-14.0)
Adjusted[a]	1 (reference)	3.79 (1.64-8.77)	3.76 (1.74-8.13)	9.36 (4.36-20.1)

[a] Adjustment for age, sex, Charlson comorbidity index (0, 1, 2, 3 4 or more), stage (1, 2, 3, 4), cirrhosis (no / yes), ASA status (1, 2, 3, 4 or more), year of surgery/diagnosis (continuous), Child-Pugh points (continuous)

Figures

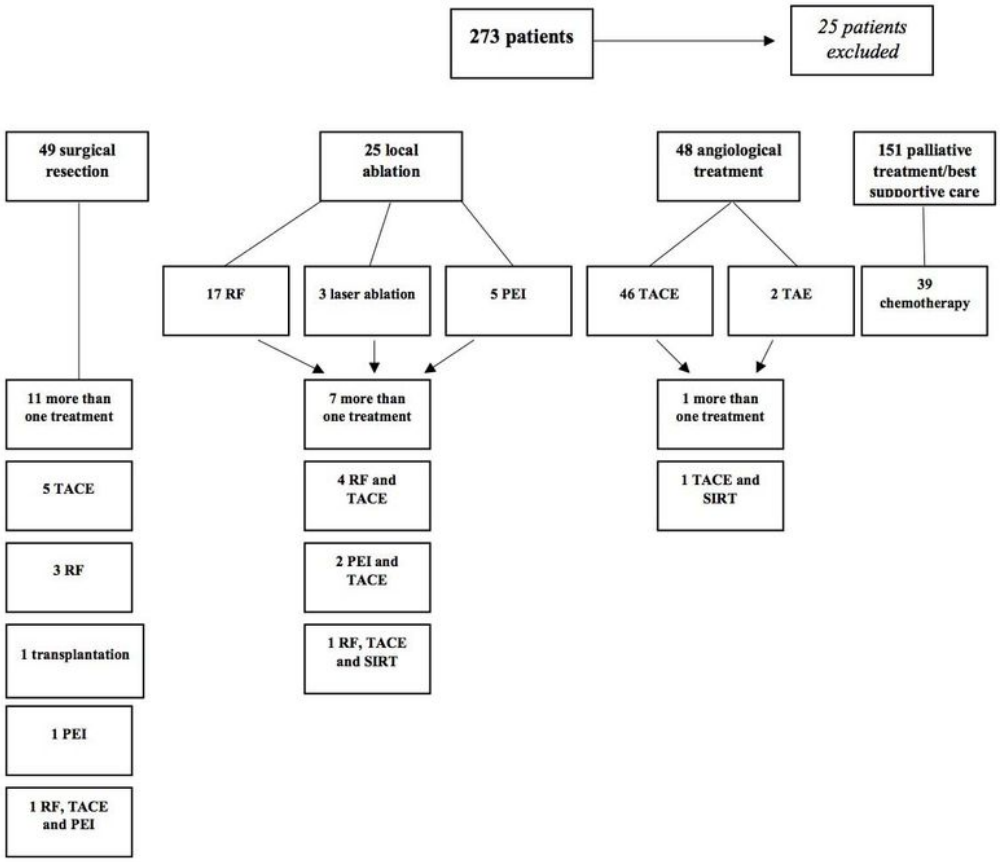


Figure 1

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

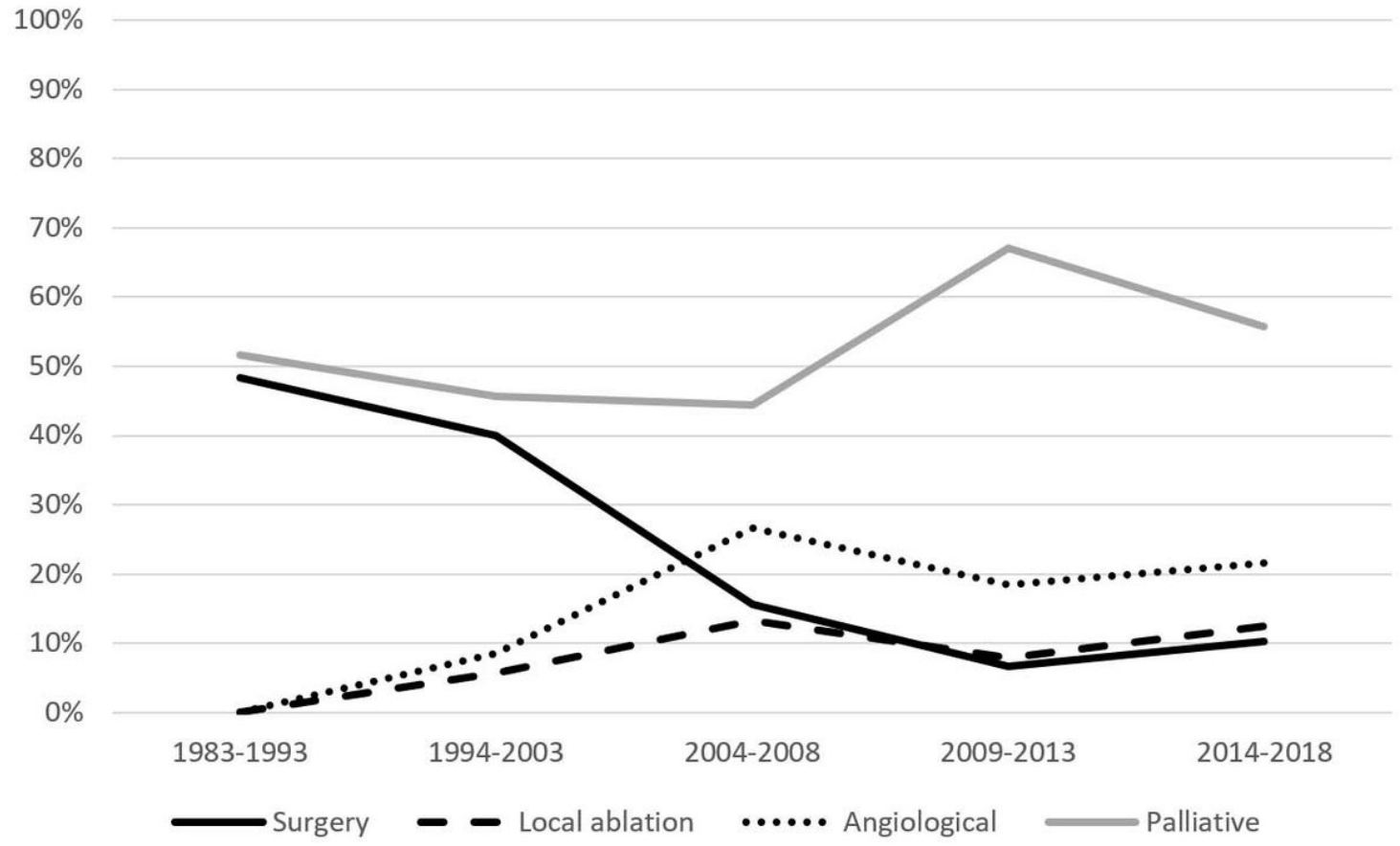


Figure 2

Trends in treatment modalities of hepatocellular carcinoma.

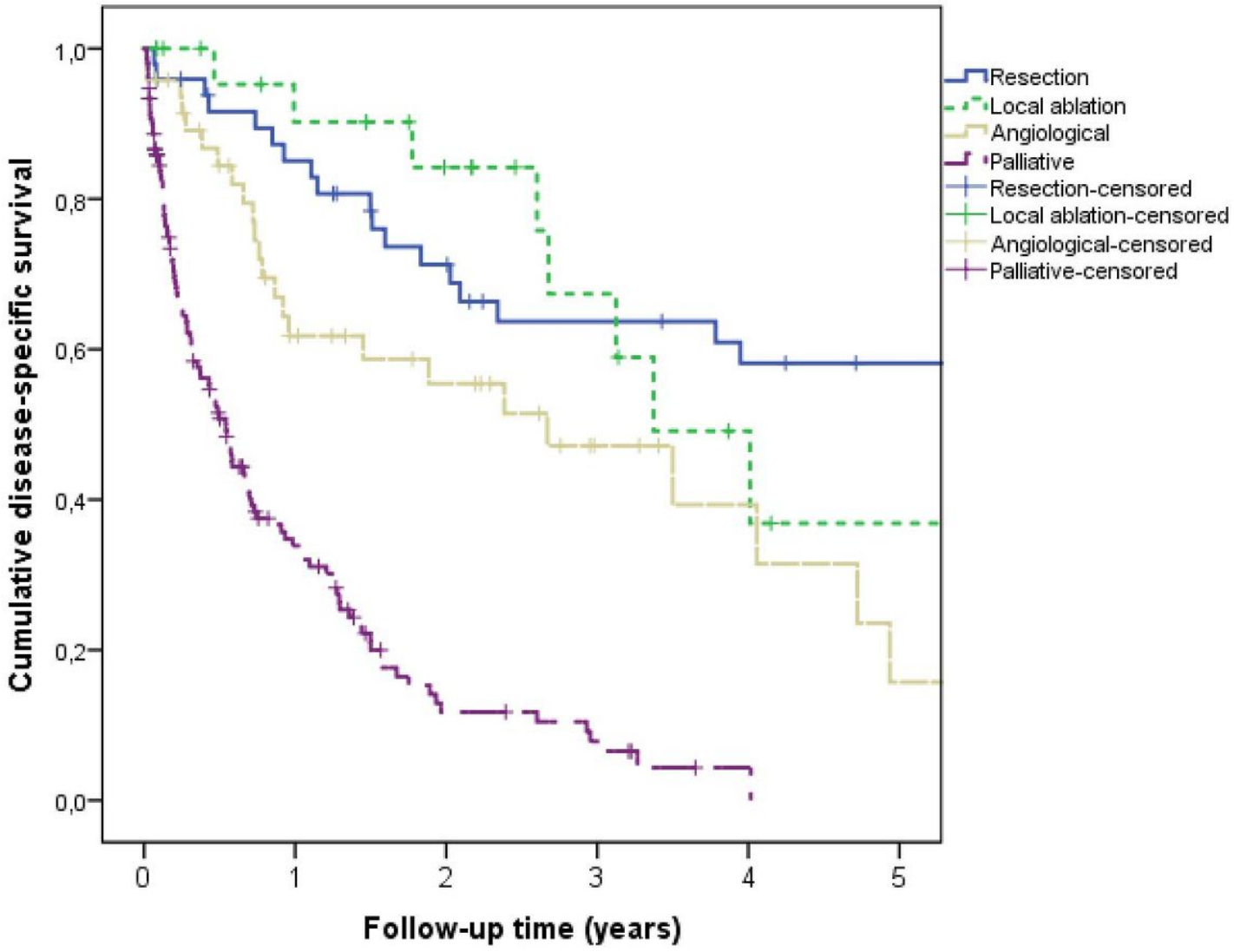


Figure 3

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

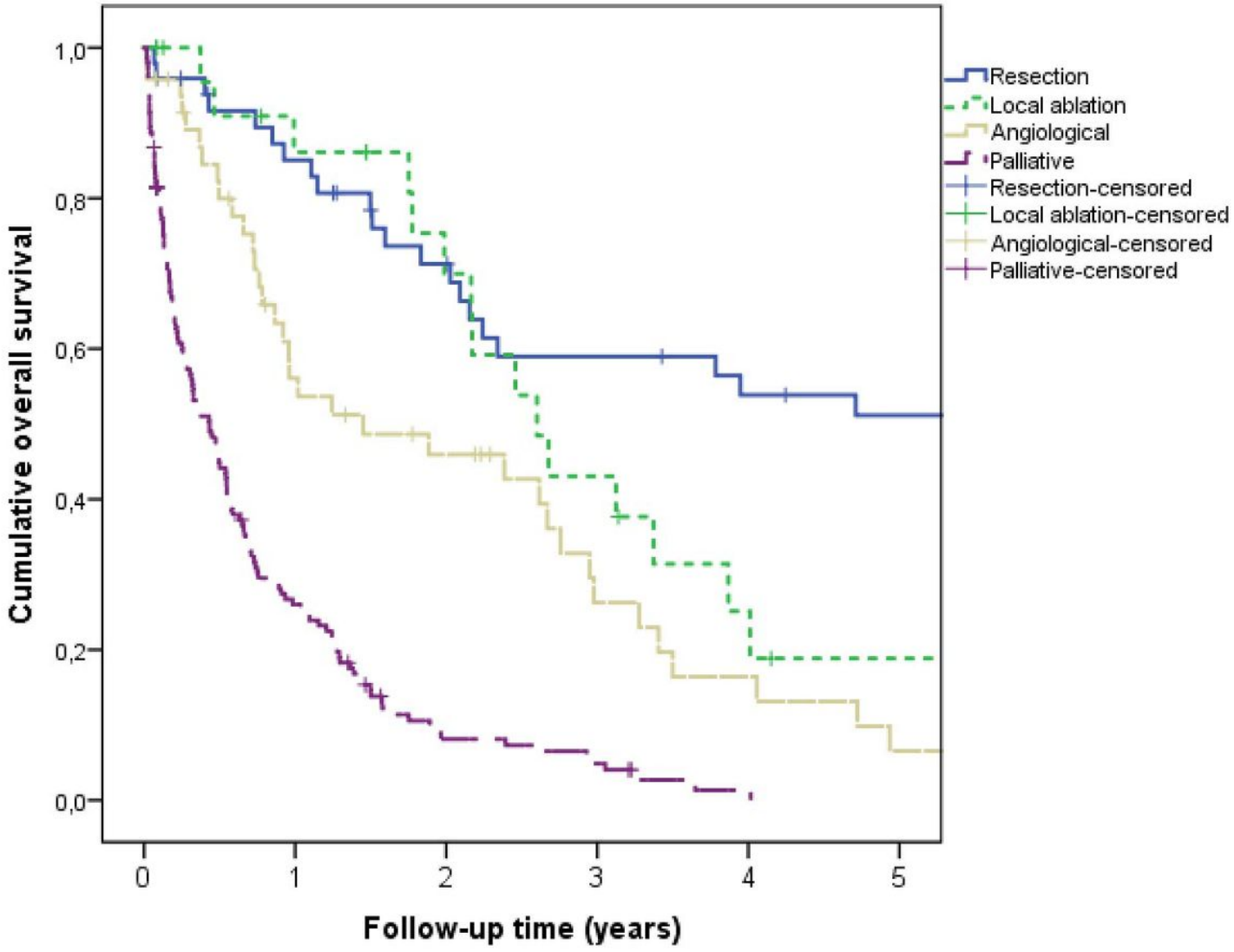


Figure 4

Overall survival of hepatocellular carcinoma stratified by treatment modality.