Prognostic factors and treatment of hepatocellular cancer

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To my family

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ABSTRACT

Background: Hepatocellular carcinoma (HCC) is one of the most common causes of cancer-related death worldwide. Prognosis is related to tumor burden, liver function, and performance status as well as treatment factors. Accurate prognostication is a requisite for optimal treatment decisions.

Aims: The general aim was to explore specific prognostic factors in different settings of HCC, and to evaluate outcome after treatment with curative intent in patients eligible for multiple treatments.

Methods: This thesis is based on four clinical studies in patients with HCC. Study I is a prospective observational study, investigating if patient-reported quality of life (QoL) can predict survival and increase the prognostic accuracy of established staging models. Study II is a review of medical records in a national cohort of patients with liver transplantation from 1996-2014, investigating if AFP levels increase the prognostic accuracy of current selection criteria. Study III is a prospective feasibility study, evaluating neo-adjuvant systemic treatment with sorafenib before liver transplantation. In the fourth study, data from a national registry 2008-2016, was used to assess risk factors and compare outcome in patients eligible for multiple treatments. Overall and recurrence-free survival rates were estimated using Kaplan-Meier and comparisons using log rank tests. Risk factor assessment was performed using Cox Regression analyses.

Results and Conclusions: QoL data was prognostic for survival. Adding QoL data improved the prognostic accuracy of established scoring systems. Pre-transplant AFP was a prognostic factor for survival after liver transplantation for HCC. AFP combined with traditional criteria improved the accuracy of patient selection. Sorafenib treatment before liver transplantation was associated with low tolerability and inadequate tumor control. Survival differences after liver transplantation, resection, or ablation were limited in subgroups with well-preserved liver function and limited tumor burden. Liver function variables predicted survival and should be carefully considered in treatment decisions.

Keywords: hepatocellular carcinoma, liver transplantation, prognostication

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SAMMANFATTNING PÅ SVENSKA

Hepatocellulär cancer (HCC) är den vanligaste formen av primär levercancer. I Sverige är HCC relativt ovanligt, men i världen är HCC en av de vanligaste cancer-relaterade dödsorsakerna. HCC är speciellt eftersom patienterna oftast även har en leverparenkymsjukdom som orsakar skrumplever och nedsatt leverfunktion. Detta påverkar både prognosen i sig och möjligheten att behandla tumörsjukdomen. För att kunna välja den bästa behandlingen i varje läge måste många olika riskfaktorer vägas in. I denna avhandling studerades riskfaktorer i olika sammanhang, samt överlevnad hos HCC-patienter med välbevarad leverfunktion och tumör i tidigt stadium som genomgått olika kurativt syftande behandlingar.

I den första studien fick 205 patienter med HCC i olika stadier fylla i livskvalitetsformulär. Livskvalitetsparametrarna visade sig kunna användas för att skatta risken för död. När livskvalitetsdata kombinerades med kliniska riskfaktorer kunde risken för död skattas med bättre precision.

I den andra studien granskades journaler på alla patienter som genomgått levertransplantation pga HCC i Sverige 1996-2014. Vi fann att nivån av tumörmarkören Alfa Fetoprotein (AFP) före transplantation var relaterad till risken för tumöråterfall och död efter transplantation. De urvalskriterier som används rutinmässigt inför transplantation i Sverige baseras på tumörstorlek och antal. När dessa kriterier kombinerades med AFP, kunde patienter med ökad risk för tumöråterfall och död identifieras med större precision. Ett poängsystem för användning av både AFP och de gamla kriterierna föreslogs.

I den tredje studien studerades systemisk behandling med sorafenib på 14 HCC-patienter som väntade på transplantation. Sorafenib används normalt i tumörbromsande syfte vid avancerad HCC. Flera patienter fick mycket biverkningar. Dosjusteringar och behandlingsuppehåll gjorde resultaten svårtolkade. Sorafenib-behandling kan därför inte rekommenderas i väntan på levertransplantation.

I den fjärde studien användes data från ett nationellt register (SweLiv). Alla HCC-patienter som hade genomgått primär transplantation, resektion eller ablation 2008-2016 inkluderades. Eftersom patienter med liten tumörbörda och god leverfunktion kan behandlas på flera sätt jämfördes överlevnaden efter olika behandlingar i grupper med liknande riskfaktorer. Vi fann ingen markant fördel med transplantation hos dessa utvalda patienter. Faktorer som speglar leverfunktionen, var viktiga för val av behandling.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Sternby Eilard, M, Hagström, H, Mortensen, KE, Wilsgaard, T, Vagnildhaug O M, Dajani, O, Stål, P, Rizell, M. Quality of life as a prognostic factor for survival in hepatocellular carcinoma. Liver International 2018; 38(5): 885-894. doi:10.1111/liv.13593

II. Sternby Eilard, M, Holmberg, E, Naredi, P, Söderdahl, G, Rizell, M. Addition of alfa fetoprotein to traditional criteria for hepatocellular carcinoma improves selection accuracy in liver transplantation. Scandinavian J Gastroenterology 2018; 53(8):976-983 doi.org/10.1080/00365521.2018.1488180

III. Sternby Eilard, M, Andersson, M, Naredi, P, Geronymakis, C, Lindnér, P, Cahlin, C, Bennet, W, Rizell, M. A prospective clinical trial on sorafenib treatment of hepatocellular carcinoma before liver transplantation. Submitted.

IV. Sternby Eilard, M, Naredi, P, Helmersson, M, Hemmingsson, O, Isaksson, B, Lindell G, Sandström, P, Strömberg, C, Rizell, M. Survival outcome after liver transplantation versus resection and ablation for early HCC - a national registry based study. Submitted.

CONTENT

ABBREVIATIONS

AASLD	American Association for the Study of Liver Diseases
AE	Adverse events
AF	Arterial Blood Flow
AFP	Alpha fetoprotein
AFP-L3	Lens culinaris agglutinin-reactive alpha-fetoprotein
AIC	Akaike information criterion
ASA	American Society of Anesthesiologists Classification
BCLC	Barcelona Clinic Liver Cancer
BF	Blood Flow
BV	Blood Volume
CI	Confidence interval
CLIP	Cancer of the Liver Italian Program
CT	Computed tomography
DCD	Donation after circulatory death
DCP	Des-γ-carboxy prothrombin
EASL	European association for study of the liver
ECOG	Eastern Cooperative Oncology Group
ERC	Endoscopic Retrograde Cholangiography
FACT-G	Functional Assessment of Cancer Therapy - General
HAF	Hepatic Arterial Fraction

HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HBV	Hepatitis B virus
HKLC	Hong Kong Liver Cancer
HR	Hazard Ratio
ICG	Indocyanine green
INR	International Normalized Ratio
LI-RADS	Liver Imaging Reporting and Data System
MARS	Molecular Adsorbent Recirculating System
MELD	Model for End-Stage Liver Disease
mRECIST	Modified Response Evaluation Criteria In Solid Tumors
MRI	Magnetic resonance imaging
mTOR	Mammalian target of rapamycin
MTT	Mean Transit Time
NASH	Non-alcoholic steatohepatitis
PIVKA-II	Protein induced by vitamin K absence-II
PD	Progressive disease
PS	Permeability Surface
PT	Prothrombin Time
PVTT	Portal vein tumor thrombosis
OoL	Quality of life

RECIST	Response Evaluation Criteria In Solid Tumors
SBRT	Stereotactic body radiation therapy
SD	Stable disease
SIRT	Selective Internal Radiation Therapy
SF-36	Short Form 36
TACE	Transcatheter Arterial Chemoembolization
TAI	Transarterial Infusion
TNM	Tumor Node Metastasis
UCSF	University of California San Francisco
UNOS	United Network for Organ Sharing
VEGF	Vascular endothelial growth factor

DEFINITIONS IN SHORT

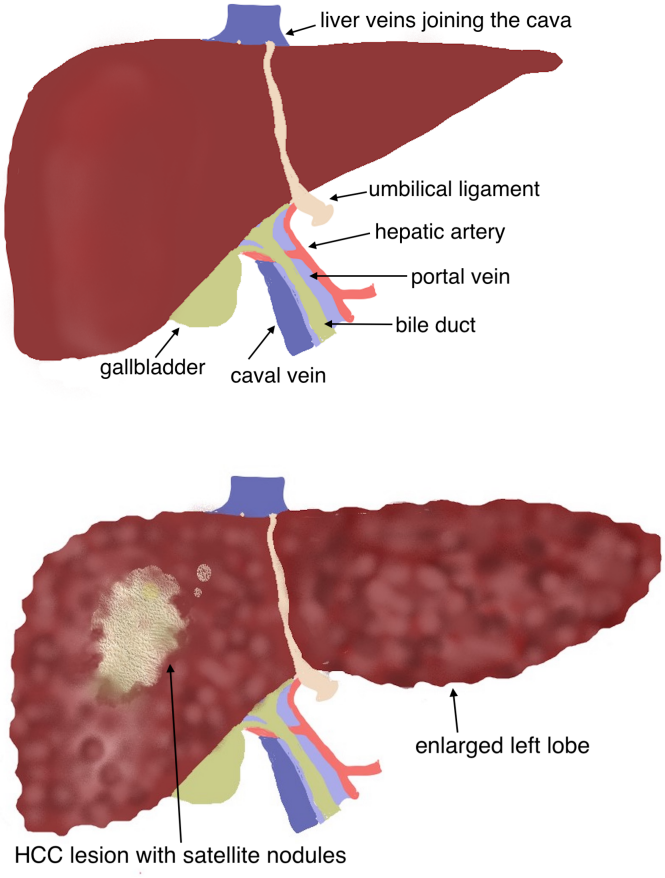
Competing risks	Cumulative incidence of tumor recurrences and of deaths without recurrence
Five-year overall survival (5yOS)	The proportion of patients alive after five years, censoring living patients with a shorter follow-up
Five-year recurrence-free survival (5yRFS)	The proportion of patients alive and free from disease recurrence after five years, censoring patients free from disease recurrence with a shorter follow-up (events; death or recurrence).
Five-year disease-specific survival (5yDSS)	The proportion of patients free from disease recurrence after five years, censoring patients with a shorter follow-up, including patients who died from unrelated causes.
Five-year cumulative incidence of tumor recurrence (5yTumorRec)	Cumulative incidence of tumor recurrences after five years
Transplantation selection criteria	Tumor criteria for selection of HCC-patients for liver transplantation
Milan Criteria	One tumor $\leq$ 5 cm or $\leq$ 3 tumors $\leq$ 3 cm each and no extrahepatic metastases or vascular invasion.
UCSF Criteria	One tumor $\leq$ 6.5 cm or $\leq$ 3 tumors $\leq$ 4.5 cm each and a total tumor diameter $\leq$ 8 and no extrahepatic metastases or vascular invasion.
Cold ischemia time (CIT)	The time period from the start of perfusion in the organ donor to the revascularization of the liver in the organ recipient.
Extended criteria liver	A donor liver associated with an increased risk for impaired organ function due to different factors such as donor age, liver steatosis, donation after circulatory death or split liver

Child-Pugh (Child)	A score used to categorize liver functional reserve in patients with cirrhosis (tab 1)
EORTC QLQ C30	A standardized quality-of-life questionnaire developed for use in cancer patients
HCC18	A supplement questionnaire to the EORTC QLQ C30, developed for patients with liver disease.
Clavien-Dindo	A scoring system that categorize complications after surgical treatments depending on the way they are treated.

1 INTRODUCTION

Metastatic disease from primary tumors of other organs is the most common cancer in the liver. The two main forms of cancers originating from the liver itself are intrahepatic cholangiocarcinoma and hepatocellular carcinoma (HCC), of which the latter accounts for about three fourths of all primary liver cancers in Sweden[1]. A large majority of HCC occurs in patients with an underlying liver disease and cirrhosis (fig 1).

Figure 1. *Normal liver and cirrhotic liver with enlargement of the left lobe and HCC development*



1.1 HISTORY

Liver resection for tumors was performed as early as the late 19th century[2]. In 1902, the Pringle maneuver was described to control bleeding and the following year the finger fracture technique was described, but became popular much later[2]. In 1911, the first right lobectomy was performed in a patient with hepatocellular carcinoma, who survived an additional 9 years[2]. The first liver transplantation was performed in 1963, though prolonged survival (13 months) after transplantation was not seen until 1967 in a young woman with HCC[3]. Before the introduction of selection criteria for HCC in 1996, five-year survival rates were 30-40% lower for HCC patients than for non-HCC diagnoses after liver transplantation[4]. In 1993 the first adult-to-adult living donor liver transplantation was performed in Japan and in subsequent studies 96% of liver transplantations for HCC in Asia were performed with living donors[5].

Thanks to the access technique, introduced in 1953 by Seldinger, transarterial therapies were developed in the 1970s. In the early 1980s transcatheter arterial chemoembolization (TACE) was an established treatment for HCC[6]. The first percutaneous ablation therapy was performed in 1983, using ethanol injection[7], while thermal ablation with radiofrequency was introduced a decade later[8].

In 2008 sorafenib was the first systemic treatment shown to prolong life in advanced stages of HCC[9]. During the last decades, the field of HCC research has grown very large with more than 100,000 results in PubMed when searching “hepatocellular carcinoma”.

1.2 EPIDEMIOLOGY

Despite a global decrease in overall cancer-related mortality during the recent decades, mortality associated to liver cancer still appears to increase in many countries[10]. In 2015, HCC was the sixth most common cancer worldwide, with a global incidence of 854,000 cases, and among the most common causes of cancer-related mortality[11]. Globally, more than 80% of cases occur in Asia and Africa, south of the Sahara, while the incidence in Northern Europe is much lower[12]. In Sweden, the annual HCC incidence is about 400-500 cases[1], with an age-standardized mortality rate of 3.1/100 000 compared to rates over 15/100 000 in many Asian and African countries[13].

Most cases of HCC occur in patients with liver cirrhosis of different etiology. Ten-year cumulative incidence of HCC in patients with liver cirrhosis and viral hepatitis has been reported to range from 4-22%[14, 15]. The varying HCC-incidence globally is largely related to the prevalence of viral hepatitis. The highest risk for HCC development is found in patients with liver cirrhosis and HCV infection, and though successful antiviral treatment reduces the risk greatly, a considerable risk remains in patients with cirrhosis[16].

About 5% of the world population has a chronic hepatitis B infection, which accounts for about half of HCC cases worldwide. In chronic hepatitis B, the risk of HCC is influenced by many factors, such as viral load, infection duration, viral co-infection, exposure to aflatoxin, and the presence of cirrhosis. However, HCC can occur in HBV-carriers even in the absence of cirrhosis[12].

Alcohol is an important etiology of cirrhosis, but alcohol also seems to potentiate the HCV-induced risk for HCC[17]. The most serious form of metabolic liver disease, non-alcoholic steatohepatitis (NASH), is associated with an increased risk for HCC, especially in those who develop cirrhosis[18, 19]. Hence, the incidence of HCC attributed to the prevalence of obesity and diabetes is increasing.

In a Swedish HCC-cohort from 2005-2012, hepatitis C (25%) and alcohol (18%) or both (17%) were the most common underlying etiologies. Hepatitis B-related HCC accounted for only 6%, while previously healthy livers were described in 11%[20]. In our national HCC cohort treated with curative intent according to SweLiv 2008-2016, about 25% had no reported underlying liver disease (paper IV).

1.3 HCC DIAGNOSIS

There is consensus that the diagnosis of HCC can be made non-invasively, given the presence of cirrhosis and tumor size of more than one centimeter, and a typical pattern of arterial contrast-enhancement with washout[21]. The development of HCC has been described as a multistep process from large regenerative nodules in the cirrhotic parenchyma, followed by low and high-grade dysplastic nodules, and finally hepatocellular carcinoma. During hepatocarcinogenesis, angiographic imaging and histopathology studies have demonstrated a gradual shift from the normal dominant portal blood supply to an increased proportion of arterial supply, with the development of pathologic vessels[22]. Simultaneously, the normal hepatic veins disappear within the tumors and the blood drainage changes to the portal venules[7]. These vascular changes and the high probability for HCC development in cirrhotic livers are the basis for the radiologic criteria[23].

Multiphase computed tomography (CT) and magnetic resonance imaging (MRI) are recommended imaging modalities, while contrast-enhanced ultrasound is a useful complementary tool for lesion characterization. The Liver Imaging Reporting and Data System (LI-RADS) was launched to improve standardization of CT and MRI evaluations in patients with increased risk, with an algorithm to estimate the probability of HCC in lesions[24]. Sensitivity and specificity of the radiologic criteria are lower in small lesions. Especially intrahepatic cholangiocarcinoma, mixed HCC/CCC, and benign lesions can be mistaken for HCC[25]. Therefore, biopsy with histopathology confirmation is recommended whenever the imaging presentation is not typical and always in the absence of cirrhosis [23, 26].

Three common growth patterns of HCC are described in histopathology; trabecular, pseudoglandular (or pseudoacinar), and solid (or compact)[27]. A frequent heterogeneity of HCC impairs the utility of biopsies. In cirrhotic livers, precursor lesions such as high-grade dysplastic nodules are often difficult to differentiate from HCC, warranting the use of immunostaining and/or gene expression profiles[28]. Cases with less differentiation are challenging, as no immunohistochemical marker is entirely specific or sensitive of HCC[27]. The HCC diagnosis is based on resemblance of tumor cells to hepatocytes and the production of bile is common in well-differentiated tumors and a typical sign. However, many tumor cells of different origins may look ”hepatoid” and need to be considered for differential diagnosis[27]. Capsule formation is a good prognostic marker, while

diffuse/infiltrative growth is associated with bad prognosis[29, 30]. Other typical histological features for HCC are vascular invasion and satellite nodules, which are more common in larger tumors[31, 32]. Liver tumors sometimes have mixed hepatocellular and cholangiocellular differentiation, which is associated with worse prognosis[27].

A majority of HCC cases in Sweden (60%) are diagnosed at clinical presentation, while one fourth of cases are discovered with surveillance procedures and 13% are found en passant on imaging indicated for other conditions[1].

In patients with decompensated liver cirrhosis who are treated with liver transplantation, hepatocellular cancer is sometimes diagnosed first in the explant histopathology. Such incidental hepatocellular cancers were found in 53 patients out of the total of 389 patients who underwent liver transplantation with HCC in Sweden from 1996-2014 (paper II) and accounts for less than one percent of all cases[1].

1.4 PROGNOSTICATION AND STAGING

As in many other cancers, tumor burden is a prognostic factor in HCC and is categorized by the TumorNodeMetastasis (TNM) staging system with different versions and updates[33]. However, due to the large proportion of HCC patients with underlying liver disease and cirrhosis, liver functional reserve has a major impact on survival, as well as treatment possibilities and performance status.

The possibility to predict survival probabilities in cancer patients is crucial for treatment decisions and planning of care in the individual patient, but is also a prerequisite for treatment comparisons. The prognostic factors in HCC can be grouped into four categories:

1. Tumor-related factors; tumor size and number, vascular invasion, metastases, lymph node involvement, tumor differentiation, AFP and other tumor markers
2. Patient factors; age, gender, ethnicity, etiology of liver disease, performance status, comorbidity, symptoms
3. Liver function parameters; cirrhosis, portal hypertension, platelets, Model of End-Stage Liver Disease (MELD), indocyanine green (ICG) clearance and Child–Pugh including albumin, bilirubin, INR, encephalopathy and ascites
4. Treatment factors; no treatment or treatment modality and factors regarding each treatment such as blood loss during surgery, donor factors in transplantation and response to treatment, delayed treatment

1.4.1 TUMOR FACTORS

Tumor size and number: Increasing tumor size is a risk factor for death and tumor recurrence after treatment and is included in most suggested staging systems[34, 35]. Different cut-offs are used depending on the setting and even very large tumors (more than 10cm) can be resected with acceptable outcomes[36]. Larger size has been correlated with an increased risk for vascular invasion, higher tumor grade, and satellite nodules, which are also negative prognostic factors in HCC[23, 31]. Tumor size is also a limiting factor for ablation and affects the treatment efficiency of TACE[37-39].

The number of HCC nodules is a well-established prognostic factor, included in many staging systems[35]. However, a multifocal growth pattern is difficult to distinguish from the presence of intrahepatic metastases, which might influence outcome differently[40, 41]. Measures combining size and number are frequently used, such as total tumor diameter and tumor volume[42, 43].

Vascular tumor invasion: Tumor growth in the portal vein, or sometimes the liver veins, is typical of HCC and has a strong negative impact on prognosis[35, 44]. Results after surgery with vascular invasion of intrahepatic portal branches are poor, and surgery should not be performed in cases with invasion of the main portal vein or the liver veins[5, 45]. Microscopic vascular invasion is by definition found only by histopathology. It is also a risk factor for mortality and tumor recurrence, though not as strong as macroscopic vascular invasion at imaging.

Extrahepatic tumor: Extrahepatic metastases from HCC are associated with short survival[46] and curative treatments are not feasible[23]. Still, it has been suggested that intrahepatic tumor burden and treatment might impact prognosis despite the presence of extrahepatic metastases[47, 48].

In a study in HCC patients with extrahepatic metastases, lymph nodes were the most common site and had the most impact on survival[49]. In 774 patients who underwent resection for HCC, only 4.4% had lymph node metastases[50]. In a literature review, rates of lymph node dissection varied, as well as the proportion with lymph node metastases. When present, lymph node metastases were associated with decreased survival[51].

Differentiation: Hepatocellular tumor differentiation is usually categorized into four grades according to Edmonson-Steiner[26]. Prognosis is better with well-differentiated tumors (low grade according to Edmonson-Steiner), but

due to the radiologic diagnosis, the differentiation is usually not known before surgical treatment. Liver biopsy has been proposed for pre-transplant risk assessment[52]. However, the value of biopsies for grading is not clear, due to the risk of sampling error with the heterogeneous nature of HCC[26, 53].

AFP and other tumor markers: The glucoprotein Alpha-fetoprotein (AFP) is the most common tumor marker in HCC and has been suggested to play a role in the regulation of several cellular functions, such as cell growth, differentiation, apoptosis, angiogenesis, and immune regulation[54]. Elevated levels are seen in up to 70% of HCC cases, but also during pregnancy and in patients with cancer of the testis[54]. In patients with chronic liver disease, AFP levels have been associated with the severity of liver disease, female gender and black race[55].

AFP is no longer included in the diagnostic criteria, but has regained popularity for prognostication during the last decade, especially in the setting of liver transplantation for HCC[56]. In a large registry study (n>45000), HCC patients with normal AFP-levels had similar post-transplant survival as recipients without cancer[57]. Outcome for HCC patients outside the Milan criteria but with normal AFP levels was similar to HCC patients within the Milan[57]. Several other tumor markers have been reported to be prognostic in the setting of transplantation for HCC; such as des-γ-carboxy prothrombin (DCP), the protein induced by vitamin K absence-II (PIVKA-II) and Lens culinaris agglutinin-reactive alpha-fetoprotein (AFP-L3)[58], but are not routinely used in Sweden. In advanced HCC patients, angiopoetin2 and vascular endothelial growth factor (VEGF) were prognostic for survival, whereas no factor could predict response to sorafenib treatment[59]. VEGF has also been reported as a prognostic factor in the setting of TACE, resection, or transplantation, but is not routinely used in the clinical setting[60-62].

Dynamic measures: Doubling times for tumor volume[63] or tumor markers[64, 65], have been suggested to give more accurate predictions, but the need for repeated measures is inconvenient and consequently there is less data than for static measures.

1.4.2 COMORBIDITY AND PERFORMANCE STATUS

Cancer-related symptoms are unspecific and therefore difficult to distinguish from symptoms caused by comorbidity. Still, the presence of cancer-related symptoms (fatigue, pain, nutritional issues among others) is a sign of advanced tumor stage and consequently a risk factor for death. This is the rationale for including performance status in several staging systems, such as the BCLC and HKLC[66-68]. The Eastern Cooperative Oncology Group (ECOG) is a widely used measure for performance status. ECOG 0 represents an asymptomatic patient, whereas ECOG 4 refers to a terminally ill, bedbound patient[69]. ECOG correlates with liver function and tumor burden as well as with survival and impacts treatment decision-making[70].

Comorbidities, such as cardiopulmonary disease, are also important for survival and treatment decisions. Metabolic factors, such as being overweight, have been associated with an increased risk for liver cancer-related death[71].

Male gender is about three times more common among HCC patients and with a suggested association between female gender and better outcome, a possible role of estrogens has been hypothesized[72, 73]. However, others have reported that high AFP has more negative impact in women[74].

Studies regarding ethnicity have reported that black and Asian patients have worse prognosis than Hispanic and white patients, but many confounding factors, such as differences in treatment assignment and tumor stage at the time of diagnosis need consideration[75-77].

There is no established association between etiologic factors and prognosis[78].

1.4.3 LIVER FUNCTION

The liver is the largest internal organ and accounts for a large number of vital functions. These include synthesis of proteins, such as albumin and clotting factors, production of bile, glucose homeostasis, storage of vitamins and iron, as well as clearance of bilirubin and other products[79]. Impaired liver function decreases expected survival and limits treatment possibilities in HCC.

A healthy liver has a large functional reserve and a remarkable regenerative capacity, which is the prerequisite for major liver surgery. Liver functional reserve decreases incrementally with cirrhosis development, but is difficult to estimate before treatment. Imaging factors, such as splenomegaly, varices and ascites might reveal portal hypertension, which is a risk factor both for survival and for outcome after surgery[80]. There are multiple laboratory tests for evaluation of liver excretion (bilirubin), cholestasis (ALP, GT), synthesis (albumin and coagulation factors) and portal hypertension (platelet count), but no single measure is reliable for this purpose[81]. Combined tools have been developed to improve liver function stratification, of which the Child-Pugh score is probably the most common[82]. It combines data regarding bilirubin, INR and albumin levels with information about ascites and encephalopathy into three risk groups (tab 1). Child-Pugh stratifies survival in cirrhotics and is in turn included in several HCC staging systems[35, 83].

Table 1. Child-Pugh-Turcotte score[82]

Scores	1p	2p	3p
Ascites	Absent	Slight	Moderate/refractory
Bilirubin (µmol/L)	< 35	35-51	> 51
Albumin (g/L)	> 35	28-35	< 28
PT-INR	<1.7	1.7-2.3	> 2.3
Encephalopathy	Absent	Moderate	Severe
Overall Child-Pugh Score:	A=5-6p	B=7-9p	C=10-15p

The MELD algorithm is based on levels of creatinine, bilirubin and INR and was originally developed for patients with trans-jugular intrahepatic portosystemic shunts[84]. It is now widely used for prognostication and prioritization among liver transplant recipients and sometimes for other surgical treatments[85]. Among dynamic tests for liver function assessment, ICG clearance tests are commonly used before surgery[86] and incorporated in some decision algorithms[87, 88].

1.4.4 TREATMENT FACTORS

Given treatment is a common prognostic factor, associated with survival in cancer. Selection bias normally precludes conclusions about cause, except in randomized studies. Treatment strategies differ around the world, which may impact prognosis. In Asia, Western guidelines are considered too conservative and surgery can be recommended regardless of tumor number and intrahepatic portal invasion[5, 89].

Factors related to specific treatment can also impact prognosis. The rate of tumor recurrence has been associated to treatment radicality and surgical margins after resection[90, 91]. A similar association has been described with the radio-frequency ablation margin[92]. In the TACE setting, more selective embolization has also been associated to a lower rate of tumor recurrence[93].

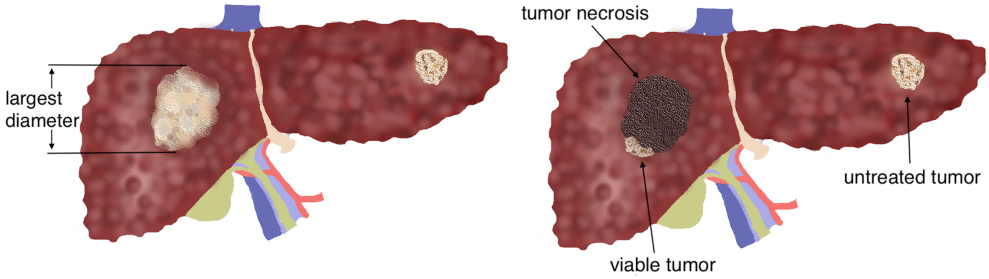
Some association between recurrence-free survival and blood loss during liver resection and transplantation has been suggested[94, 95]. In a literature review, transfusion during surgery was above all associated with post-operative complications, but some impact on long-term cancer outcomes was also suggested[96]. In the setting of liver transplantation many potential factors may influence outcome including donor factors, immunosuppression and unpredictable waiting time with the risk for tumor progression and dropout[97-99].

Adjuvant treatment: Neo-adjuvant treatment before liver transplantation is routine, and a benefit on overall survival has been suggested[100], although, evidence is limited[101]. In the adjuvant treatment setting, a large randomized study on adjuvant sirolimus in liver transplant recipients, failed to demonstrate a significant increase in recurrence-free survival[102]. Still, mTOR after liver transplantation is sometimes advocated[103, 104]. Systemic doxorubicin has also been evaluated in a small, randomized study, without any benefit[105]. Neo-adjuvant treatment is not routinely used prior to resection and ablation and a large randomized controlled study after resection and ablation reported no benefit with adjuvant sorafenib treatment[106].

Treatment response: In solid tumors, the treatment effect with systemic chemotherapy can be categorized as complete response, partial response, stable disease or progressive disease according to the response evaluation criteria in solid tumors (RECIST). With the frequent use of locoregional treatments for HCC such as ablation and TACE, a modified version

(mRECIST) has been developed. With mRECIST only contrast-enhancing tumor areas are interpreted and measured as viable residual tumors[107] (fig 2). For evaluation of systemic treatments of HCC both RECIST and mRECIST are used[23].

Figure 2. *Assessment of tumor burden before treatment and response evaluation according to RECIST and mRECIST after treatment. With RECIST, the largest diameter of the entire tumor including tumor necrosis is measured, whereas with mRECIST only the viable (contrast-enhancing) parts are measured.*



Tumor progression after treatment is a negative prognostic factor and warrants careful consideration whether to retreat rapidly or to change treatment strategy, depending on the setting and time frame. In patients with neo-adjuvant treatment before liver transplantation, several reports emphasize the prognostic impact of tumor response, which might be increasingly used as a selection tool[108-111]. Although tumor responses are not included in routine criteria, reported tumor measures are often the remaining contrast-enhancing tumors on imaging after treatment and sometimes a mix of pre- and post-treatment measures[112, 113].

1.4.5 STAGING SYSTEMS

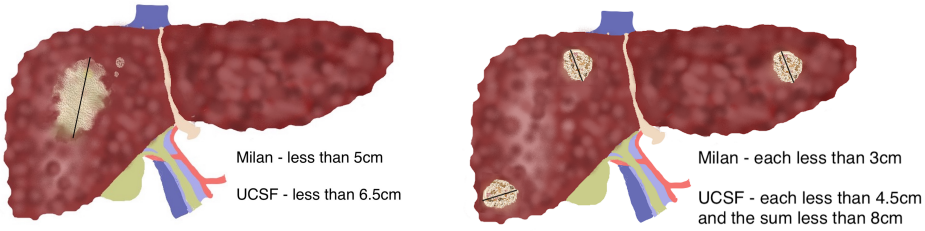
Combining independent factors improves prognostic accuracy. Several different staging systems for HCC have therefore been suggested for clinical decision-making and research. Some of the staging systems have specific aims, such as the UNOS-TNM, which is used for transplantation selection and priority[114], whereas Barcelona Clinic Liver Cancer (BCLC) and Hong Kong Liver Cancer (HKLC) aim to stratify all stages of HCC[66, 68]. The performance of various systems differs depending on the cohort selection. For instance, the Cancer of the Liver Italian Program (CLIP) score includes four variables; Child-Pugh, tumor nodularity or spread >50% of the parenchyma, AFP >400ng/ml, and portal vein thrombosis[115]. CLIP has been demonstrated to perform well in palliative settings and predict short-term survival (3 or 6 months)[116], while the TNM-systems stratify earlier stages best[33]. Also, follow-up time influences prognostic performance, as tumor factors have a large impact on shorter follow-up, while factors regarding liver function seem to influence long-term survival more[117].

The BCLC combines tumor burden (including size, number, vascular invasion, and metastases) with Child-Pugh and performance status, and has been frequently validated[83]. It links each stage of the entire HCC-population with a treatment suggestion, which has resulted in wide use of the BCLC algorithm. However, the treatment recommendations are sometimes considered too strict[5, 118]. Because of heterogeneity of the intermediate stage, several modified BCLC-versions have been suggested, allowing for higher performance status and introducing subclasses[70, 119]. A recently proposed staging system is the ItaLiCa, which includes AFP and the variables of the BCLC, but combines them in a more flexible way[120].

Transplantation selection criteria: For prognostication in the setting of liver transplantation, special considerations are needed. First, because risk factors regarding liver functional reserve become irrelevant after liver transplantation, but also because outcome after liver transplantation for HCC must be related to other indications, competing for the same donor livers. Strict selection for transplantation was introduced in 1996 with the Milan criteria (one tumor of $\leq$5cm or $\leq$3 tumors of $\leq$3cm and no metastases or macroscopic vascular invasion)[121]. They remain the gold standard, with 5yOS rates of more than 75% repeatedly reported. Numerous alternative and extended criteria have been suggested and debated, both stricter and more generous, but to a large extent based on tumor size and number.

In Sweden, we have had a generous attitude due to a relatively well-balanced transplantation waiting list situation. The former Karolinska criteria allowed for a total tumor diameter <10cm[122]. In the National Treatment Guidelines of 2012, consensus was to use the University of California San Francisco (UCSF) criteria (one tumor of ≤6.5cm or ≤3 tumors of ≤4.5cm and a total tumor diameter ≤8cm and no metastases or macroscopic vascular invasion)[123]. This was judged to yield the most benefit per donor liver[122].

Figure 3. *Accepted tumor burden according to Milan and UCSF criteria*



More recent criteria have included new factors, such as tumor markers and/or differentiation. The UNOS criteria use AFP with cutoffs of 1000 and 500 ng/ml[114]. The Up-to-Seven criteria (the sum of tumor size in centimeters + tumor number ≤7) have been supplemented with different AFP cutoffs depending on tumor burden[113]. The Kyoto criteria imply a DCP-level of no more than 400mAU/ml, but are extremely generous regarding size and number (≤5cm and ≤10) with a reported five-year overall survival (5yOS) of 82%[124]. The Toronto group has reported a 5yOS of 72%, allowing any tumor size and number given that biopsy has ruled out poor differentiation in tumors >5cm and the absence of cancer-related symptoms[112]. The Hangzhou group previously suggested a combination of those factors, allowing total tumor diameter ≤8cm or histopathology grade I or II on biopsy and AFP ≤400 ng/ml in larger tumors[125].

A recent study presented criteria based on tumor markers PIVKA-II and AFP in 205 patients beyond the Milan, and a large proportion (40%) with portal branch invasion. Patients with a low score were reported with 5yOS of 83% [126]. The advantages with tumor markers are that they are easily available and more objective than imaging measures, especially after neo-adjuvant treatments.

1.5 TREATMENT ALTERNATIVES

Traditionally, the different treatment options in HCC can be grouped into treatments with curative intent, including liver transplantation, liver resection and local ablative therapies, and palliative treatments, including local trans-arterial therapies, and systemic treatments such as sorafenib. Presently about one third of HCC patients in Sweden receive treatments with curative intent[1]. With increasing knowledge and availability, patients are frequently treated more than once and often with combined modalities. Consequently, the treatment intention becomes more difficult to categorize as curative or palliative.

1.5.1 LIVER TRANSPLANTATION

Liver transplantation enables maximum surgical margins and simultaneously treats the underlying liver disease with 5yOS rates of >70% in selected patients with HCC[127-129]. It is the only treatment possibility for patients with HCC and decompensated liver cirrhosis, given that selection criteria are fulfilled and that no comorbidity contraindicates transplantation. In patients considered for liver transplantation, a thorough work-up is performed regarding cardiopulmonary disorders, previous malignancy, systemic and infectious diseases, kidney function, musculoskeletal and nutritional status as well as psychiatric disorders, including drug or alcohol use, which are closely monitored. The work-up aims to ensure that only patients who can truly benefit from liver transplantation are accepted, despite long-term immunosuppression and the risk for serious complications. This is important with respect to patients with other diagnoses on the waiting list, competing for the same donor livers.

Waiting time: The waiting time for liver transplantation differs between centers with varying allocation rules and donor pools, and also depends on the blood group and MELD score, which affects the priority. In the Nordic countries, median and maximum waiting times for liver transplantation in blood group 0, irrespective of diagnosis, were 66 and 715 days respectively in 2015[130]. According to National US data the corresponding median was 1638 days (95% CI 1270 – 2381) in 2011-2014[114]. Therefore, special rules for priority of low-MELD HCC patients have been developed and an HCC-specific $MELD_{EQ,}$ including tumor burden and AFP-level in addition to MELD, has been proposed to stratify HCC patients in comparison with other indications[131]. The waiting time influence on outcome after transplantation in HCC patients has been debated. Higher tumor recurrence rates have been described, with waiting times less than six months or longer than 18 months[132], whereas waiting time did not significantly affect post-transplant overall survival[133].

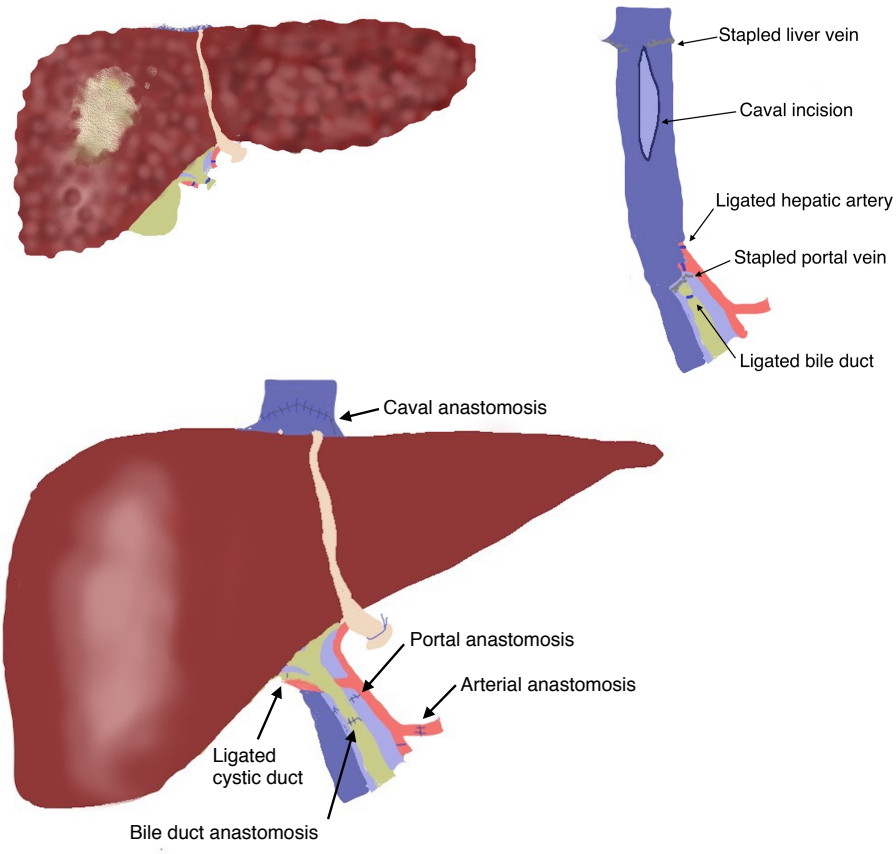
Neo-adjuvant treatment and down-staging: Neo-adjuvant antitumor treatments are routinely administered in HCC patients on the waiting list for liver transplantation, in order to reduce the risk for tumor progression and dropout from the waiting list, despite a low level of evidence[101]. Ablative therapies and TACE are most common, but selective internal radiation therapy (SIRT) and stereotactic body radiation therapy (SBRT) are also used. Prerequisites are an acceptable liver functional reserve (Child-Pugh score $\leq$7-9) and no technical limitations. In patients with tumor burden outside accepted transplantation criteria, but with acceptable general work-up, local antitumor treatments can be administered to achieve sufficient reduction of

radiographic tumor measures and/or tumor-markers to fulfill accepted transplant criteria[110, 111, 134, 135].

Surgery and donor factors: In many countries deceased donors are few and living donor liver transplantation is routine. Large series have been reported, especially from Asia[5, 136]. In Sweden, living liver donors are mostly used for transplantation in children[130]. Donation after circulatory death (DCD) is another used strategy to increase the number of potential organ donors. Livers from DCD donors have not been used in Sweden so far.

The various procedures of transplantation are carefully coordinated in order to reduce the risk for graft injury by minimizing cold ischemia time (CIT). Improvements in surgery and anesthesia have reduced the former problems of massive intraoperative bleeding, which is now quite unusual[137]. The liver transplantation technique (fig 4) is no different for HCC patients, except for an initial exploration to rule out extrahepatic disease.

Figure 4. *Liver transplantation. Above, the explanted cirrhotic liver with HCC and the remaining recipient structures including an incision for the side-to-side anastomosis of the caval vein. Below the new liver transplant with anastomoses.*



Complications: Complication rates after liver transplantations for HCC are not considered different than for other indications. Primary non-function and vascular complications are unusual, but of concern as they might warrant re-transplantation. In HCC patients there have been concerns with pre-transplant TACE[138-140], but no significant associations have been established.

Infections are common, related to mandatory immunosuppression along with surgical trauma and complications such as bile leakage. Renal failure is also common, though the mechanisms in the early postoperative period are not fully understood. Immunosuppressive agents with renal toxicity can impair long-term renal function.

Postoperative bile duct complications might warrant interventions such as draining tubes, ERC or additional surgery. Long-term, intrahepatic strictures are a major problem after transplantation and may cause infections and impaired liver function. Endoscopic and interventional treatments are routine, but eventually re-transplantation may be required.

Regarding immunosuppressive strategies, some advocate a switch to or the addition of mTOR-inhibition after about a month[103, 141], although sirolimus did not significantly increase recurrence-free survival in a randomized controlled study[102].

Likely related to the long-lasting immunosuppression, the risk for de novo malignancy has been reported two to four times higher in liver transplant recipients compared to age- and sex-matched controls[142].

Tumor recurrence: Lower HCC recurrence rates after transplantation compared with other surgical treatments have been repeatedly reported, although the rate is highly related to the selection criteria of the cohort. The majority of tumor recurrences are diagnosed within three years from transplantation, and though occasional resections of solitary recurrences have been reported, prognosis is dismal.

1.5.2 LIVER RESECTION

Resection is considered when all tumor tissue can be resected with margins, while leaving enough parenchyma to preserve adequate liver function. In patients with healthy livers, about 30% or at least two adjacent segments should be preserved. Since underlying liver disease is common in HCC patients, they need special focus on liver functional reserve evaluation. Patients with cirrhosis and Child A are routinely considered for resection, with minor resections preferred. The incidence of micrometastases and satellite nodules is described to correlate with tumor size. Therefore resection margins of 2 cm are often recommended for medium or large-size HCC[143]. Whether anatomical resections (fig 5) rather than minimal non-anatomical wedges (fig 6) decrease the risk for tumor recurrence is debated. In patients with marginal liver function, the risk for liver failure may be more important to consider[144-148]. In patients with healthy livers, resection of very large tumors may be performed successfully. Tumors located centrally in the liver require larger resections than do peripheral ones. Small central tumors might therefore be more efficiently treated with ablation than resection, while the opposite might be true for peripheral tumors adjacent to other vulnerable organs.

Figure 5. *Anatomical right-sided lobectomy including the entire segments 5-8.*

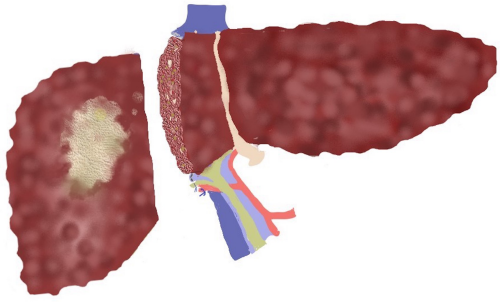
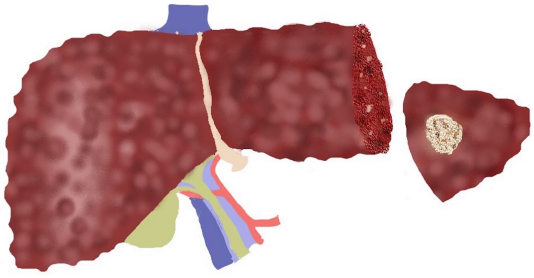


Figure 6. *Non-anatomical wedge resection including part of the left lateral segments.*



Complications: The most feared complication after resection is liver failure. In a Swedish cohort 2005-2009, 90-day mortality after resection for HCC was 2%[149]. The Molecular Adsorbent Recirculating System (MARS) has been suggested as liver replacement therapy, but the benefit is debated[150]. Supportive treatment is the routine, with antibiotics to prevent deleterious super-infections and supportive treatments such as laxatives to prevent symptoms of encephalopathy. Severe postoperative infections might induce liver failure even in patients with limited resections.

Similar to transplantation, renal function is often transiently altered after resection. This may be due to the fluid restriction during surgery to reduce bleeding. Impaired renal function is also a risk factor for other postoperative complications.

Bile leakage is the most common liver-specific complication, and can usually be treated conservatively. Sometimes a percutaneous drainage tube is needed, and/or decompression with a biliary stent.

Tumor recurrence: Resection for HCC is associated with high rates of tumor recurrence[127, 128]. The rate of tumor recurrence correlates to tumor stage[151]. This might be due to an aggressive biology or inadequate resection margins, but also to de novo tumors in a cancer-prone liver parenchyma. Repeated resections can be done in cases of limited recurrence. Salvage liver transplantation in case of tumor recurrence after resection, given criteria fulfillment, has been proposed as a strategy to save donor livers[152, 153].

1.5.3 LIVER ABLATION

Ablative treatments are performed with heat-generating needles using either radiofrequency or microwave energy (fig 7). Tumor size is a limiting factor and the best results have been demonstrated for tumors 2-3cm[23, 154-156]. Larger tumors can sometimes be treated, when no other options are possible, but with an increased risk for incomplete ablation and tumor recurrence. Proximity to central bile ducts is a contraindication and ablation is difficult when tumors cannot be visualized with ultrasound. Peripheral tumors in the vicinity of vulnerable organs such as the heart, stomach, intestines or gall bladder and tumors located close to the diaphragm, may not be possible to treat percutaneously, but can often be treated with laparoscopic or open techniques.

The lack of histopathology confirmation of the tumor after ablation is a disadvantage, which also precludes tumor classification and verification of treatment margins. Therefore, the diagnosis needs to be confirmed by biopsy before or at the time of treatment in uncertain cases. Treatment success needs to be evaluated with follow-up imaging, where remaining arterial contrast-enhancement might be a sign of incomplete ablation.

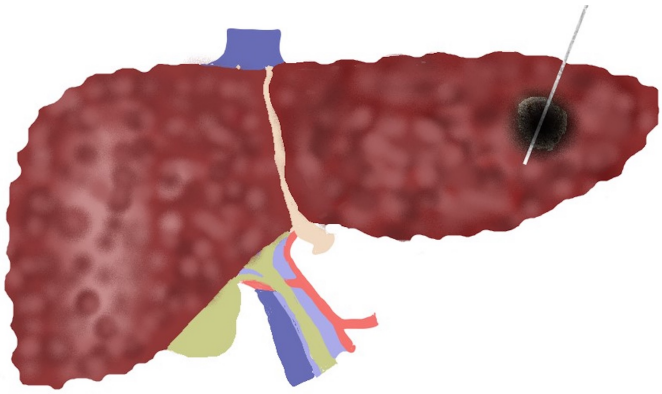


Figure 7. *Ablation*

The advantage with ablation is that it is easily available and associated with low morbidity rates. It can be tolerated even in patients with impaired liver function or a high load of comorbidity and implies short hospital stay and low costs. With expanded indications both in the neo-adjuvant and palliative settings, the use of ablation has increased recently. Recurrence rates are, however, reported to be higher with ablation than with resection, especially during the first year after treatment, leading some to advocate closer follow-up after ablation.

1.5.4 TRANSARTERIAL TREATMENTS

The liver has a dual blood supply, with about 3/4 of the flow from the portal vein, providing venous blood from the gastrointestinal organs, while about 1/4 is more oxygenated blood from the hepatic artery, with importance for the intrahepatic bile ducts, but also for liver tumors[157]. The arterial blood supply of HCC tumors is the rationale for trans-arterial treatments, including TACE, which is the most common, trans-arterial infusion (TAI) and SIRT. TACE is indicated in palliative patients, with tumors confined to the liver, well-preserved liver function (Child Pugh $\leq$7) and acceptable performance status, but who are not eligible for surgical treatments. TACE is also routinely used as a neoadjuvant or down-staging treatment in HCC-patients waiting for liver transplantation.

TACE is performed by catheterization of the coeliac trunk and hepatic artery to a super-selective position, where drug-eluting beads (doxorubicin) or a Lipidiol-chemotherapy mixture is delivered until stagnation. The treatment is evaluated with CT or MRI, and renewed treatment is planned if contrast-enhancement suggests residual viable tumor. Sustained complete tumor responses are not unusual, but the need for repeated treatments is the rule.

Marginal liver function (Child Pugh >7) and compromised portal flow are contraindications as well as heart failure. Low-grade fever, liver and hematological toxicity, pain and vomiting are common side effects, mostly included in the post-embolization syndrome[158]. Median survival in a large systemic review was 19 months[158].

1.5.5 SORAFENIB

The tyrosine-kinase inhibitor sorafenib was the first and only systemic treatment option in HCC for several years. It has been associated with anti-angiogenic effects as well as direct anti-tumor effects[159]. The approval of sorafenib was based on randomized controlled trials in patients with advanced HCC (vascular invasion or extrahepatic metastases) and preserved liver function (Child Pugh $\leq$7)[9, 160]. A survival gain of approximately 3 months was seen without corresponding radiographic responses and sorafenib is still the standard of care in advanced stage HCC, although an alternative, lenvatinib has recently been approved[161]. However, sorafenib did not improve recurrence-free or overall survival when evaluated as an adjuvant treatment after surgery or ablation[106].

Many patients experience considerable side effects, such as hand-foot-skin reaction, abnormal hepatic function and fatigue[9, 106]. Close initial monitoring is crucial as some side effects can be anticipated and prophylactic treatments prescribed. Some adverse events are transient and others might be managed by dose adjustments and treatment pauses, as symptoms often cease quickly after the treatment is stopped. However, for some patients the treatment is insufferable.

In recent years many new systemic treatments have been explored, but only levantinib and second-line regorafenib have been approved for routine use in advanced stages of HCC[23].

Sorafenib and transplantation: Despite some concerns about the use of anti-angiogenetic therapy in a perioperative setting[162], sorafenib treatment in HCC patients waiting for liver transplantation has been reported in a few small studies[163, 164] and case series[165-167]. One study compared 15 HCC patients who received sorafenib to 64 patients, who did not, while on a waiting list for transplantation. No differences in survival, recurrence or complication rates were observed[163]. However, higher rates of rejection and biliary complications were noted in a study, where 10 patients who received sorafenib before transplantation were compared to a non-randomized control group[164]. With small sample sizes conclusions are not certain.

1.6 QUALITY OF LIFE (QOL)

Most people agree that quality of life is important, but there is no distinct definition. Health-related QoL commonly involves aspects influenced by health status, such as physical, psychological, and social factors[168]. In HCC patients, QoL is affected by symptoms related to the tumor and the underlying liver disease, as well as side effects from treatments[169, 170]. In addition, QoL is influenced by the coping mechanisms of the patient and the perception of support from the health care system and family and friends, and may vary with cultural and educational factors[169, 170].

Questionnaires for patient-reported QoL: To standardize health-related evaluation, questionnaires for patient self-assessment of QoL have been developed. The main focus of the questionnaires is assessment of symptom burden and the general ability to function during daily life. Questionnaires for general health include the Short Form 36 (SF-36) and the EuroQoL-5D, and for patients with any cancer, the Functional Assessment of Cancer Therapy - General (FACT-G)[169]. Supplements to be used with the corresponding general cancer form in patients with specific diseases are also available; such as the FACT-Hep for patients with liver disease.

EORTC QLQ C-30 and HCC18: The general cancer questionnaire QLQ-C30 was developed by the European Organization for Research and Treatment of Cancer (EORTC)[171] and has been found useful in several studies[172-176]. It includes global health and quality-of-life scales, functional scales (physical, role, cognitive, emotional and social), symptom scales (fatigue, pain and nausea and vomiting) and several single items.

The validated liver-specific supplement EORTC QLQ-HCC18 addresses specific problems of impaired liver function with 5 multi-item symptom scales: fatigue, nutrition, jaundice, pain and fever; 2 single-item symptom scales: abdominal swelling and sexual interest; and one multi-item functional scale: body image[177, 178]. The QLQ C30 has been reported to be the most frequently used QoL-questionnaire in HCC patients, with or without the supplement HCC18[179].

QoL in HCC: Decreased patient-reported QoL has been associated both with chronic liver disease without cancer and with advancing stages of HCC[170, 180, 181]. HCC patients reported better social/family QoL compared to the general population, while physical, emotional and functional QoL was decreased[170]. Fatigue, pain, nausea and performance status have been associated with worse QoL in HCC patients[170].

2 AIMS

The overall aim was to improve our ability to make the most optimal treatment decisions for individual HCC patients. Therefore we wanted to study prognostic factors available at the time of treatment decision-making in different clinical settings.

We asked the following questions:

- Can patient-reported quality of life-questionnaires prognosticate patient survival and increase the prognostic accuracy of established staging models in HCC?
- Can the use of AFP levels increase the prognostic precision of currently used selection criteria for liver transplantation in HCC?
- Which prognostic factors could help guide treatment decisions in HCC patients, who are eligible for more than one treatment alternative with curative intent?
- Is survival after liver transplantation better than after liver resection and liver ablation in HCC patients with limited tumor burden and well-preserved liver function (Child A)?
- Is systemic neo-adjuvant treatment with sorafenib feasible for HCC patients awaiting liver transplantation?

3 PATIENTS AND METHODS

We performed four clinical studies (tab 2). Two were conducted as prospective clinical studies. Paper I was an observational study and paper III was an interventional study. Paper II was a retrospective review of medical records in a Swedish national cohort. Paper IV was a register study, using the Swedish Registry for cancer of the liver and bile ducts (SweLiv), which was started in 2008 and is linked to the Swedish population registry. Register completeness for 2009-2016 was 95.6%.

Table 2. Overview Study Methods

	Patients and setting	Study design	Cause	Effects
Paper I	185 patients recruited in Norway (Oslo, Tromsö) and Sweden (Gothenburg, Stockholm) Apr 2011 - Jan 2015	Clinical prospective observational study	QoL- data; QLQ C-30 and HCC-18	Mortality
Paper II	a national cohort of 336 patients who had liver transplantation due to HCC 1996-2010	Retrospective study of in a Swedish national cohort	AFP	5yOS 5y cumulative incidence of tumor recurrence
Paper III	12 patients with HCC within UCSF-criteria who were assigned for liver transplantation 2011-2014	Clinical prospective interventional feasibility study	Sorafenib treatment	CTperf changes Feasibility Toxicity Transplant rate 90day surgical complication rate
Paper IV	1022 patients with HCC and primary transplantation, resection or ablation in SweLiv 2008-2016	Retrospective analysis of prospectively collected national register-data	Treatment modality	5yOS

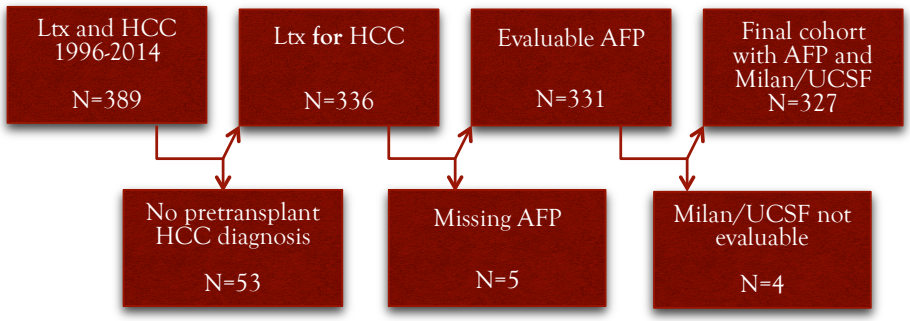
All four studies were approved at the regional ethical vetting board in Gothenburg, paper I also in Norway. All included patients were older than 18 years of age and diagnosed with HCC according to the European association for study of the liver (EASL)/American Association for the Study of Liver Diseases (AASLD) criteria[28], or according to histopathology. Studies were conducted simultaneously, and some patients were included in more than one study. Written informed consent was obtained in paper I and III.

3.1 PATIENTS

In paper I patients with HCC at any stage were included at the time of a clinical visit, provided that radiological evaluation was performed within 6 weeks. Included patients completed the quality of life (QoL) questionnaires EORTC QLQ C30 and the liver supplement EORTC QLQ HCC18. QoL-data, demographic, laboratory and tumor data were registered as well as treatment plan. Since this was a collaboration study with Oslo and Tromsö in Norway and with Stockholm, a common study Access-database was constructed and data was entered at each site. Last follow-up was performed in December 2015– January 2016.

Paper II was a retrospective review of medical records of all patients who underwent liver transplantation for HCC in Sweden from 1996-2014 (fig 8). Patients were identified in operation and transplant registries in Stockholm and Gothenburg. Patients with incidental tumors, first diagnosed in the explant histology report, were excluded. The latest follow-up data were collected in early 2016.

Figure 8. *Flow Chart paper II*



Paper III was a prospective phase II study on sorafenib as a neo-adjuvant treatment in HCC patients, who were waiting for liver transplantation. Patients were included between November 2011 and August 2014 at Sahlgrenska University Hospital after informed consent. We had two aims; to

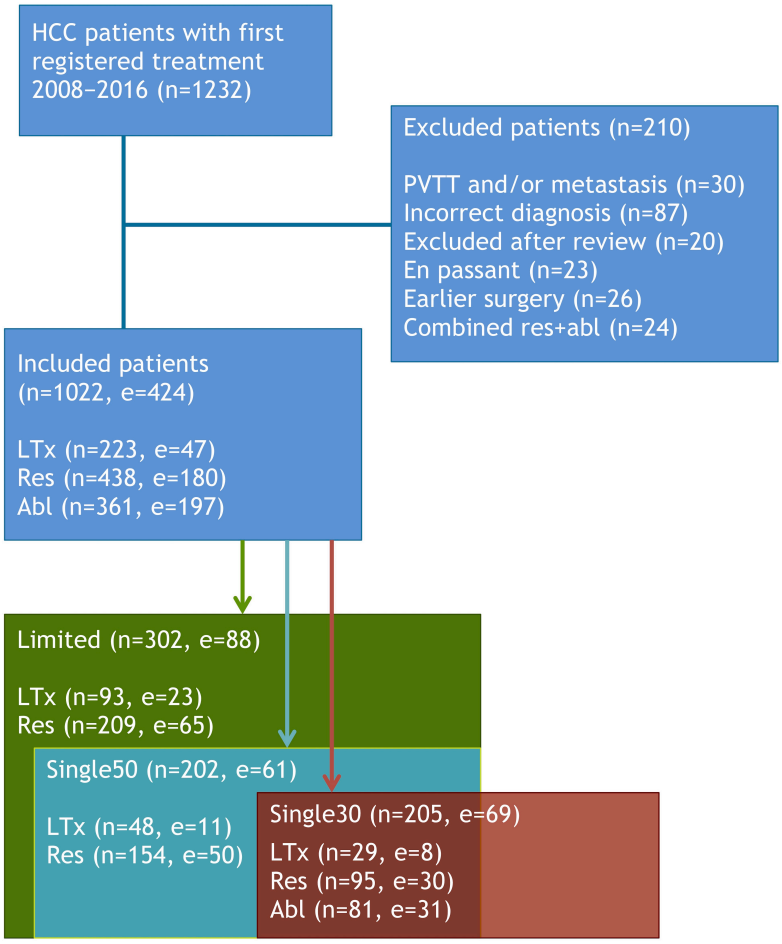
evaluate if early CT perfusion parameters could be used to predict subsequent radiologic tumor response to sorafenib treatment and to assess the feasibility of sorafenib in the neo-adjuvant setting before liver transplantation (tab 3). We used good clinical practice (GCP) standards and had regular external monitoring (Gothia Forum, Gothenburg, Sweden). 14 patients within the UCSF criteria were included, but two were later excluded due to misdiagnosis.

Table 3. Study Schedule Paper III.

	Screening/Baseline	Day 1	1w (+/-2d)	4w (+/-1w)	8w (+/-1w)	12w (+/-1w)	Every 4w on treatment (+/-1w)	Every 8w until tx (+/-1w) or until 2 CTp after terminating study drug	High priority	Before tx	Control after tx (90d)
Written Consent	X										
Medical History	X										
Baseline Characteristics	X										
Perfusion CT	X		X	X		X		X			
QoL assessment	X		X	X		X			X		
Clinical control / lab	X		X	X	X	X	X			X	X
Sorafenib treatment		X	X	X	X	X			stop		
Registration surgical complications											X
AE Assessment	Continuous Monitoring										
Concomitant Therapies	Continuous Monitoring										

In paper IV, patients with a primary curative HCC treatment (transplantation, resection or ablation) registered in SweLiv during 2008-2016, were identified among a total of 2846 patients with a final diagnosis of HCC. Patients without suspected HCC diagnosis before treatment, or with changed diagnosis in the postoperative histopathology report were excluded. Subgroups with limited tumor burden and well-preserved liver function were created according to clinical criteria to achieve more comparable treatment cohorts (fig 9).

Figure 9. *Flow chart paper IV.*
PVTT, portal vein tumor thrombosis, Ltx, liver transplantation; Res, liver resection; Abl, liver ablation; e, events (deaths)



3.2 STATISTICS

Power calculations were performed for paper I and III. To detect changes of 20% in QoL (paper I), with an event rate of 0.5 and 80% power at a 0.05 significance level, 150 observations would be required. In paper III power calculation were performed to detect CT perfusion changes of 30% and indicated that 14 subjects would be sufficient.

Descriptive statistics was used in all studies.

QoL assessment was performed according to the EORTC scoring manual[182]. Items were grouped into domains and converted to scores ranging from 0 to 100. Higher score represent more problems in the symptom scales, while for QLQ C30 functional or global scores, higher scores represent better functioning. Total index scores were calculated as the mean of all domain score for each questionnaire.

Risk factor assessment using Univariate and Multiple Cox proportional hazard regression models were used in paper I, II and IV. In paper II, risk factors for overall survival and recurrence were evaluated**,** while risk factors of five-year mortality were assessed after imputation in paper IV.

Table 4. QoL models

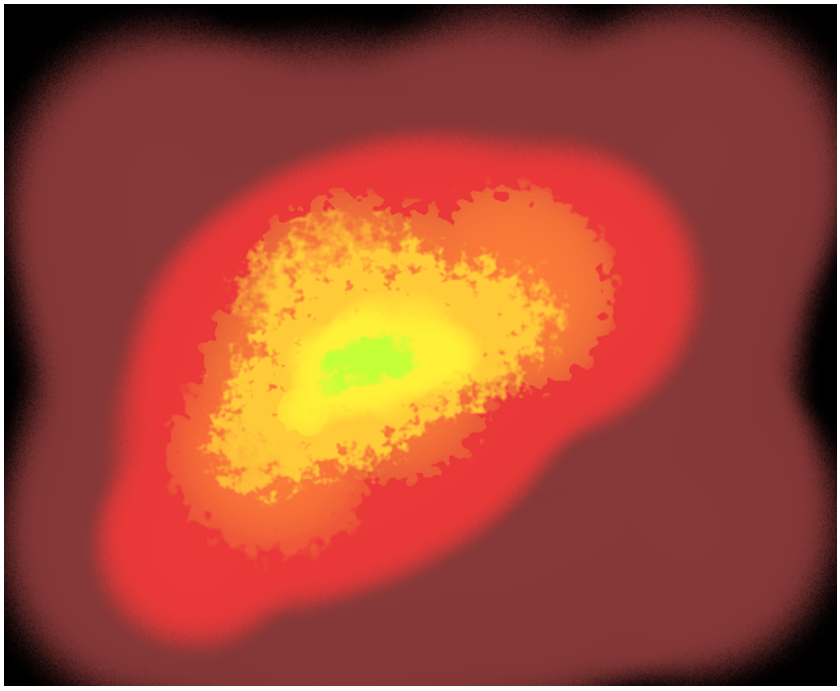
Model	QLQ C30 scores	HCC18 scores	Clinical background variables	BCLC stage	CLIP stage
1	x				
2		x			
3	x	x			
4			x		
5	x		x		
6		x	x		
7	x	x	x		
8	x	x		x	
9	x	x			x

In paper I, hazard ratios (HRs) for mortality were estimated per 20% of each calculated QoL domain score and per level of clinical background variables. Several multivariable models were fitted using stepwise selection to evaluate the prognostic significance of the questionnaire items alone and whether they added prognostic information when combined with non-overlapping clinical factors or established staging systems (tab 4).

Survival estimations: Five-year overall survival rates were estimated using Kaplan-Meier (paper II and IV) and compared using Log-Rank tests (paper IV). In paper II, competing risk evaluation and recurrence-free survival estimation using Kaplan-Meier was also performed.

Other statistical methods: To explore possible thresholds of AFP, the Flexible parametric survival model was used (paper II). The Wilcoxon Rank Sum was used to compare QoL parameters after repeated measures (paper III). The Mann-Whitney U was used to compare demographic factors in excluded patients (paper I).

4 RESULTS



Liver Cancer by Minna Eilard

4.1 QUALITY OF LIFE AS A PROGNOSTIC FACTOR IN HCC (PAPER I)

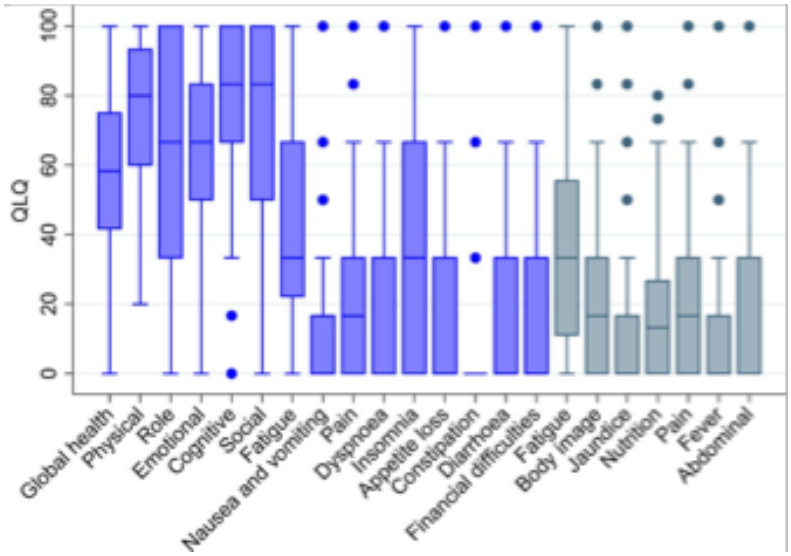
The final cohort of 185 subjects was quite heterogeneous regarding stages, but with a majority of patients in palliative phases, demonstrated by the different treatment plans (fig 10).

Figure 10. *Treatment plan proportions, reflecting the heterogeneity of the cohort*

Mean age was 67 years and three fourths were men. Almost half had tumor stage T3N0M0 or TxN1 or M1 and more than half were staged as BCLC C or D. Liver function was well preserved (Child A) in 70% and performance status was unaffected (ECOG 0) in more than half. The most common comorbidities were diabetes (32%) and cardiovascular disease (24%) and combined comorbidities were found in 36%. The most common etiology of liver disease was hepatitis C (50%) and alcohol (40%) alone or combined. While 74 % of patients had cirrhosis, 19 % did not. The group with unknown status of cirrhosis (7%) had the worst prognosis, which was interpreted as a limited work-up ambition in patients with very advanced disease.

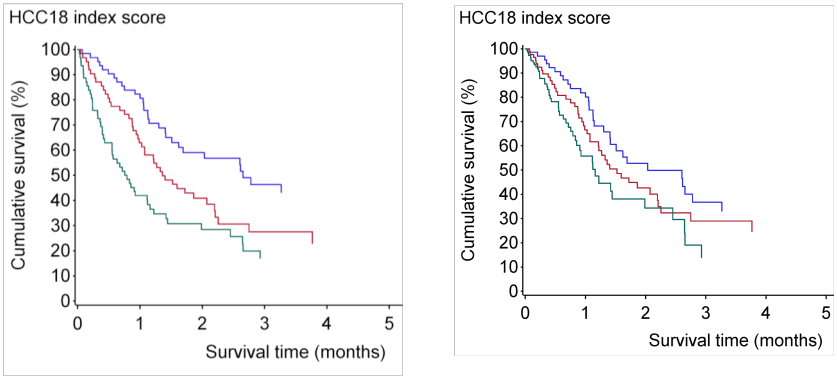
QoL scores varied greatly between individuals. The median QoL scores are presented in figure 11 (paper I). Emotional and role functioning were the most affected scores among functional scales, while deterioration with fatigue, dyspnea, sleeping disorders and abdominal swelling were most common among symptom scales.

Figure 11. *Boxplot of median QLQ variables; blue for QLQ C30 and grey for HCC18. The length of the whiskers equals to 1.5 times the interquartile range and dots are outside values. High scores represent well-being according to functional scales (Physical, Role, Emotional, Cognitive and Social), while high scores in symptom scales, indicate the presence of symptoms (paper I).*



The prognostic role of QoL: Total index scores of each questionnaire were prognostic for survival; C30 HR 1.34 (95%CI 1.10-1.64) and HCC18 HR1.79 (95%CI 1.34-2.39). In unadjusted log rank curves, the survival difference between tertiles of the HCC18 index score was significant ($p<0.0001$) (fig 12, left). When adjusted for age, Child, ECOG, TNM and AFP, the survival difference was borderline significant ($p=0.06$) (fig 12, right). Several QLQ-scales were prognostic for mortality in the age-adjusted Cox analysis. Global health status, physical functioning, role functioning, social functioning, fatigue, nausea and vomiting, dyspnea and appetite loss in the QLQ C30 were significant. Fatigue, body image, nutrition, fever and abdominal swelling in the HCC18 were also noted. However, in stepwise selection, the C30 fatigue (HR 1.32 [95% CI 1.16, 1.50]) and HCC18 nutrition scale (HR 1.51 [95% CI 1.28, 1.79]) were the only significant predictors of each questionnaire respectively.

Figure 12. *Overall survival stratified by tertiles of the HCC18 index score (Fatigue+BodyImage+Jaundice+Nutrition+Pain+Fever+abdominal swelling)/7). The left curves are unadjusted and the difference between groups was significant (p<0.0001). The right curves are adjusted for age, Child, ECOG TNM and AFP. The difference was borderline significant (p=0.06).*



The Prognostic value of QoL-data in addition to clinical factors: Child-Pugh status, ECOG, TNM and AFP levels were significant predictors of death in the multivariable analysis with stepwise selection of background variables. When stepwise selection was performed among the QLQ C30 items added to the background variables, only physical functioning was significant (HR 0.76 [95% CI 0.62-0.94]). The same procedure among the HCC18 scores, revealed only nutrition scale as a significant predictor (HR 1.37 [1.14-1.65]). When all QoL scores were combined, still keeping background variables, the resulting model was identical to the one with background variables and HCC18. The prognostic impact of background variables remained relatively stable when combined with C30 physical functioning or HCC18 nutrition scale.

The prognostic value of QoL data added to established scoring systems: The staging systems BCLC and CLIP were significant predictors of mortality in the age-adjusted analyses. Keeping age and either BCLC or CLIP scores, stepwise selection was performed among all QoL variables. When added to BCLC, the HCC18 nutrition scale turned out to be a significant predictor and improved the prognostic accuracy of that model according to Harrell's C-statistics and the Akaike information criterion (AIC). In the model combining QoL with CLIP, both the C30 fatigue and the HCC18 nutrition scale were significant and improved that model correspondingly.

4.2 ADDITION OF AFP TO TRADITIONAL CRITERIA IMPROVES SELECTION ACCURACY IN LIVER TRANSPLANTATION (PAPER II)

This study included 136 patients who underwent liver transplantation for HCC 1996 - 2007 (old cohort) and 200 patients 2008–2014 (new cohort). 163 transplantations were performed in Stockholm and 173 in Gothenburg. The causes of liver disease were registered only in the new cohort and there were often more than one; hepatitis C in 63%, hepatitis B in 11%, alcohol in 32%, NASH in 6% and autoimmune or primary biliary liver disease in 5%. Eight patients underwent transplantation because of HCC recurrence after a previous liver resection.

At follow-up, 137 (41%) patients had died and mean follow-up time for patients still alive was 5.3 years. Estimated 5yOS in the entire cohort was 62%. Tumor recurrence was diagnosed in 79 (24%) after a median time of 11 months, while recurrence status was unknown in nine patients (2.7%). Estimated five-year recurrence-free survival (5yRFS) was 61%

Tumor factors: More than half (53%) had single tumors. Two, three or more tumors were seen in 26%, 11% and 11% respectively. Median diameter of the largest tumor was 34 mm and 77% had tumors less than 50 mm. Median total tumor diameter was 44 mm, but 31 (9%) had a total tumor diameter of 100 mm or more. According to imaging before any tumor treatment, Milan criteria were fulfilled in 61% with a 5yOS of 70% (5yOS outside Milan 51%). UCSF criteria were fulfilled in 257 (76%) with a 5yOS of 66% (5yOS outside UCSF 50%).

Neo-adjuvant treatment was only evaluated in the new cohort (2008-2014), since such treatments were registered in very few patients in the older cohort, and then non-established study treatments, such as systemic doxorubicin were being used. In the new cohort, neo-adjuvant treatment was given in 110 patients (55%) and 26 patients of these were initially outside UCSF criteria. The most common treatment was TACE, alone (n = 63) or combined with other treatments (n = 19). In this pretreated subgroup, traditional criteria did not discriminate well, neither based on imaging before neo-adjuvant treatment nor after.

AFP-levels: Median AFP-levels were 23 ng/mL (range 1 – 48300). Almost half (48%) had near normal levels (<20) and 72% had levels <100ng/mL.

Decreasing 5yOS rates and a progressive risk increase for death were observed with higher AFP-levels (Table AFP-levels). Similar patterns were seen for AFP (tab 5) in multivariable Cox models including Milan and UCSF fulfillment, time period, or other tumor variables (tumor number and largest diameter or total tumor diameter).

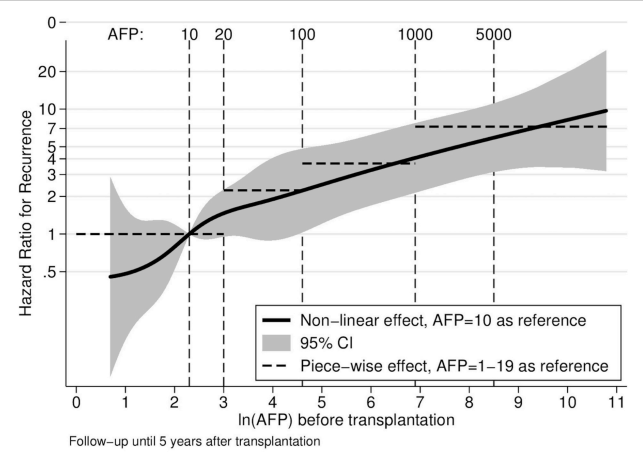
Table 5. Outcome and risk depending on AFP-level

AFP-levels (ng/mL)	n	5yOS[a]	HR[b]	p-value	95% CI
<20	159	74	ref	-	-
20-99	79	61	1.67	0.047	1.01–2.77
100-999	56	51	2.45	0.001	1.48–4.05
≥1000	34	31	4.28	<0.001	2.52–7.28

[a] Estimated according to Kaplan-Meier
[b] Univariate Cox Regression regarding five-year mortality

We did not identify any AFP cut-off level, but rather a continuous risk increase for death and tumor recurrence even with slightly increased levels (fig 13). Five-year tumor recurrence rate was 12% with AFP-level 0–19 ng/mL compared to 26% with AFP-level 20–99 ng/mL.

Figure 13. *Continuous risk increase for tumor recurrence with higher AFP-levels (paper II)*



In the pretreated subgroup, the prognostic value of AFP measured before neo-adjuvant treatment was not significant, while post-treatment, pre-transplant AFP of 100–999ng/mL was a significant risk factor for mortality (HR 4.84 [1.90–12.34]) and recurrence (HR 5.60 [1.93–16.23]) (univariate analysis). Therefore post-treatment AFP levels were used in all analyses.

Combined score: The risk increase seen with higher AFP was independent of the risk depending on traditional criteria fulfillment. To improve prognostic accuracy, a combined score was created, with AFP and traditional criteria categorized into three risk levels each (low risk 0 points, intermediate risk 1 point and high risk 2 points). The combined score (0–4 points) was achieved with the sum of points (criteria + AFP). A generous cut-off was chosen, excluding only patients with at least one "high" risk and one "intermediate" risk factor.

When this score was used in the entire cohort, 294 out of 327 would be transplanted, compared to the 257 accepted with our currently used UCSF criteria and 203 patients within Milan.

Table 6. Combined Score. Numbers and risks depending on the combination of Milan/USCF fulfillment and AFP-level.

Criteria ↓	**AFP-level →** (ng/mL)	**0-99** 0p	**100-999** 1p	**1000-** 2p
MilanIn	N	157	31	15
	5yOS	75%	65%	40%
	5yTumorRec	9%	26%	49%
0p	Score	0p	1p	2p
MilanOut UCSFin	N	31	11	7
	5yOS	62%	42%	29%
	5yTumorRec	20%	33%	71%
1p	Score	1p	2p	3p
UCSFout	N	49	14	12
	5yOS	61%	32%	25%
	5yTumorRec	39%	57%	42%
2p	Score	2p	3p	4p

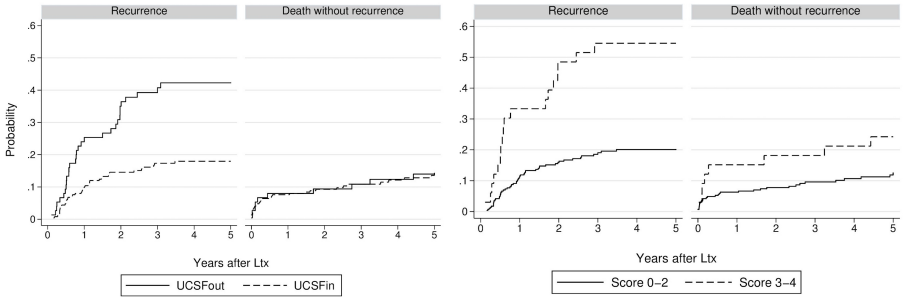
Estimated 5yOS in patients fulfilling our score (0-2) was 67%, which was quite similar to patients within the UCSF. Patients outside this score (n=33) had a 5yOS of 29%, compared with 50% for the patients outside the UCSF. Patients outside Milan, but within our score (n=91) had a 5yOS of 59% and a tumor recurrence rate of 32% (tab 6). In the new cohort, 5yOS for 182 patients with a score of 0-2 was 76% compared with 17% for 14 patients with a score of 3-4.

There were 75 patients with a score of 2, with three different risk profiles; UCSFout + AFP 0-99, MilanoutUCSFin+ AFP 100-999 and MilanIn + AFP ≥1000. In the entire cohort 5yOS was 54% in patients with a score of 2 (61%, 42% and 40% respectively). Results were generally better in the new cohort.

Five-year cumulative incidence of tumor recurrence increased with higher scores; Score 0 9%, score 1 23 %, score 2 40% and score 3-4 55%. In the new cohort, recurrence rates for 181 patients with score 0-2 was 14% compared with 64% for 14 patients with score 3-4.

Competing risks (cumulative incidence of tumor recurrences and of deaths without recurrence) were compared for patients inside and outside the UCSF and within and without the combined score cut-off (fig 14). Patients outside the score cut-off had a higher rate or tumor recurrence, but also a higher rate of death without recurrence.

Figure 14. *Competing risks depending on fulfillment of UCSF and Combined score (paper II)*



The score increased selection accuracy in both treated and untreated patients of the new cohort compared with traditional criteria. Accuracy was best in the untreated patients, with 5yOS of 80% with score 0-2 and 14% with score 3-4, while in patients with neo-adjuvant treatment the corresponding 5yOS rates were 73% and 21%. Recurrence rates were correspondingly 12% and 71% in the untreated and 15% and 57% in patients with neo-adjuvant treatments.

4.3 NEO-ADJUVANT SORAFENIB TREATMENT IN PATIENTS WITH HCC WAITING FOR LIVER TRANSPLANTATION (PAPER III)

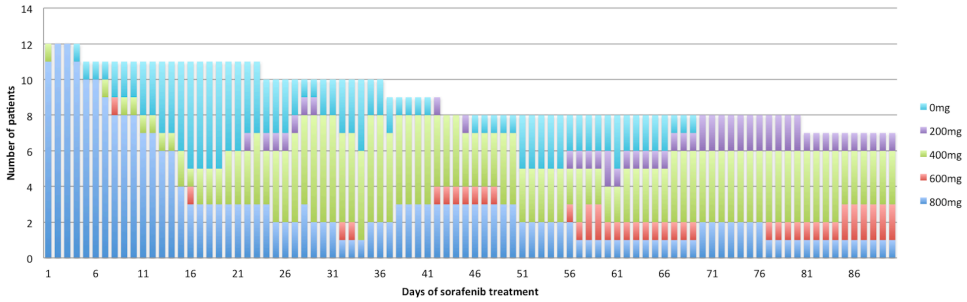
We included 14 patients according to inclusion and exclusion criteria in this prospective study. Two patients were excluded from most of the analyses due to misdiagnosis. One patient underwent transplantation quickly after inclusion and received only one dose of sorafenib treatment. The explant histology report revealed a different type of cancer and this patient was not included in any analysis. In the second excluded patient, the malignant diagnosis was questioned after repeated CT evaluations and no transplantation was performed. Since sorafenib treatment had been given for a period of time, we included this patient in the adverse event assessment (n=13), while the other analyses were done in the remaining twelve patients.

At inclusion, median age was 55 years and nine were men. All twelve fulfilled the UCSF criteria and one was outside the Milan criteria. One patient had no cirrhosis, but fibrosis and hepatitis B. The etiology of cirrhosis in the others was hepatitis C in eight patients and hepatitis B in one, while alcoholic liver disease alone or combined with hepatitis was reported in five patients. No other comorbidity was reported in six patients, while four had hypertension, two had diabetes and one had pulmonary disease. ECOG performance status was 0 in seven and 1 in five patients. Eleven patients had Child-Pugh score A (five patients had 5 points and six patients had 6 points) and one patient had Child-Pugh score B (7 points). Nine patients had inclusion AFP-levels of <100 ng/mL and seven patients had single tumors. The median longest and total tumor diameter at baseline was 25 and 26 mm respectively (n=11). The mean tumor longest diameter was 28±11 mm at baseline and 30±11 mm at 12 weeks. The longest and total median tumor diameters according to explant histology were 43 and 50 mm respectively. The explant histology revealed one case of mixed type HCC with cholangiocellular differentiation, one case of macrovascular invasion and one case of undifferentiated HCC (Edmonson-Steiner 4).

Study treatment and tumor response: Patients started sorafenib treatment after a median of 70 days from HCC diagnosis. Treatment was continued for a median of 155 days, including temporary treatment breaks. Dose modifications were required in ten patients and treatment pauses in nine (fig 15). Mean daily dose was 474 mg. Median time with active treatment was 103 days and after 12 weeks five patients had stopped sorafenib treatment. Six patients stopped due to side effects, while four stopped according to

protocol because they had reached priority on the waiting list. Two patients stopped sorafenib because of HCC progression, which was also noticed in one of the patients who was treated until prioritized on the waiting list.

Figure 15. *Overview of daily doses of sorafenib during the first 90 days of treatment, reflecting frequent dose modifications and treatment pauses.*



Patients with tumor progression while on treatment had a mean treatment time of 30 weeks and their median time to progression was 20 weeks. Mean time of treatment was only 10 weeks in patients with stable disease while on treatment.

CT perfusion parameters: Initially, the perfusion parameters Blood Flow (BF) and Arterial Blood Flow (AF) of the HCC lesions were significantly higher than the respective values of surrounding liver parenchyma. After one week of sorafenib treatment, the mean values for Blood Volume (BV), BF and Hepatic Arterial Fraction (HAF) were lower in tumors as well as in the liver parenchyma, while the mean values for Mean Transit Time (MTT) and Permeability Surface (PS) were higher than at baseline, but the differences were not statistically significant. After 4 and 12 weeks the values tended to regress to the baseline.

Tumor responses: Seven patients had stable disease (SD) according to RECIST and mRECIST response evaluation 12 weeks after start of treatment, while three patients had progressive disease (PD), and two could not be evaluated. Patients with PD had significantly lower mean BF (80.5±13.3 vs 241.3±162.4 ml/100 g/min) and AF (27.1±18.9 vs 105.0±92.0) at baseline than patients with SD.

No correlation was registered between perfusion parameters at baseline or changes after one week and the growth of the longest diameter after 12

weeks. Median time to progression according to both RECIST and mRECIST was 20 weeks.

Adverse events and liver toxicity: The patients experienced between 4 and 13 adverse events during the sorafenib treatment, with a median number of 10. Three patients had at least one adverse event grade 3, but there were no serious adverse events. There was no significant impairment in lab parameters during treatment. Some variation in Child–Pugh score was seen, but never a score higher than 8. Dermatology disorders were seen in 11 patients after a median of 15 days. Fatigue and pain was seen in nine patients after a median of seven and nine days respectively. Diarrhea or related disorders were registered in eight patients after a median of 61 days.

Quality of Life: QoL scores during treatment varied between patients, but mean values were most impaired at one week after starting treatment in several QoL domains. Significant differences compared to baseline were observed in the C30 domains Nausea and Vomiting ($p = 0.043$), Appetite Loss ($p = 0.008$), and Pain scores ($p = 0.045$). A similar but non-significant pattern for the C30 Global health, Physical, Social, Role, Cognitive functioning, and the HCC18 domains of Fatigue, Fever and Pain was also observed. The highest symptom burden appeared later for the HCC18 Nutrition scale (4w), and for C30 Diarrhea (8w), though the changes were not significant.

Transplantation and Complication Rates: All 12 HCC patients underwent transplantation after a median of 231 days (range 81–515) from inclusion and of 86 days (range 4–462) from sorafenib withdrawal. At 90-day follow-up after liver transplantation, 11 were registered with a complication at least grade 1 according to Clavien-Dindo. The most serious complications were grade 3b, which occurred in two patients. One had a cardiac arrhythmia treated by electrocardioversion and both developed pseudoaneurysms of the hepatic artery after treatments for rejection and bile leakage.

Survival and recurrence: The patients who remained alive at the end of the study had a median follow-up of 1200 days. Two-year survival rate was 83% and the Kaplan-Meier estimated five-year survival was 56%. Tumor recurrence occurred in five patients after a median of 401 days (range 122-744).

4.4 TRANSPLANTATION, RESECTION AND ABLATION IN PATIENTS WITH EARLY HCC AND WELL PRESERVED LIVER FUNCTION (PAPER IV)

Entire cohort: 1022 patients with primary transplantation, resection or ablation were included in this study. Median follow-up time was 4.4 years. Most resection patients had single tumors and nearly half had no known underlying liver disease. Patients in the resection group had the largest tumors with a mean diameter of 61 mm, compared to 32 mm and 25 mm in the transplantation and ablation groups respectively. Patients were younger and had worse liver function in the transplantation group. TACE was planned in 79 patients (35%) and 29 (13%) received other treatments before transplantation. ASA class 3 or 4 was more common in the ablation group, as was alcohol etiology.

Kaplan-Meier estimated 5yOS, adjusted for age and gender, was 78.3% (CI 72.0-85.2), 57.3% (CI 51.5-63.8) and 36.5% (CI 30.2-44.3) respectively after transplantation, resection and ablation. AFP >100 was a risk factor after transplantation and resection, but significance was not reached in the ablation group (Univariate Cox). In the multiple Cox Regression models, AFP >100 was associated with an increased risk in the transplantation group, while ASA 3-4 was associated with an increased risk in the resection group and Age and Tumor Number >1 in the ablation group. For liver function variables (Child >5, Albumin <36, Bilirubin >26), an interaction effect was noticed both in the univariate and multiple Cox analyses. Worse liver function was associated with a decreased risk in the transplantation group, but an increased the risk in the other groups.

Subgroups with limited tumor burden and liver function Child A: Demographic differences between the treatment cohorts were reduced, but did not disappear in the selected groups.

The Limited-group included 302 patients with tumors corresponding to the UCSF criteria (single tumors $\leq$65 mm or $\leq$3 tumors of $\leq$45 mm). Estimated 5yOS, adjusted for age and gender, was 73.8% (CI 63.8-85.3) in 93 patients after transplantation and 65.3% (CI 57.3-74.5) 209 patients after resection (fig 16). The difference in survival was not significant according to the Log rank test (p=0.431). Only AFP >100 was significantly associated with five-year mortality in the Limited-group (HR 2.05, CI 1.27-3.29), while the

factors with unequal distribution between the treatments were not (univariate analyses). Survival rates were not affected by the presence of an underlying liver disease, neither in the total cohort, nor the Limited-subgroup.

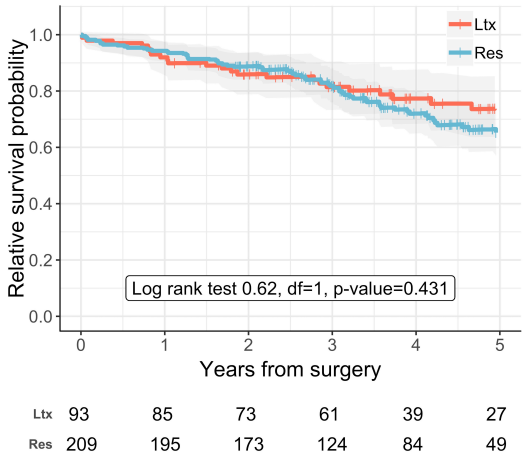
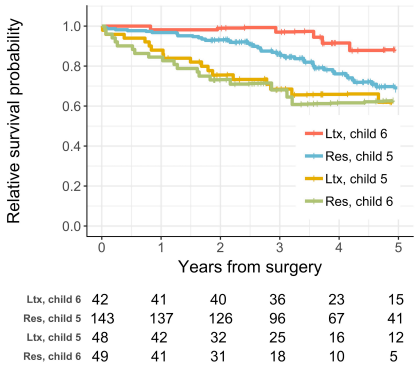


Figure 16. *5yOS in the Limited-subgroup including patients with Child A and single tumors ≤65 mm or ≤3 tumors of ≤45 mm (adjusted for age and gender)*

Separate analyses for each treatment in the Limited-group revealed an interaction effect regarding liver function variables (Child >5 and Albumin ≤36, but not significant for Bilirubin ≥26) (fig 17), similar to the total cohorts. Though planned TACE was a confounder and previous anti-tumor treatment tended to be, we found no sufficient explanation for the risk difference between transplanted patients with Child A5 and A6 respectively.

Figure 17. *Interaction effect of Child A5/6 on 5yOS in the Limited-subgroup*



In the multivariate models of the Limited-group, compound variables were created for patients with resection-Child A5 and resection-Child A6, while all Child A transplantation patients were analyzed together, so as not to emphasize a possible chance effect. A significantly increased risk was seen in patients with resection and Child A6 or Albumin <36 compared to transplantation, but not with resection and Child A5 or Albumin ≥36. AFP> 100 remained a significant risk factor in the multiple Cox models and ASA 3-4 improved the model when including albumin level, though it was not a significant factor itself.

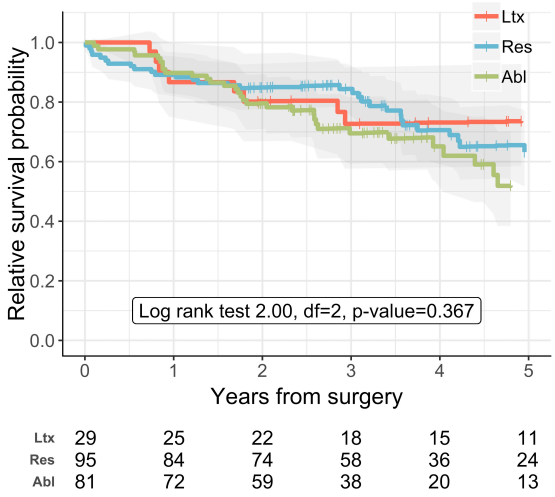


Figure 18. *5yOS in the Small30-subgroup including patients with Child A and single tumors ≤30 mm (adjusted for age and gender)*

The Single30-group included 205 patients with single tumors of no more than 30 mm. Estimated 5yOS, adjusted for age and gender, was 73.6% (CI 58.4-92.8), 63.9% (CI 52.3-78.0) and 52.0% (CI 38.5-70.1) respectively in the transplantation, resection, and ablation groups (fig 18). Log rank test did not show any significant survival difference between the treatment groups (p=0.367). ASA 3-4 was more common among ablation patients, who were included in addition to patients with transplantation or resection in this subgroup.

5 DISCUSSION

Real life patient cohorts are heterogeneous, and with prognostication as a main theme in this book, the impact of selection on risk factor profiles has been made very clear, both in selection of the cohort and of studied variables. The more heterogeneous the cohorts, the more risk factors will influence outcomes and confound results. Therefore several steps of stratification might be needed to assign individual patients the most optimal treatment plan. First, among all stages, and then within each stage.

We evaluated prognostic factors in different settings of HCC, from the general prognostic value of QoL in a mixed cohort to a very specific suggestion of how to use AFP for transplantation selection.

Quality of Life

QoL measures have often been regarded as subjective or "soft" parameters, and less reliable than other clinical factors. In our study several functional scales and symptom scores of the QLQ C30 and HCC18 were prognostic for mortality. These findings and previous studies show that QoL measures, though variable between individuals, have prognostic value and are reproducible.
However, for QoL measures to be useful, one needs to be aware of how they correlate to clinical parameters. In some settings, QoL measures might replace clinical data, while in others, they could complement clinical factors. This was demonstrated by the prognostic significance of the total index scores of both C30 and HCC18. The unadjusted scores stratified survival, reflecting some of the clinical factors, while a small residual prognostic ability demonstrated the additional value of QoL (fig 12). The prognostic impact of such index scores was even higher in a larger cohort, with more advanced tumor stages, where total scores discriminated five groups with different survival rates[183]. Such measures have the potential to be used in registries or for research, since patients are stratified without knowledge of clinical factors and could be assessed at distance by digital techniques.

Performance status, measured by ECOG, is an important factor for treatment decision-making and an obvious prognostic factor for survival. However, ECOG is subjectively assessed and significant differences depending on the setting have been described[184]. ECOG is frequently overlooked when deviations from treatment recommendations are made[185]. Although QoL

questionnaires are also subjective, they reflect the patients' perspective rather than the opinion of the physician, which could be an advantage[186]. Moreover, for repeated measures, the same individual always assesses patient-reported QoL whereas ECOG is frequently assessed by different physicians. The QLQ C30 was early reported to be prognostic in patients with different advanced stage cancers[187], and the C30 physical functioning scale was specifically correlated to performance status in patients with hematologic malignancies[188]. In patients with colorectal cancer, C30 physical functioning was reported to be more prognostic than performance status[186].

In our study, the addition of the C30 physical functioning scale improved prognostic accuracy when added to clinical factors, which was consistent with previous reports[172, 173]. The best independent predictors were the QLQ C30 fatigue and HCC18 nutrition scales. However, in models including ECOG, the significance of C30 fatigue consistently disappeared, suggesting collinearity. Whether ECOG could be replaced by physical functioning or fatigue score remains to be investigated, but collinearity is important to consider when the value of individual prognostic factors in general and QoL scores in particular are assessed, as the various QoL scales often correlate to clinical factors.

With a limited size of the cohort, we focused on the overall prognostic value in a cohort with mixed HCC stages, and did not perform subgroup analyses. However, with the wide range of treatment strategies, the development of tools for accurate individualized prognostication within stages is warranted. QoL assessment is accessible, standardized, low-cost, and non-invasive, and has the potential to add relevant prognostic information that could discriminate patients within stages. In a recent study, survival after resection for HCC was significantly prognosticated by dichotomized FACT-Hep score, but not by ECOG[189]. In patients with infiltrative HCC, portal vein thrombosis and SIRT treatment, SF-36 normalized physical component summary score predicted overall survival and time to progression[190].

Since symptoms are unusual in early HCC stages, functional QoL scales might offer complementary prognostic information in those patients, while symptom scales might be important in more advanced stages. Four previous studies evaluated the QLQ C30 for prognostication[172, 173, 183, 191], of which two also used the HCC18[183, 191]. One cohort was quite similar to ours regarding tumor stages and Child proportions[172], while two included more advanced tumor stages, but similar Child[173, 183] and one study described earlier tumor stages, but worse Child scores[191]. Mean values of the functioning scales were quite similar and consistent with the cohorts including similar or worse tumor

stages[172, 173, 183]. Among the HCC18 scales, fatigue and abdominal swelling rendered the highest scores in our study, as well as in a more advanced tumor cohort[183]. In the study including earlier BCLC stages, the mean values were highest for sexual interest and body image[191].
High mean values were repeatedly reported for C30 symptom scales of fatigue, pain, insomnia and financial difficulties[173, 183, 191]. We observed a similar pattern, although the mean values for financial difficulties were lower. This could be related to the favorable social welfare system in Sweden and if so, highlights the impact of external factors.

Unlike previous studies[172, 183, 191], the pain item was not prognostic in our study, which might be due to confounding by misclassification, as some patients reported pain not related to HCC, such as joint pain. This emphasizes the importance of questions that cannot be misinterpreted and that lead to defined responses, which is especially important for digital use, when patients have no one to ask for clarification.

The benefit of standardized digital patient monitoring was demonstrated in patients with solid tumors and palliative chemotherapy in a randomized controlled trial comparing standard care with online self-reporting of common symptoms or side effects[192]. Longer palliative treatment duration, better QoL, and fewer emergency visits were seen in the intervention group and the five-year survival rate was 8% higher than in the usual care group. However, more research is needed to identify which questionnaires and domains are useful depending on disease stage and clinical setting.

AFP

Unlike QoL and performance status, AFP is an objective measure. The prognostic value in different settings has been described previously[38, 193], yet is not much used in treatment decisions. In Paper IV, AFP was a risk factor for mortality after transplantation, but since the trend was similar after resection and ablation, the choice between those treatment modalities could not easily be guided by the AFP-levels. In paper II, AFP was prognostic for five-year overall survival and tumor recurrence both in the univariate analyses and when tumor factors such as fulfillment of Milan/UCSF criteria, tumor size and number were included, which is congruent with previous findings[58, 98]. However, in our limited cohort results were not significant when using initial AFP levels, mostly around the time of diagnosis and before neo-adjuvant treatments. This finding emphasizes the importance of

AFP timing, which is congruent with previous reports[194-196]. Early AFP-registration, generally around the time of diagnosis, as in the SweLiv registry, might hamper the prognostic utility of AFP-data for sequential treatments. Also, in our study and others[197], the prognostic impact of AFP on tumor recurrence rate was higher than on overall survival, which is logical because unrelated causes of death would decrease the accuracy.

As many different cutoff levels for AFP have been suggested[198], we evaluated if a threshold level of AFP could be identified, but found an incremental risk increase with no natural cut-off. Which level to be used therefore, depends on the setting. AFP levels of 100, 400 and 1000 ng/ml have been proposed for exclusion of high-risk patients from transplantation[100, 199, 200, 195], while near-normal levels identified patients with favorable prognosis outside traditional criteria[57]. The aim of the combined score in paper II was neither to exclude patients, nor to transplant more, but rather to achieve more accurate selection, transplanting more patients without recurrence and excluding more with recurrences. We therefore wanted to take advantage of the continuous risk increase associated with increasing AFP levels, using more than one cut-off for transplantation selection. This strategy was used previously[113, 201, 202]. The French AFP model[202] has been validated repeatedly[203, 204], but is rather strict, excluding some patients within the Milan and AFP <1000. The MetroTicket2.0 is an update of the Up-to-Seven criteria, utilizing several AFP-levels[113].

The combined score was based on the Milan and UCSF criteria, since they are familiar in our practice. Adding a cutoff level for AFP to the Milan criteria[58] or the UCSF and Up-to-seven criteria[205] has also been shown to increase prognostic accuracy. The addition of AFP is an easy and available way to achieve some improvement, even if more refined criteria, including factors such as neo-adjuvant responses, might be desirable in the future. The combined score was constructed to be easily adopted in our clinical routine. Besides its simplicity, an advantage with the proposed score is that its construction permits monitoring of defined subgroups (tab 6). If outcome becomes worse for any subgroup with higher risk (score 2), MilanInAFP>1000 or MilanOutUCSFinAFP100-999 or UCSFoutAFP<100, then criteria can be easily adjusted. Compared to the presently used UCSF criteria, the transplantation rate would hardly be affected with combined score since only a very small number of patients would be excluded (inside the UCSF, but outside the Milan criteria and with AFP >1000). It would also be easy to adjust either tumor or AFP categories if results are not satisfactory. A system that adds scores of independent risk factors takes advantage of the prognostic information within each stage (like the Child-Pugh, MELD, CLIP,

ItaLiCa and Up-to-seven), whereas hierarchic systems (such as TNM, BCLC and HKLC) exclude any impact of factors within specific stages, resulting in loss of some prognostic information.

AFP levels alone stratified outcome almost as well as our combined score did in this study. However, the cohort was already selected based on traditional criteria, and many patients categorized outside criteria were close to the limit, which reduced the discriminative significance of those criteria. For the same reasons it is precarious to generalize the good results of the subgroup outside the UCSF and low AFP parameters. What is the upper limit of tumor burden among such patients? A few studies have suggested that criteria, using factors other than size and number, can yield good results. The extended Toronto criteria include patients without metastases and vascular invasion in the absence of symptoms and with ECOG 0, given that poor tumor differentiation has been ruled out by biopsy in patients outside the Milan. In that cohort, AFP stratified outcome and 5yOS was 75% in patients with AFP <500[206]. In patients beyond the Milan, including patients with portal vein invasion and diffuse tumors, an interesting score based only on the biomarkers AFP and PIVKA-II, was reported with 5yOS and 5yRFS of 83% and 66% respectively[126].

Improved outcome after liver transplantation for HCC has been demonstrated in patients with neo-adjuvant treatments, irrespective of treatment response [100, 207]. However, such treatments complicate the assessment of tumor burden, even when measuring only contrast-enhancing foci, according to the modified RECIST criteria[107]. In paper II, the assessment of contrast-enhancing tumor burden after neo-adjuvant treatment was difficult and imaging after the last treatment was sometimes missing. We therefore used tumor measures before neo-adjuvant treatment, which could explain the limited discriminative value of criteria fulfillment. However, even baseline radiographic assessment of tumor burden often diverges from histopathology reports[53] and these difficulties emphasize the advantage of simple measures such as AFP.

In the most recent study cohort (2008-2014), our combined score discriminated outcome for patients without neo-adjuvant treatment over pretreated patients, in whom AFP levels were more significant. Although complete radiologic response and extended tumor necrosis according to histopathology has been associated with improved outcome, this was not evaluated in our study[208, 209].

The need for multiple treatments may be a warning sign of unfavorable tumor

biology[100, 210] and an increased risk for lymphatic metastases in patients with partial tumor necrosis has been suggested[211]. Recently it has been suggested that lesions should count as fully active even if only a small part shows contrast-enhancement and washout, whereas lesions with complete response should not count[113]. Although radiologic treatment response was not properly evaluated according to mRECIST in our study, low survival rates were noticed in patients given priority due to tumor progression, who received antitumor treatments without radiologic response evaluation or evaluation of AFP prior to transplantation. The role of treatment response in transplantation selection needs to be better defined, but it is already clear that HCC-patients awaiting liver transplantation need to be closely monitored with objective measures, and that treatment decisions should be reevaluated continuously.

CT perfusion parameters

Prognostication of treatment response using perfusion CT was the primary end-point in paper III. Baseline blood flow (BF) and arterial blood flow (AF) were significantly higher in patients with stable disease (SD) than in patients with progressive disease (PD). This is consistent with the increased survival rate associated with higher arterial tumor perfusion[212-214]. Lower arterial perfusion after one week of sorafenib treatment was reported in patients with advanced HCC[212]. However, in our study, we found no changes in perfusion parameters during sorafenib treatment that could predict tumor response according to RECIST/mRECIST, tumor growth or tumor recurrence after liver transplantation.

We followed international guidelines and the intra-observer agreements were good, but the perfusion parameter results might be impaired by the lack of motion correction, which only allows large individual changes to be detected with breath-hold CT of HCC[215]. Also, though power calculations had been done, our sample size was limited compared to other studies[212-214].

With the small patient number and lack of controls, we did not intend to evaluate treatment efficacy with regard to tumor recurrences after transplantation. Nevertheless, five tumor recurrences in 12 transplanted patients was very disappointing, noting that 11 out of 12 fulfilled the Milan criteria at inclusion. Some explanations were found in the post-transplant histopathology, with cases of macrovascular invasion and cholangiocellular differentiation. Still, we cannot but interpret this as an unfortunate selection

of a small cohort, which is to be kept in mind when small cohorts render positive results.

Transplantation, Resection, or Ablation and Prognostic factors

Discrepancies between preoperative findings and histopathology are well described[53, 216], and many studies therefore include histopathology features in the risk assessment to find significant associations. However, only preoperative factors are available at the time of treatment decision-making, and consequently only preoperative factors were considered when risk factors of five-year mortality after transplantation, resection or ablation were evaluated in paper IV. Liver resection remains the gold standard of treatment for patients with liver cancer. Although liver transplantation yields high five-year survival rates, the few available donor livers should be reserved for those patients who are in greatest need.

The demographic data of the three cohorts including primary transplantation, resection, and ablation were different, reflecting current treatment guidelines. The risk factors in the respective treatment cohorts were mostly consistent with the current literature and corresponded to these differences. However, the pronounced interaction effect of liver function was unexpected. We hypothesized that patients with more advanced tumors were transplanted despite good liver function, but the interaction effect remained after adjustment for registered tumor characteristics in the multivariable analyses.

With the relatively balanced transplant waiting list situation in Sweden, we have had generous transplantation indications for HCC, due to the reported high risk for tumor recurrence after resection. Although we do not yet use DCD livers for transplantation in Sweden, the principle to use extended donor livers for low-MELD HCC recipients exists[23]. The idea of this study was raised when a patient with well-preserved liver function and early HCC, assigned for transplantation rather than resection due to the superior outcome rates, died shortly after transplantation with an extended donor liver. Livers from extended criteria donors have been associated with an increased rate of HCC recurrences[217] and the use in low-MELD recipients has been questioned[218]. Still, the overall effect of using extended donors appears to be beneficial, as more patients get transplanted[219]. Again, the balance depends on the selection of both the donors and recipients, which is why we initiated the current study. Even in larger centers, randomized studies comparing transplantation and resection are not feasible, and we therefore chose to

explore national registry data. We outlined subgroup criteria to identify patients eligible for both transplantation and resection, such as well-preserved liver function (Child A) and limited tumor burden, within transplant criteria. The second subgroup was created as resection is often advocated in patients with single tumors, but due to similar results and limited numbers, we chose to focus on the first subgroup.

We did not quite achieve subgroups with equal demographics, although more similar than in the total cohorts. Patients were older in the resection cohort, which was adjusted for in both multivariable and survival analyses. More patients had single tumors in the resection group, but this was not a significant risk factor in this cohort and analyses of the second subgroup, including only single tumors, yielded quite similar results. We included only Child A patients according to resection recommendations. Yet the more detailed liver function variables in the respective treatment groups were not equal, and affected the five-year mortality with a significant interaction effect.

Both preoperative bilirubin[220-222] and albumin levels[221, 223, 224] have been associated with decreased long-term survival after resection. A new risk score combining these, the ALBI grade, was recently proposed to stratify Child A patients into two groups with different survival expectancy[225]. The value of ALBI has been validated in several settings, including resection, TACE and sorafenib treatments[226, 227]. An increased mortality risk after resection in patients with Child A6 compared to Child A5 was described in the presence of portal hypertension[224], but mostly, the discriminative ability of Child A5 versus A6 in Child A patients was not evaluated[226-228]. It has been postulated that tumor burden impacts outcome more in the early years after resection, whereas liver function variables have an increased impact on the longer run[117].

Whether transplantation is really superior to resection has been frequently debated[127, 128, 220, 229]. Studies in patients with limited tumor burden still reported better outcomes with transplantation[127, 128, 230, 231]. However, liver function was usually not described in detail, merely as “Child A” or “MELD<12”. When liver function was considered in addition to tumor burden, survival differences were reduced[232-235]. The dropout risk while waiting for transplantation also favors resection, since impaired intention-to-treat survival after transplantation has been reported[127, 220, 229, 231]. In our study, patients with limited HCC and Child A5 had an almost similar five-year mortality risk after resection as patients with Child A and transplantation. Albumin with a cutoff at 36 was also a significant factor with interaction

effects. This emphasizes that detailed liver function consideration is of major concern for treatment decisions. HCC subgroups with very well-preserved liver function have good prognosis after resection, and do not benefit from transplantation, whereas patients with increasing liver function impairment have an increasing transplantation benefit. Where to draw the line is a complex matter, taking into account the number of available donor livers, other transplant candidates on the waiting list, and perhaps also HCC patients with more advanced tumor stages on the verge of transplantation selection criteria. This complexity is demonstrated by the different recommendations in current guidelines from Europe, the USA, and Asia[89]. In Asia, resection is the standard of care, even in Child B patients, whereas in Italy and Germany, transplantation is recommended in all patients within the Milan criteria.

Lately, the matter of transplantation benefit has been highlighted[236, 237]. Even if results after transplantation are better in groups with small tumor burden and low risk of recurrence, these patients might do nearly as well with alternative treatments such as resection or ablation[23]. Outcome after transplantation in >2500 patients with HCC and Child A was compared to outcome after resection and ablation, based on a systematic literature review. At 5 years, the estimated survival gain with transplantation was 2.8 months compared to resection and 5.7 months compared to ablation[238]. Selected patients with higher tumor burden might benefit more from transplantation compared to other treatments despite worse crude survival rates, but this has not been adequately evaluated[126, 237, 239]. Such considerations will require new perspectives in future transplantation selection[237].

The cost-benefit perspective has been suggested in favor of resection versus transplantation[240]. Overall cost-benefit is also an argument for the use of ablative treatments rather than resection in small HCC as resources are limited[241]. Tolerability favors ablation compared to resection in patients with impaired liver function. A recent study suggested similar outcome after resection and ablation in patients with ALBI grade 2[227]. The low morbidity rates after ablation also benefit patient QoL. In a study with HCC <3cm and no significant difference in survival rates, QoL was better after ablation than after resection according to FACT-hep at 3-36 months[242], although treatment preferences might influence QoL-scores without randomization[243].

Ablation is the fastest increasing treatment modality of liver tumors in Sweden, according to the SweLiv registry. However, due to its use in different settings, the intention-to-treat in ablation patients is difficult do define. In the third subgroup, adjusted to ablation limitations, we therefore excluded patients registered as “non-radical” at the time of treatment, trying

to avoid patients with palliative intent. Still, results should be interpreted with caution, but demonstrate that with similar selection, differences in results between treatments can be very limited.

Treatment algorithms outline patient selection to achieve acceptable outcome for a certain treatment. However, as the opposite perspective applies in clinical practice, we often tend to select more radical treatments if technically feasible. The fact that treatment recommendations are often overlooked could partly relate to this discrepancy and partly to the lack of prognostic accuracy.

More aggressive treatment strategies in all stages of HCC are blurring the definitions of curative intent and palliative treatments. For patients outside the transplantation criteria, locoregional antitumor treatments can be used either for downstaging or palliation and the intended purpose may not be set from the start.

Neo-adjuvant treatment before liver transplantation

Despite a limited level of evidence[101], locoregional neo-adjuvant therapy before liver transplantation is routinely used, most commonly ablation and TACE. Systemic therapy has no place in this setting, despite theoretical advantages, such as potential antitumor effects on undetected micrometastases. This was the rationale for the feasibility study on sorafenib treatment in patients with HCC awaiting liver transplantation (paper III). A lack of radiologic response to sorafenib treatment has been reported in patients with advanced stages of HCC despite a survival benefit[9]. In our cohort of early stage patients, no complete or partial response was seen. To our knowledge neo-adjuvant sorafenib as a single bridging therapy was not reported previously. We expected the treatment to be better tolerated in the cohort with high performance status and little comorbidity, but found that half of these patients stopped treatment due to side effects. At the time of response evaluation at 12 weeks only seven out of 12 patients were on treatment and only one of them without dose modifications. The lack of adequate tumor control may have been inflicted by frequent treatment pauses and reductions, but altogether we cannot recommend sorafenib treatment in this setting in future studies.

Methodological considerations

A limitation in all studies was missing data, which was especially significant for the ECOG variable in the registry study (paper IV). The retrospective nature of data was a limitation in paper II. The study cohorts of paper I and II are heterogeneous relative to the setting, which could be a strength, as significant findings despite heterogeneity could be more generalizable. Generalizability, at least within Sweden, should also be a strength with the national cohorts of paper II and IV, although the finite number of patients, which do not permit more statistical conclusions, is a limitation. The number of patients is also a limitation in paper I, where subgroup analyses could have been done with more patients. In paper III changes in perfusion parameters and QoL could have been better defined with more patients. Also, dose modifications and treatment pauses hindered the interpretation of perfusion changes and treatment responses, and similarly affected the QoL analysis. The great variations in time from sorafenib treatment stop to liver transplantation impaired the interpretation of sorafenib treatment influence on post-transplant complications.

6 CONCLUSIONS

Patient-reported QoL data was prognostic for survival in a mixed HCC cohort, in which the Fatigue and Nutrition scales had the best prognostic value. Adding QoL data improved the prognostic accuracy of established scoring systems, such as the BCLC and CLIP.

Pre-transplant AFP was prognostic for survival after liver transplantation for HCC and the addition of AFP to traditional criteria improved prognostic accuracy. A combined score for improved transplantation selection was suggested.

In patients with limited HCC and well-preserved liver function (Child A), liver function variables (Child A5 and Albumin $\geq$36) could guide treatment choice between transplantation, resection, or ablation.

In HCC patients with limited tumor burden and Child A, the mortality risk after resection with Child A6, but not Child A5, was significantly higher compared to after transplantation, which supports the recommendation for primary resection in Child A5 patients.

With similar patient selection (single HCC < 3cm and Child A), survival differences after transplantation, resection, or ablation survival were limited and not significant in this cohort.

Sorafenib treatment before liver transplantation was associated with low tolerability and inadequate tumor control.

7 FUTURE PERSPECTIVES

In the modern digital era, the possibility of patient monitoring outside the clinics is substantial as a large proportion of patients have smart phones and other online devices. Patient-reported QoL measures, customized for different settings could improve communication and symptom monitoring. The survival benefit in palliative patients with online self-reporting suggests that regular and standardized assessments may detect early signs of deterioration[192]. The symptom burden of HCC might be well suited for such monitoring. With fewer hospital beds, standardized online self-reporting might be an efficient way of monitoring patients in the outpatient clinic after treatments. Prospective studies evaluating the correlation between QoL domains and clinical deterioration after treatments and in patients receiving best supportive care would be useful. The introduction of technical solutions should be combined with the development of adjusted tools. In registries, patient-reported measures might improve stratification of prognosis and perhaps facilitate the evaluation of complex treatment schedules.

For transplantation selection, many of the newly proposed factors and criteria need validation and refinement. The role of dynamic measures for treatment decision-making needs to be better defined. Tumor growth, AFP-increase and response to neo-adjuvant treatment might be included in future selection criteria. The absence of cancer-related symptoms is already included in the Toronto criteria. Perhaps patient-reported questionnaires could yield corresponding information using standardized assessment. In Sweden, a downstaging study in an undefined group of patients outside of the UCSF criteria is already ongoing, with response to treatment as transplantation criteria. For transplantation benefit consideration in such advanced tumor stages, old criteria should be reevaluated with new perspectives.

In the transplantation setting, the potential transplant benefit has been highlighted due to the lack of donor livers[236, 237]. However, the added value of any extensive therapy must be compared to less invasive and expensive alternatives treatments. Sometimes the individual perspective could imply choosing a more extensive treatment than recommended in a standard algorithm. For instance, a patient with impaired performance status due to symptoms from a very large HCC could benefit from resection with symptom relief. Individual benefit, considering symptom burden and alternative treatments, is important to assess, although difficult.

Optimal individual treatment decisions warrant accurate prognostic tools to

compare distinguished subgroups with similar expected outcome, according to risk factors within stages. Tools also need to be updated as new factors emerge and established factors require reevaluation when modern techniques modify the associated risks. The complexity of such algorithms will probably warrant guidance with artificial intelligence. To get there we need to define more standard measures to construct useful databases.

As new registries are established, coordination to avoid overlapping and duplication is crucial. With large-scale registries, research models on treatment benefit and the optimal use of donor livers or any other limited treatment can be developed. Factors of value for future decision-making need to be prioritized such as treatment intention and reasons for choosing one treatment over another. Variables need distinct and comprehensible definitions to yield valid information and registration should be simplified to avoid missing data. Since randomized studies are seldom feasible, valuable knowledge could be gained from registry-research, if such pre-treatment factors are registered.

Emerging complex and sequential treatment strategies take a lot of human and economic resources and the efficacy in the whole population as well as in individuals need to be evaluated. However, different outcome measures may be used. The older the patient, the more we must focus on short-term effects rather than long-term results. Patient satisfaction rather than survival might be more appropriate, when dealing with older populations, where cancer-related deaths cannot be regarded as preterm. Though aggressive cancer treatment may prolong life, other considerations might be more valuable to the patient. An increased awareness is needed with older cohorts, many treatment alternatives, and limited resources. A challenge in future research!

The changing panorama of HCC etiology will create changes in HCC rates, as HCV infections are cured and vaccination programs for HBV prevention are improved. On the other hand, the prevalence of NASH increases, which will affect not only the number of NASH related HCC cases, but also the quality of the liver donor pool. In addition new patients with indications for liver transplantation, such as colorectal liver metastases, may compete for donor livers in the future. This emphasizes the need for updated and accurate tools to estimate transplant benefit compared to other treatment options.

Modern imaging may allow more accurate evaluation of liver functional reserve, which might permit increased resection rates with minimal rates of liver failure. Modern imaging may also improve pretreatment tumor staging for more optimal treatment decisions. Future response evaluation could

hopefully be used, not only for transplantation selection, but also in palliative treatments where early radiographic measures could prevent treatment and unnecessary side effects in patients who will not benefit.

The rapid development of surgical techniques can further contribute to improvements in the care of HCC, and has introduced multiple new areas of research. Though already described, the use of 3D-reconstructions for preoperative simulations and intraoperative guidance may improve the precision of resection and ablation much further. With these advancements, an entire new field of research has emerged.

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Appendix

Paper I-IV