Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2017-B-221 Lenvatinib

Stand: Dezember 2017

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Lenvatinib
[zur Behandlung des Leberzellkarzinoms]

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“*
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	Eine nicht-medikamentöse Behandlung kommt als zweckmäßige Vergleichstherapie nicht in Betracht. Hierbei wird davon ausgegangen, dass sowohl eine kurative Behandlung (entsprechend BCLC-Stadium 0 und A) als auch eine lokoregionäre Therapie im BCLC-Stadium B, insbesondere eine transarterielle (Chemo)-Embolisation (TACE oder TAE), nicht (mehr) infrage kommt.
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	• Maßnahmen zur Qualitätssicherung bei Protonentherapie bei Patientinnen und Patienten mit inoperablem hepatozellulärem Karzinom; Beschluss vom 16. Juli 2009 und 27. November 2015 • Bewertung nach § 137h SGB V: Ultraschallgesteuerter hoch-intensiverfokussierter Ultraschall zur Behandlung des hepatozellulären Karzinoms ; Beschluss vom 16. März 2017
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Beratungsanforderung/Fachinformation)
Zu bewertendes Arzneimittel:	
Lenvatinib L01XE29 Lenvima®	<u>Vorläufig geplantes Anwendungsgebiet:</u> Lenvatinib ist angezeigt zur Behandlung des Leberzellkarzinoms
Mitomycin L01DC03 (generisch)	Mitomycin wird in der palliativen Tumortherapie eingesetzt. Bei intravenöser Gabe ist es in der Monochemotherapie oder in kombinierter zytostatischer Chemotherapie bei folgenden metastasierenden Tumoren wirksam: […] − fortgeschrittenes Leberzellkarzinom
Sorafenib L01XE05 Nexavar®	Leberzellkarzinom Nexavar ist angezeigt zur Behandlung des Leberzellkarzinoms (siehe Abschnitt 5.1).
Regorafenib[1] L01 XE21 Stivarga®	Stivarga ist angezeigt als Monotherapie zur Behandlung von erwachsenen Patienten mit: […] - hepatozellulärem Karzinom (HCC), die zuvor mit Sorafenib behandelt wurden.

Quellen: AMIS-Datenbank, Fachinformationen

[1] Regorafenib ist derzeit in Deutschland nicht im Handel.

Gemeinsamer Bundesausschuss

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2017-B-221 (Lenvatinib)

Datum: 02.11.2017

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie (zVT):

Inhalt

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und evidenzbasierten systematischen Leitlinien zur Indikation Leberzellkarzinom durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 02.10.2017 abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, Clinical Evidence, CCO, DAHTA, ESMO, G-BA, GIN, IQWiG, NCCN, NCI, NGC, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 1421 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 27 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Indikation:

Zur Behandlung des Leberzellkarzinoms

Abkürzungen:

Akdae	Arzneimittelkommission der deutschen Ärzteschaft
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
ÄZQ	Ärztliches Zentrum für Qualität in der Medizin
CASP	Critical Appraisal Skills Programme
CCO	Cancer Care Ontario
DAHTA	Deutsche Agentur für Health Technology Assessment
DCR	disease control rate
DRKS	Deutsches Register Klinischer Studien
ESMO	European Society for Medical Oncology
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
HCC	hepatozelluläres Karzinom
HFSR	hand and foot skin reactions
ICTRP	International Clinical Trials Registry Platform
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
ISRCTN	International Standard Randomised Controlled Trial Number
MPV	main portal vein
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NGC	National Guideline Clearinghouse
NHS CRD	National Health Services Center for Reviews and Dissemination
NICE	National Institute for Health and Care Excellence
OS	Overall survival
PEI/PAI	percutaneous ethanol injection /percutaneous acetic acid injection
PVB	portal vein branches
RFA	radiofrequency ablation
SIGN	Scottish Intercollegiate Guidelines Network
TACE	Transarterial chemoembolization
TAE	Transarterial embolization
TRIP	Turn Research into Practice Database
TTP	Time to progression
TTSP	time to symptomatic progression
WHO	World Health Organization

IQWiG-Berichte/G-BA-Beschlüsse

G-BA, 2015 [5]. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung des Beschlusses über Maßnahmen zur Qualitätssicherung bei Protonentherapie bei Patientinnen und Patienten mit inoperablem hepatozellulärem Karzinom (HCC): Verlängerung der Gültigkeitsdauer Siehe auch: **G-BA, 2015 [6].**	**Fazit:** ,,Die Aussetzung des Bewertungsverfahrens zur Protonentherapie beim inoperablen HCC und der Beschluss über Maßnahmen zur Qualitätssicherung der Protonentherapie bei Patientinnen und Patienten mit inoperablem HCC werden bis zum 31. Dezember 2020 verlängert.''

Cochrane Reviews

Roccarina D et al., 2017 [17]. Management of people with intermediate-stage hepatocellular carcinoma	1. Fragestellung To assess the comparative benefits and harms of different interventions used in the treatment of intermediate-stage hepatocellular carcinoma (BCLC stage B) through a network meta-analysis and to generate rankings of the available interventions according to their safety and efficacy.
	2. Methodik Population: Participants with intermediate-stage hepatocellular carcinoma (BCLC stage B) irrespective of the presence of cirrhosis, size and number of the tumours (provided they met the criteria of intermediate-stage hepatocellular carcinoma), presence or absence of portal hypertension, aetiology of hepatocellular carcinoma, and the future remnant liver volume. Randomised clinical trials in which participants had undergone liver transplantation previously were excluded. Intervention / Komparator: The following interventions that are possible treatments for intermediate-stage hepatocellular carcinoma either alone or in combination tested versus each other, or versus placebo or sham, or no intervention (supportive care) were condisered: • liver resection; • liver transplantation; • radiofrequency ablation; • microwave ablation; • other ablations (laser ablation, cryoablation, HIFU, irreversible electroporation); • alcohol injection; • acetic acid injection; • radiotherapy (stereotactic body radiotherapy or radioembolisation); • systemic chemotherapy; • TAE; • TACE; • supportive care. Endpunkte: Mortality, Adverse events, Quality of Life, Disease recurrence, Length of hospital stay and complications Suchzeitraum (Aktualität der Recherche): The Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, Science Citation Index Expanded, World Health Organization International Clinical Trials Registry Platform, and randomised clinical trials registers to September 2016 were searched. Hinweis: We found only one comparison. Therefore, we did not perform the network meta-analysis Anzahl eingeschlossene Studien/Patienten (Gesamt): 3 trials with 430 participants. All three trials included supportive care (treatment to prevent, control, or relieve complications and side effects and improve comfort and quality of life) as a co-intervention. The trials assessed transarterial

	chemoembolisation (where anti-cancer drugs block the blood supply and treat the cancer through the vessels supplying the cancer), chemotherapy using sorafenib (a drug which blocks cancer growth), or a combination of transarterial chemoembolisation and sorafenib. Qualitätsbewertung der Studien: Cochrane risk of bias / GRADE
	3. Ergebnisdarstellung Qualität der Studien: The overall quality of evidence was low or very low and all the trials were at high risk of bias. • Over 18 to 30 months, 50% to 75% of participants died. There was no evidence of any difference between the people who received chemotherapy and those who did not receive chemotherapy. • None of the trials reported complications, health-related quality of life (a measure of a person's satisfaction with their life and health), cancer recurrence, or length of hospital stay. • Overall, there is currently no evidence for benefit of any active treatment in addition to supportive treatment for intermediate-stage hepatocellular carcinoma. There is significant uncertainty on this and further high-quality randomised clinical trials are required.
	4. Fazit der Autoren: This review included only trial participants with intermediate stage hepatocellular carcinoma (i.e. BCLCB stage; i.e. large, multinodular, Child-Pugh status A to B, and performance status 0). Therefore, this review is applicable only to people with intermediate-stage hepatocellular carcinoma. It included a mixture of viral and non-viral aetiologies and people with cirrhotic and non-cirrhotic livers. Hence, the review is applicable to viral or non-viral aetiologies and people with cirrhotic and non-cirrhotic livers. None of the trials reported the proportion of people with portal hypertension. Therefore, it is not clear whether the findings of the review are applicable in people with portal hypertension. 5. Kommentar zum Review • Two trials were funded by the pharmaceutical industry; one trial did not report the source of funding.

Systematische Reviews

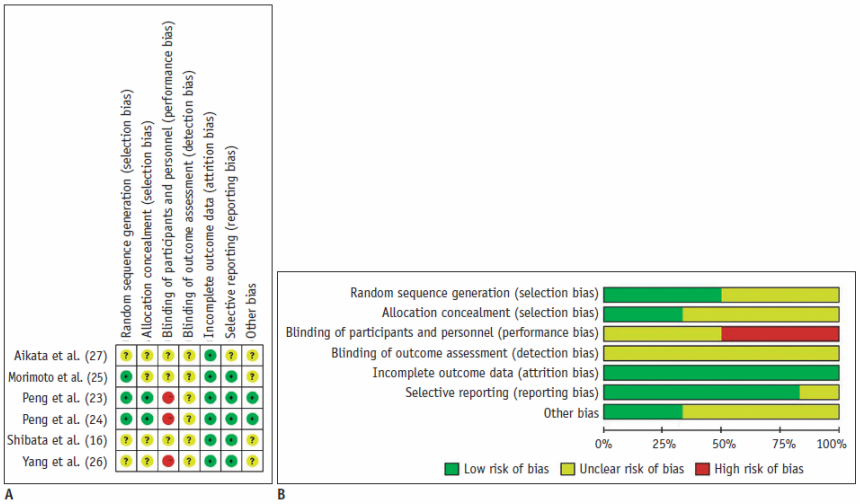
Silva JP et al., 2017 [19]. Transarterial chemoembolization in hepatocellular	1. Fragestellung This systematic review sought to examine the role of TACE in the treatment of HCC with PVT in either the main portal vein (MPV) or portal vein branches (PVB).
	2. Methodik

carcinoma with portal vein tumor thrombosis: a systematic review and meta-analysis	Population: HCC patients with PVT. Intervention / Komparator: comparing TACE to another treatment for management of HCC with PVT Endpunkte: overall survival (OS), mRECIST response, and complication incidence Suchzeitraum (Aktualität der Recherche): PubMed was searched from January 1, 2006 to August 31, 2016. Anzahl eingeschlossene Studien/Patienten (Gesamt): 13 studies with 1933 TACE patients were included. Qualitätsbewertung der Studien: Newcastle–Ottawa Scale
	3. Ergebnisdarstellung Qualität der Studien: Several of the studies were non-randomized or retrospective, allowing for patient selection bias to influence the results (keine weiteren Angaben im Text) • Median OS (95% CI) was eight (5–15) months. Survival rates after one, three, and five years were 29% (20%–40%), 4% (1%–11%), and 1% (0%–5%), respectively. • Only 1% experienced liver failure and 18% had post-treatment complications. • Patients with MPV thrombosis had worse survival than PVB patients ($p < 0.001$), but similar mRECIST response rates (14% vs. 16%).
	4. Fazit der Autoren: TACE is a safe treatment for a highly selected population of HCC patients with PVT. Despite worse survival rates compared to PVB thrombosis, PVT in the MPV should not be considered an absolute contraindication to TACE. 5. Kommentar zum Review: • All studies were from Asian countries, with eight from China, one from Japan, three from Korea, and one from Taiwan. • heterogeneity between the studies
van Rosmalen BV et al., 2017 [20]. Systematic review of transarterial embolization for hepatocellular	1. Fragestellung This systematic review provides an overview of clinical outcomes after TAE, in bleeding and non-bleeding HCA.
	2. Methodik Population: patients with HCA Intervention/Komparator: TAE techniques

adenomas	Hinweis: Studies considering hepatic malignancies and tumours other than HCA, those reporting techniques other than TAE (such as radiofrequency ablation or hepatic artery ligation) and reviews were excluded. Endpunkte: tumour size, malignant transformation or adverse events. Suchzeitraum (Aktualität der Recherche): systematic literature search, up to 7 January 2016, of the PubMed and Embase databases was undertaken Anzahl eingeschlossene Studien/Patienten (Gesamt): 40 articles included a total of 851 patients (20 cohort studies and 20 case reports), of whom 151 (17,7 %) underwent TAE for 196 lesions. Qualitätsbewertung der Studien: To assess the quality of the selected studies, the Critical Appraisal Skills Programme (CASP) for cohort studies was used. Three items (what are the results of this study, how precise are the results and what are the implications of this study for practice?) of the CASP tool were left out of the critical appraisal. Regarding point 6 of the CASP tool, a follow-up of at least 12 months was considered appropriate to judge the effect on tumour size. The quality of case reports was not assessed because of likely selection bias. The Oxford Centre for Evidence-Based Medicine Levels of Evidence were determined for all studies, where level 1 is the highest level of evidence, and level 5 the lowest.
	3. Ergebnisdarstellung Qualität der Studien: Among the 20 studies, 18 were considered to provide level 2b evidence and two level 1b. Seven cohort studies scored 'yes' on all 11 items of the CASP tool. All case reports were considered as level 4 evidence. • Surgical treatment was avoided in 68 of 151 patients (45.0%). Elective TAE was performed in 49 patients involving 66 HCAs, with 41 of these patients (84%) not requiring surgery. • Major complications occurred in eight of 151 patients (5,3%); no death was reported. • Among cohort studies, complete tumour disappearance was observed in 10% of patients, and regression in 75%.
	4. Fazit der Autoren: Acute or elective TAE in the management of HCA seems safe. TAE in the elective setting offers a reasonable alternative to surgery, considering its minimally invasive and parenchyma-sparing properties, and the ability to reduce the size of tumours situated in a difficult anatomical position for surgery. Its influence on symptoms and whether it modifies risks of neoplastic regression remain unknown. 5. Kommentar zum Review: • Ausschließlich Kohortenstudien und Fallserien

Facciorusso A et al., 2017 [4]. Transarterial chemoembolizatio n vs bland embolization in hepatocellular carcinoma: A meta-analysis of randomized trials	1. Fragestellung The objective of this article is to systematically analyze the results provided by randomized controlled trials comparing these two treatments in hepatocarcinoma patients.
	2. Methodik Population: hepatocarcinoma patients Intervention / Komparator: TACE vs. TAE Endpunkte: Survival rates assessed at one, two, and three years, objective response, one-year progression-free survival, and severe adverse event rate Suchzeitraum (Aktualität der Recherche): PubMed/Medline, Embase, Google Scholar, and Cochrane library databases were searched until February 2016. Anzahl eingeschlossene Studien/Patienten (Gesamt): 6 RCTs with 676 patients (342 treated with TACE and 334 with TAE) were included in the meta-analysis. Qualitätsbewertung der Studien: Cochrane Collaboration's tool. Comparisons were performed by using the Mantel-Haenszel test in cases of low heterogeneity or DerSimonian and Laird test in cases of high heterogeneity.
	3. Ergebnisdarstellung <u>Qualität der Studien</u>: Three RCTs were considered high quality and three moderate quality. • No difference in one-year (risk ratio: 0.93, 0.85–1.03, p=0.16), two-year and three-year survival was observed. • Objective response and one-year progression-free survival showed no significant difference between the two treatments. • A statistically significant increase in severe toxicity after chemoembolization was found (risk ratio: 1.44, 1.08–1.92, p=0.01), although this result could be affected by the heterogeneity of techniques adopted.
	4. Fazit der Autoren: In conclusion, despite these weaknesses, our meta-analysis supports the non-superiority of TACE with respect to TAE, which in turn appears even safer particularly when compared to conventional chemoembolization. These conclusions need to be confirmed in broad non-inferiority trials with a large number of cases, strict selection of patients in terms of tumour burden, severity of liver dysfunction (as this strongly affects OS) as well as comorbidities (as these as well affect survival) and standardized modality of endovascular tumour treatment

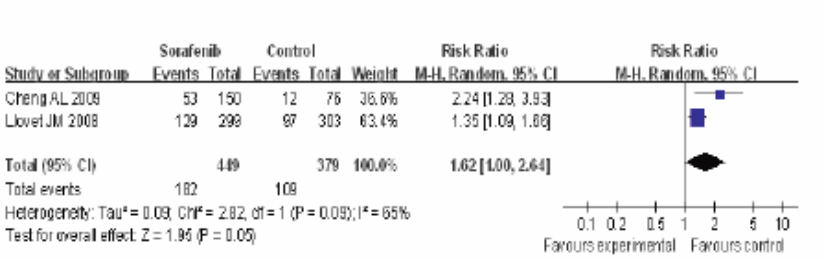
	and reporting of adverse events.22 In the lack of a better source of evidence, the present meta-analysis appears to provide the most possible solid information on the comparison of TACE with TAE.
Wang X et al., 2016 [22]. Efficacy and Safety of Radiofrequency Ablation Combined with Transcatheter Arterial Chemoembolization for Hepatocellular Carcinomas Compared with Radiofrequency Ablation Alone: A Time-to-Event Meta-Analysis Siehe auch: **Wang Y et al., 2016 [23]; Kong QF et al., 2014 [8]; Ni JY et al., 2013 [15]; Liu Z et al., 2014 [12]; Cao JH et al., 2014 [3]; Huo YR**	1. Fragestellung To compare the efficacy and safety of combined radiofrequency ablation (RFA) and transcatheter arterial chemoembolization (TACE) with RFA alone for hepatocellular carcinomas (HCC).
	2. Methodik Population: Patients with HCC Intervention / Komparator: combination therapy of TACE and RFA versus RFA monotherapy Endpunkte: Overall survival, recurrence-free survival, major complications Suchzeitraum (Aktualität der Recherche): Pubmed, Embase, Cochrane Library, Chinese Biomedical Database (CBM), CNKI, and Google Scholar from their inception years to February 13, 2015 Anzahl eingeschlossene Studien/Patienten (Gesamt): 6 RCTs (16, 23-27) published between 2005 and 2013 with 534 patients were analyzed in this meta-analysis. Qualitätsbewertung der Studien: Risk of bias tool suggested by the Cochrane Handbook for Systematic Reviews of Interventions. In addition, to evaluate the quality of evidence from the pooled results, the Grading of Recommendations Assessment, Development, and Evaluation system (GRADE system) was employed.
	3. Ergebnisdarstellung <u>Qualität der Studien:</u>

et al., 2015 [7].	 **Fig. 1. Assessment of risk of bias in this meta-analysis.** **A.** Summary of risk of bias for each trial assessed by Cochrane Collaboration's tool. **B.** Risk of bias graph about each risk of bias item presented as percentages across all included studies. • The meta-analysis showed that the combination of TACE and RFA is associated with a significantly longer overall survival (HR = 0.62, 95% CI: 0.49–0.78, p < 0.001) and recurrence-free survival (HR = 0.55, 95% CI: 0.40–0.76, p < 0.001) in contrast with RFA monotherapy. • The seemingly higher incidence of major complications in the combination group compared with RFA group did not reach statistical significance.
	4. Fazit der Autoren: In conclusion, this meta-analysis suggested that the combination of TACE and RFA is associated with significantly higher overall survival and recurrence-free survival than RFA monotherapy in the patients with HCC without significant difference in major complication between them. These results need to be validated in RCTs with better quality and larger sample sizes.
Li J et al., 2017 [11]. Transcatheter hepatic arterial chemoembolization and sorafenib for hepatocellular carcinoma: a meta-analysis of randomized, double-blind controlled trials. Siehe auch: **Zeng J et al., 2016**	1. Fragestellung A meta-analysis of transcatheter hepatic arterial chemoembolization (TACE) combined with sorafenib for hepatocellular carcinoma (HCC)
	2. Methodik Population: Patients with HCC. Patients were not suitable candidates for surgical resection; participants were 18 years of age or older. Intervention: TACE + sorafenib Komparator: Placebo Endpunkte: TTP or overall survival (OS); and reported adverse events Suchzeitraum (Aktualität der Recherche): MEDLINE, EMBASE, EBSCO, Springer, Ovid, and Cochrane Library databases search ending in 2016. Anzahl eingeschlossene Studien/Patienten (Gesamt): 4 placebo-controlled

[26].	RCTs were included in the meta-analysis with a total of 877 HCC cases from 14 countries, including China and the USA. Qualitätsbewertung der Studien: Quality assessment was performed based on the following criteria: Allocation was sufficiently randomized; blinding for allocation was sufficient; blinding for the intervention was sufficient; and loss to follow-up or exit status were evaluated.
	3. Ergebnisdarstellung Qualität der Studien: The various studies used different methods of randomization for allocation to the experimental and control groups. Blinding and randomization were determined to be adequate in all of the selected RCTs, whereas only one of these studies adequately described allocation concealment. The risks of selection, performance, or detection biases were not quantified in any of the included studies. • The TTP increased significantly in the experimental groups (hazard ration [HR]: 0.82; 95% CI: 0.69–0.97; $p = 0.02$), but OS did not improve significantly, compared with the control groups. • The risks of hand and foot skin reactions (HFSR), rash, fatigue, and diarrhea were significantly greater in the experimental groups ($p < 0.05$ for all), compared to those in the control groups, whereas the risk of nausea was statistically similar. Among these, the risk of HFSR was highest (risk ratio [RR]: 5.93; 95% CI: 2.00–17.53; $p = 0.001$), and a subgroup analysis of studies that lacked significant heterogeneity in the HFSR data showed a higher risk of HFSR (RR: 10.96; 95% CI: 5.54–21.69; $p < 0.05$).
	4. Fazit der Autoren: In conclusion, although TACE plus sorafenib increases TTP in patients with HCC, it does not improve OS. Therefore, the increased risk of adverse events in patients receiving TACE plus sorafenib suggests that this combination therapy might not represent an improvement over treatment with TACE alone. The relatively small number of RCTs that met the selection criteria for our meta-analysis demonstrate the need for uniform application of clinical outcome indicators to facilitate future comparisons of studies of TACE plus sorafenib for the treatment of HCC. 5. Kommentar zum Review: • (…) We did not assess statistical power for our analysis, but the relatively small number of RCTs included in our meta-analysis represents a potential confounder of our findings. • (…) The small number of selected RCTs also precluded the use of funnel plots to assess whether publication bias influenced our findings, but the randomization and double blinding performed in all of the RCTs included in our meta-analysis likely minimized the potential effects of selection, performance, and detection biases.

Wang G et al., 2016 [21]. Sorafenib combined with transarterial chemoembolization in patients with hepatocellular carcinoma: a meta-analysis and systematic review. Siehe auch: **Zhang L et al., 2014 [27].**	1. Fragestellung This study evaluated the efficacy and safety of TACE + sorafenib.
	2. Methodik Population: patients with advanced HCC Intervention/Komparator: TACE vs. TACE + Sorafenib Endpunkte: The primary outcome measure was time to progression (TTP), and the secondary outcomes measures were overall survival (OS) and adverse events. Suchzeitraum (Aktualität der Recherche): MEDLINE, the Cochrane Library, EMBASE, and the ISI Web of Knowledge were searched until 31 December 2013. Anzahl eingeschlossene Studien/Patienten (Gesamt): Five comparative studies (2 were randomized control trials) that included 899 patients Qualitätsbewertung der Studien: The Delphi list was used to assess the quality of the randomized controlled trials. The Newcastle-Ottawa scale was used to assess the quality of the nonrandomized controlled study.
	3. Ergebnisdarstellung <u>Qualität der Studien</u>: The quality of the data was evaluated for the two included studies that were randomized control trials using the Delphi list. The study of Kudo et al. received 8 points and of Sansonno et al. 7 points, indicating the data were of good quality. A risk for detection bias was present because the outcome assessors in both studies were not blinded. The Sansonno et al. study also did not include an intention-to-treat analysis. The quality of the Bai et al., Muhammad et al. and Qu et al. studies, which were non-randomized, was evaluated using the Newcastle-Ottawa scale. The Bai et al. data were considered of high quality as they received a score of 9. Muhammad et al. and Qu et al. received a score of 6 because they may have had selection bias as they did not explain the selection of participants. • Patients treated with TACE + sorafenib had better prognoses in terms of time to progression (TTP) compared to those with TACE + placebo or TACE alone; hazard ratios (HRs) ranged from 0.40 to 0.87, with the combined HR 0.61 (95 % CI 0.39–0.95, p = 0.031). • However, the combined HR for overall survival (OS) did not differ significantly between patients treated with TACE + sorafenib and those with TACE + placebo or TACE alone. • Sensitivity analysis indicated the findings for TTP may be overly influenced by at least one of the studies.
	4. Fazit der Autoren: In summary, our meta-analysis found that TACE + sorafenib can improve TTP. We did not find the combined therapy

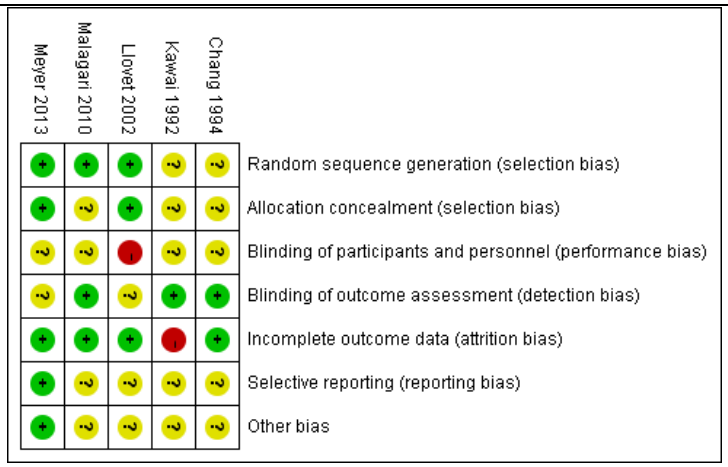
	improved OS. Additional randomized controlled studies are necessary to further investigate the clinical benefit of TACE + sorafenib in treating advanced HCC
Wang Z et al., 2013 [24]. Meta-analysis of the Efficacy of Sorafenib for Hepatocellular Carcinoma	1. Fragestellung By carrying out a meta-analysis of randomized controlled trials that compared sorafenib or combined chemotherapy with placebo or combined chemotherapy, the effectiveness of sorafenib in hepatocellular carcinoma was evaluated in the present study, which also provided clinical practice guidelines of evidence-based-medicine.
	2. Methodik Population: hepatocellular carcinoma patients Intervention: Sorafenib Komparator: Placebo Endpunkte: Overall survival (OS), time to progression (TTP), time to symptomatic progression (TTSP), disease control rate (DCR) and adverse reactions Suchzeitraum (Aktualität der Recherche): Review of PubMed citations concerning sorafenib treating hepatocellular carcinoma in randomized controlled trials from Jan 2000 to July 2012 Anzahl eingeschlossene Studien/Patienten (Gesamt): Finally, four papers documenting randomized controlled studies were included Qualitätsbewertung der Studien: RCT bias risk assessment methods in Cochrane handbook
	3. Ergebnisdarstellung Qualität der Studien: All trials included in this analysis were double-blind placebo-controlled randomized phase 3 clinical trials. Efficacy: Compared with controls, sorafenib was shown to significantly increase overall survival (OS), time to progression (TTP), and disease control rates (DCR), but not the time to symptom progression (TTSP) in hepatocellular carcinoma patients. **Table 2. Overall Survival (OS), Time to Progression (TTP) and Time to Symptomatic Progression (TTSP) Reported in the Four Eligible Literatures/trials** Research | Therapic regime | Neutral OS and 95%CI (month) | *P* value | Neutral TTP and 95%CI (month) | *P* value | Neutral TTSP and 95%CI (month) | *P* value Llovet JM 2008 | Sorafenib | 10.7(9.4-13.3) | <0.001 | 5.5.(4.1-6.9) | <0.001 | 4.1(-) | 0.77 Placebo | 7.9(6.8-9.1) | | 2.8(2.7-3.9) | | 4.9(-) | Cheng AL 2009 | Sorafenib | 6.5(5.6-7.6) | 0.014 | 2.8(2.6-3.6) | 0.0005 | 3.5(2.8-4.24) | 0.5 Placebo | 4.2(3.7-5.5) | | 1.4(1.3-1.5) | | 3.4(2.40-4.08) | Abou-Alfa GK 2010 | Doxorubicine + sorafenib | - | - | 6.4(4.8-9.2) | 0.02 | - | - Doxorubicine + placebo | - | | 2.8(1.6-5.0) | | - | Kudo M 2011 | Sorafenib | 13.7(8.9-NA) | 0.006 | 7.2(5.6-9.1) | 0.049 | - | - Placebo | 6.5(4.5-9.9) | | 5.3(3.8-5.6) | | - |

	 **Figure 1. Meta-Analysis Forest Plots of Disease Control Rate in Hepatocellular Carcinoma Patients in Sorafenib And Control Groups** <u>Adverse events:</u> The incidence of grade-III/IV adverse reactions, including hand-foot-skin reactions, diarrhea, hypertension and skin rash or desquamation, in sorafenib treatment group was higher than that in controls. However, there was no significant difference in the incidence of hypodynamia between the two groups.
	4. Fazit der Autoren: Sorafenib exerts significant curative effects in hepatocellular carcinoma.
Belinson S et al., 2013 [2]. Local Therapies for Unresectable Primary Hepatocellular Carcinoma	1. Fragestellung To characterize the comparative effectiveness and harms of various local hepatic therapies for patients with unresectable primary hepatocellular carcinoma (HCC) who are not candidates for surgical resection or liver transplantation. Local hepatic therapies include those related to ablation, embolization, and radiotherapy. **KQ1.** What is the comparative effectiveness of the various liver-directed therapies in patients with HCC who are not otherwise candidates for surgical resection or transplantation with no evidence of extrahepatic disease regarding survival and quality of life? **KQ2.** What are the comparative harms of the various liver-directed therapies in patients with HCC who are not otherwise candidates for surgical resection or transplantation with no evidence of extrahepatic disease regarding adverse events? **KQ3.** Are there differences in comparative effectiveness of various liver-directed therapies in patients with HCC who are not otherwise candidates for surgical resection or transplantation for specific patient and tumour characteristics, such as age, gender, disease etiology, and Child-Pugh score?
	2. Methodik Population: HCC in patients who meet all of the following criteria: • No extrahepatic spread • No portal invasion

	• Child-Pugh class A or B disease • Eastern Cooperative Oncology Group (ECOG) status ≤1 *and/or* • BCLC stage A or B, or equivalent Intervention / Komparator: Local therapies (siehe Ergebnisteil) Endpunkte: overall survival and quality of life—and various adverse events Suchzeitraum (Aktualität der Recherche): MEDLINE and Embase from January 2000 to July 2012 Anzahl eingeschlossene Studien/Patienten (Gesamt): Siehe Ergebnisteil! Qualitätsbewertung der Studien: In the assessment of risk of bias in individual studies, we followed the Agency for Healthcare Research and Quality (AHRQ) “Methods Guide for Effectiveness and Comparative Effectiveness Reviews” (Methods Guide) / GRADE
	3. Ergebnisdarstellung Qualität der Studien: Siehe Ergebnisteil **Overall Conclusions for Key Questions 1–3** • Six RCTs, four nonrandomized comparative studies, 35 case series, and three case reports comprised the body of literature. One RCT was rated as good, three were rated as fair and two were rated as poor quality. • The body of evidence for RFA compared with PEI/PAI was rated moderate strength to support better overall survival at 3 years for RFA compared with PEI/PAI with a low risk of bias. • The body of evidence for RFA compared with PEI/PAI was rated low strength to support increased TTP, improved local control, and a longer LOS for RFA compared with PEI/PAI, with a high risk of bias. • For all other comparisons, the body of evidence on overall survival, quality of life, disease progression, local control, LOS, days of missed work, and adverse events for local hepatic therapy for the treatment HCC is insufficient to support the effectiveness of one local hepatic therapy over another, due to the lack of comparative studies. • Studies with subgroup analyses were limited to the three studies reporting on the comparison of RFA to PEI/PAI. These analyses reviewed Child-Pugh class, lesion size, and multifocal disease for their effects on overall survival, but were not pre-specified. Lesion size was also examined by Lin et al 2004 for its effects on cancer-free survival and local recurrence. There is a low strength of evidence to support increased overall survival for RFA compared with PEI/PAI in patients with larger lesions with a high risk of bias. The evidence is insufficient to assess the effects lesion size on other outcomes of interest in this report and of other patient subgroups on any outcome of interest in this report. • The assessment of applicability of the study findings to clinical practice is limited by the poor characterization of the patient populations (e.g., number and size of metastases, performance status) and variations in the delivery of the interventions (e.g., surgical approach and dose and drugs delivered).

	4. Fazit der Autoren: (…) For the comparison of RFA to PEI/PAI, our conclusions suggest that for these patients treatment with RFA confers a survival benefit at 3 years compared with PEI/PAI. In addition, TTP and local recurrence may be improved in patients treated with RFA compared with PEI/PAI. Patients treated with RFA also seem to have longer LOS after treatment compared with those treated with PEI/PAI. Beyond this evidence on the comparative effectiveness of these procedures was insufficient. Subsequent comparisons had only one or no comparative studies on a given treatment comparison. For these comparisons, evidence was insufficient for all outcomes; thus, there is no comparative evidence base to support decision making. In cases where comparative evidence existed, data were judged to be insufficient due to high risk of bias and/or imprecision of estimates.
Peng S et al., 2014 [16]. An Updated Meta-Analysis of Randomized Controlled Trials Assessing the Effect of Sorafenib in Advanced Hepatocellular Carcinoma.	1. Fragestellung The efficacy of sorafenib in the treatment of advanced hepatocellular carcinoma (HCC) remains controversial. Therefore, we conducted a meta-analysis to evaluate the efficacy and safety of sorafenib for treating patients with advanced HCC.
	2. Methodik Population: adult patients with advanced (unresectable or metastatic) HCC Intervention: sorafenib or sorafenib-based therapy Komparator: placebo or placebo-based (without sorafenib) therapy Endpunkte: primary: overall survival (OS); secondary: time to progression (TTP), overall response rate (ORR), and toxicity Suchzeitraum (Aktualität der Recherche): bis 03/2014 Anzahl eingeschlossene Studien/Patienten (Gesamt): 7 (n=3807) Qualitätsbewertung der Studien: The methodological quality of each study was assessed with the Jadad scale.
	3. Ergebnisdarstellung Qualität der Studien: In the present meta-analysis, all included studies were well-designed and of high quality (Jadad score range from 4 to 5). *Overall survival (n=7 studies):* • sorafenib was associated with a significant improvement in OS • (HR=0.74, 95% CI: 0.61, 0.90; P=0.002) • heterogeneity was significant (P=0.000, I^2=77.0%) • Subgroup analysis: sorafenib was an effective treatment for patients with ECOG PS of 1–2 (HR=0.77, 95% CI: 0.60, 1.0; P=0.05), or macroscopic vascular invasion (MVI) and/or extrahepatic spread (EHS) (HR=0.65, 95% CI: 0.46, 0.93; P=0.02) • Begg and Egger tests provided no evidence of publication bias

	Time to progression (n=6 studies): • TTP benefit existed in the sorafenib group when compared with the control group (HR=0.69, 95% CI: 0.55, 0.86; P=0.001) • heterogeneity was significant (P=0.000, I^2=84.4%) • Subgroup analysis: significant TTP benefits of sorafenib treatment in the patients irrespective of MVI, EHS, and ECOG status • Begg and Egger tests provided no evidence of publication bias *Overall response rate (n=5 studies):* • sorafenib did not have a higher ORR when compared with other treatments (RR=0.85, 95% CI: 0.65, 1.11; P=0.10) • Begg and Egger tests provided no evidence of publication bias *Adverse events (n=5 studies):* • Sorafenib induced a significantly higher rate of hand-foot syndrome (RR=5.4, 95% CI: 1.8, 16.2; P=0.003), diarrhea (RR=1.45, 95% CI: 1.21, 2.34; P=0.003), fatigue (RR=1.70, 95% CI: 1.30, 2.23; P=0.000), and rash (RR=3.21, 95% CI: 1.65, 6.26; P=0.001)
	4. Fazit der Autoren: Treatment with sorafenib significantly improved OS and TTP in patients with advanced HCC. Additional large-scale, well-designed RCTs are needed to evaluate the efficacy of sorafenib-based therapy in the treatment of advanced HCC.
Xie ZB et al., 2014 [25]. Transarterial embolization with or without chemotherapy for advanced hepatocellular carcinoma: a systematic review.	1. Fragestellung We investigated the efficacy and safety of TACE with or without chemotherapy in patients with advanced HCC.
	2. Methodik Population: patients with advanced HCC Intervention: arterial embolization with an antitumor drug (any type of embolization material or antitumor drug) Komparator: arterial embolization Endpunkte: primary: all-cause mortality (all-cause mortality defined as death due to any cause) or overall survival (OS); secondary: tumor response rate, adverse events, quality of life, liver function, and tumor reduction Suchzeitraum (Aktualität der Recherche): bis 04/2014 Anzahl eingeschlossene Studien/Patienten (Gesamt): 5 (n=582) Qualitätsbewertung der Studien: Two reviewers independently assessed the risk of bias for each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions.
	3. Ergebnisdarstellung <u>Qualität der Studien:</u> *Risk of bias summary:*

	 *All-cause mortality (n=5 studies):* • no significant effect of all-cause mortality (RR=1.21, 95 % CI=0.74–1.98, P=0.16) *Survival (n=5 studies):* • 1-year survival did not differ between TACE and TAE (RR=0.92, 95 % CI=0.83–1.01, P=0.53) Tumor response rates(n=1 study) • No significant difference were observed between TACE and TAE *Adverse events (n=k. A.)* • The most common adverse events were post-TACE syndromes (pain, fever, nausea, vomiting). • In the TACE group, the incidence of nausea and vomiting appeared to be increased compared with the TAE group • In contrast to TAE, TACE was found to cause myelosuppression due to the use of an antitumor drug. *Quality of life (n=1 study)* • None of the scores was significantly different between the two groups. *Tumor reduction (n=k. A.)* • The difference between TACE group and TAE group was not significant in this outcome. *Liver function (n=1 study)* • No significant differences of liver function between the two groups was observed (RR=1.17, 95 % CI=0.48–2.86, P=0.48).
	4. Fazit der Autoren: The efficacy of TACE is not superior to TAE in advanced HCC patients. Moreover, TACE was associated with an increased rate of adverse events than TAE. Improved strategies are needed to reduce the risk of post-TACE complications.
Shen A et al., 2013 [18]. A systematic Review of Sorafenib in Child-Pugh A Patients	1. Fragestellung We performed a systematic review of the efficacy and safety of sorafenib in Child-Pugh A patients with unresectable HCC. The value of sorafenib treatment in different subgroups was examined.
	2. Methodik

With Unresectable Hepatocellular Carcinoma.	Population: Child-Pugh A patients with unresectable HCC Intervention: sorafenib Komparator: placebo Endpunkte: disease control rate (DCR), time to progression (TTP), overall survival (OS), adverse events *<u>Definition DCR:</u> DCR was defined as the percentage of patients who had a complete response, a partial response or stable disease (according to RECIST) that was maintained for at least 28 days after the first demonstration of that rating.* Suchzeitraum (Aktualität der Recherche): bis 07/2012 Anzahl eingeschlossene Studien/Patienten (Gesamt): 5 (n=1462) Qualitätsbewertung der Studien: Two independent reviewers (A.S. and C.T.) evaluated the quality of each trial, according to the Cochrane Handbook for Systematic Reviews of Interventions.
	3. Ergebnisdarstellung <u>Qualität der Studien</u>: Two of the studies were found to have a low risk of bias and 3 trials had a high risk of bias. *DCR (n=3 studies):* • Sorafenib group had an 85% higher response rate than the placebo group (sorafenib vs. placebo, RR, 1.85; 95% CI, 1.55, 2.20; P<0.001; I^2=0.0%) *TTP (n=5 studies):* • sorafenib improved the TTP significantly over placebo (HR, 0.61; 95% CI, 0.51, 0.73; P<0.001; I^2=31.8%) *Overall Survival (n=4 studies):* • sorafenib treatment improved the survival of patients (HR, 0.71; 95% CI, 0.56, 0.89; P<0.001; I^2=46.5%) *Adverse events (n=5 studies):* • sorafenib increased the incidence of overall AEs, such as fatigue (21.4%), alopecia (24.5%), hand-foot skin reaction (HFSR; 33.2%), rash or desquamation (23.0%), diarrhea (29.8%), nausea (11.8%), and hypertension (14.9%)
	4. Fazit der Autoren: Sorafenib was a moderately effective and safe oral drug for use in Child-Pugh A patients with unresectable HCC. Sorafenib monotherapy is not recommended for treating intermediate-stage HCC. More research is needed on the efficacy of sorafenib treatment in patients with prior local therapy.

Leitlinien

<table>
<tr>
<td>Alberta Health Services, 2015 [1].

HEPATOCELLULAR CARCINOMA</td>
<td>GUIDELINE QUESTIONS
What are the goals of therapy and recommendations for the treatment of adult patients with:
• intermediate stage hepatocellular carcinoma?
• advanced stage hepatocellular carcinoma?
• terminal stage hepatocellular carcinoma?</td>
</tr>
<tr>
<td></td>
<td>Methodik

Grundlage der Leitlinie

This guideline was developed to promote evidence-based practice in Alberta. It was compiled from the results of randomized controlled trials and systematic reviews, derived from an English language and relevant term search of PubMed and MEDLINE from 1990 forward. It takes into consideration related information presented at local, national, and international meetings as well as the Alberta Provincial Gastrointestinal Tumour Team’s interpretation of the data.
Suchzeitraum: This guideline was developed to promote evidence-based practice in Alberta. It was compiled from the results of randomized controlled trials and systematic reviews, derived from an English language and relevant term search of PubMed and MEDLINE from 1990 forward. It takes into consideration related information presented at local, national, and international meetings as well as the Alberta Provincial Gastrointestinal Tumour Team’s interpretation of the data. The 2015 update did not necessitate a full literature review; recommendations were modified based on a consensus discussion at the 2014 Annual Gastrointestinal Tumour Team Meeting.

LoE/GoR

<table>
<tr><th>Level</th><th>Description of Evidence</th></tr>
<tr><td>1a</td><td>Systematic reviews of randomized controlled trials</td></tr>
<tr><td>1b</td><td>Individual randomized controlled trials</td></tr>
<tr><td>1c</td><td>All or none randomized controlled trials</td></tr>
<tr><td>2a</td><td>Systematic reviews of cohort studies</td></tr>
<tr><td>2b</td><td>Individual cohort study or low quality randomized controlled trial</td></tr>
<tr><td>2c</td><td>Outcomes research</td></tr>
<tr><td>3a</td><td>Systematic review of case-control studies</td></tr>
<tr><td>3b</td><td>Individual case-control study</td></tr>
<tr><td>4</td><td>Case series</td></tr>
<tr><td>5</td><td>Expert opinion without explicit critical appraisal or based on physiology, bench research, or “first principles”</td></tr>
</table>
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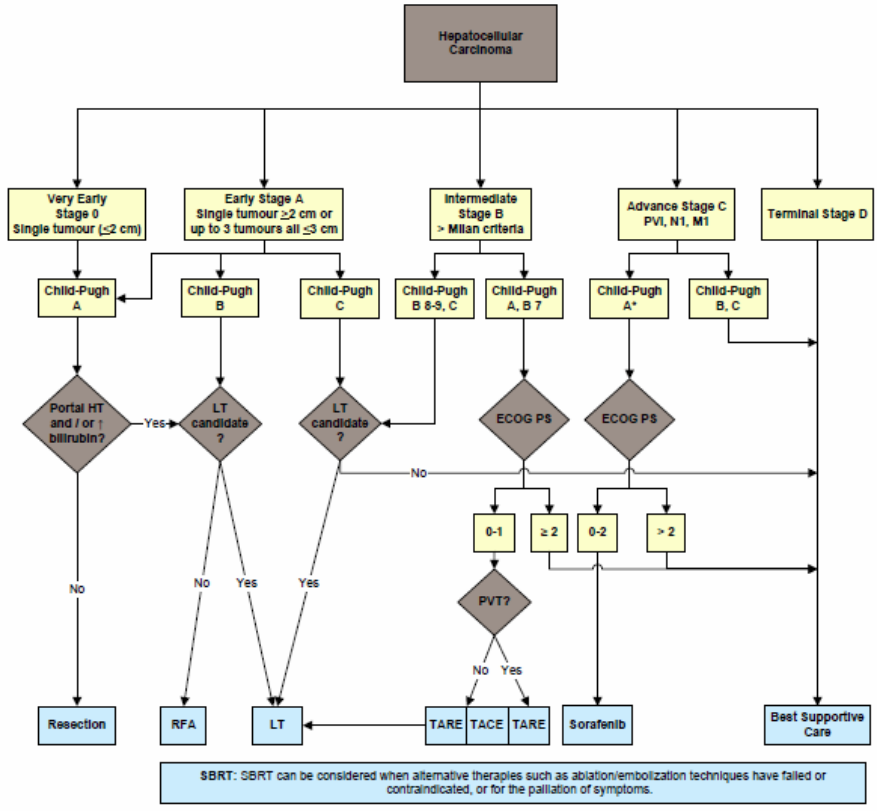
<td>Freitext/Empfehlungen/Hinweise</td>
</tr>
</table>

Table 1. Barcelona Clinic Liver Cancer Staging System.[7]*

BCLC Stage	Tumour Stage	Child-Pugh Class	ECOG PS	Therapy options recommended by Sherman et al. 2011[7]
Very early (0)	Single ≤ 2cm	A	0	Resection or Transplantation or RFA
Early (A)	Single ≤ 5cm Or up to three all ≤ 3cm	A or B	0	
Intermediate (B)	Multinodular	A or B	0	TACE
Advanced (C)	PVI, N1, M1	A or B	1-2	Sorafenib
End-stage (D)**	Any	C	>2	Symptomatic treatment

*This table is adapted from Sherman et al. 2011[7] Please see Figure 2 for Alberta specific recommendations for the management of HCC
**Patients who are PVI, N1, M1 and Child-Pugh B or C may be treated as end-stage.
BCLC = Barcelona Clinic Liver Cancer; PS = performance status; PVI = portal vein invasion; N1 = lymph node metastasis; M1 = distant metastasis; PS = Performance Status; RFA = radiofrequency ablation; TACE = transarterial chemoembolization

Figure 2. Algorithm for the Management of HCC According to the Updated AHS Clinical Practice Guidelines (adapted from the Alberta[8] and Canadian[7] HCC algorithms).



Abbreviations / Notes: Milan criteria = single HCC ≤5cm or 3 HCC largest ≤3cm; PVI = portal vein invasion; N1 = lymph node metastasis; M1 = metastasis; portal HT = portal hypertension (splenomegaly, esophageal varices, ascites, platelets < 100 or hepatic venous pressure gradient >10mmHg); LT candidate = liver transplant candidate = total tumour volume <115mm³ AND alphafetoprotein <400ng/mL, age <70 (if age 65-69 no major comorbidities), good social support and appropriate abstinence and rehabilitation if addiction issues; ECOG PS= Eastern Cooperative Oncology Group performance status; PVT = portal vein thrombosis (bland); RFA = radiofrequency ablation; LT = liver transplantation; TACE = transarterial chemoembolization; TARE = transarterial radioembolization with yttrium90 microspheres; SBRT = stereotactic body radiotherapy.
* Consider enrollment of patients with Child-Pugh A, B 7 in a clinical trial

DKG, 2013 [9,10].	Fragestellung/Zielsetzung: Empfehlungen zur Diagnostik und Therapie des hepatozellulären Karzinoms
Diagnostik und	Methodik

Therapie des hepatozellulären Karzinoms	Grundlage der Leitlinie Grundlage der Leitlinie: Die Entwicklung der Leitlinie erfolgte in einem strukturierten Prozess nach dem AWMF-Regelwerk (http://www.awmf.org/leitlinien/awmf-regelwerk.html). Als Ausgangspunkt für eine Literaturrecherche erfolgte im Vorfeld eine Gliederung der Leitlinie nach verschiedenen Themenkomplexen. Die Schlüsselfragen wurden im interdisziplinären Konsensus auf dem ersten Arbeitstreffen (Kick-off-Meeting) identifiziert. Um die Schlüsselfragen beantworten zu können, wurde ein Konzept zu ihrer gegenüberstellenden Darstellung mit den Aussagen internationaler Leitlinien und der ihnen zugrundeliegenden Literatur entwickelt. In einem zweiten Treffen unter Beteiligung aller Mandatsträger der unterschiedlichen Fachgesellschaften und Institutionen wurde geklärt, auf welcher Grundlage (De-Novo-Recherche, Leitlinienadaptation oder reiner Expertenkonsens) die Schlüsselfragen beantwortet werden sollen Suchzeitraum: Im Oktober 2009 und Januar 2010 erfolgte die zentrale und systematische Suche nach Leitlinien für die Diagnostik und Therapie des hepatozellulären Karzinoms, die entweder auf Englisch oder Deutsch zwischen Januar 2000 bis November 2009 publiziert wurden. • **Gültigkeit nach Überprüfung durch das LL-Sekretariat verlängert bis 30.04.2018** **Schema der Evidenzgraduierung nach Oxford** Zur Klassifikation des Verzerrungsrisikos der identifizierten Studien wurde in dieser Leitlinie das in Tabelle 7 aufgeführte System des Oxford Centre for Evidence-based Medicine in der Version von 2009 verwendet. Dieses System sieht die Klassifikation der Studien für verschiedene klinische Fragestellungen (Nutzen von Therapie, prognostische Aussagekraft, diagnostische Wertigkeit) vor. LoE/GoR **Schema der Evidenzgraduierung nach Oxford**

Tabelle 7: Schema der Evidenzgradulerung nach Oxford (Version März 2009)

Level	Therapy / Prevention, Aetiology / Harm	Prognosis	Diagnosis	Differential diagnosis / symptom prevalence study	Economic and decision analyses
1a	SR (with homogeneity of RCTs	SR (with homogeneity)of inception cohort studies; CDR validated in different populations	SR (with homogeneity) of Level 1 diagnostic studies; CDR with 1b studies from different clinical centres	SR (with homogeneity)o f prospective cohort studies	SR (with homogeneity) of Level 1 economic studies
1b	Individual RCT (with narrow Confidence Interval)	Individual inception cohort study with > 80% follow-up; CDR validated in a single population	Validating cohort study with good reference standards; or CDR tested within one clinical centre	Prospective cohort study with good follow-up	Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses
1c	All or none	All or none case-series	Absolute SpPins and SnNouts	All or none case-series	Absolute better-value or worse-value analyses
2a	SR (with homogeneity) of cohort studies	SR (with homogeneity) of either retrospective cohort studies or untreated control groups in RCTs	SR (with homogeneity) of Level > 2 diagnostic studies	SR (with homogeneity) of 2b and better studies	SR (with homogeneity) of Level > 2 economic Studies
2b	Individual cohort study (including low quality RCT; e.g., < 80%	Retrospective cohort study or follow-up of untreated control	Exploratory cohort study with good reference standards;	Retrospective cohort study, or poor follow-up	Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and

Level	Therapy / Prevention, Aetiology / Harm	Prognosis	Diagnosis	Differential diagnosis / symptom prevalence study	Economic and decision analyses
	follow-up)	patients in an RCT; Derivation of CDR or validated on split-sample only	CDR after derivation, or validated only on splitsample or databases		including multi-way sensitivity analyses
2c	"Outcomes" Research; Ecological studies	"Outcomes" Research		Ecological studies	Audit or outcomes Research
3a	SR (with homogeneity) of case-control studies		SR (with homogeneity) of 3b and better studies	SR (with homogeneity) of 3b and better studies	SR (with homogeneityi) of 3b and better studies
3b	Individual Case-Control Study		Non-consecutive study; or without consistently applied reference standards	Non-consecutive cohort study, or very limited population	Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations
4	Case-series (and poor quality cohort and case-control studies)	Case-series (and poor quality prognostic cohort studies)	Case-control study, poor or non-independent reference standard	Case-series or superseded reference standards	Analysis with no sensitivity analysis
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on economic theory or "first principles"

Schema der Empfehlungsgraduierung

Die OL-Methodik sieht eine Vergabe von Empfehlungsgraden durch die Leitlinien-Autoren im Rahmen eines formalen Konsensusverfahrens vor. Dementsprechend wurde ein durch die AWMF moderierter, mehrteiliger nominaler Gruppenprozess durchgeführt. Am Ende dieses Gruppenprozesses wurden die Empfehlungen von den stimmberechtigten Mandatsträgern (siehe Kapitel 1.7) formal abgestimmt. Die Ergebnisse der jeweiligen Abstimmungen sind entsprechend den Kategorien in Tabelle 9 den Empfehlungen zugeordnet.

In der Leitlinie werden zu allen evidenzbasierten Statements (siehe Kapitel 2.2.3) und Empfehlungen das Evidenzlevel (siehe 2.2.1) der zugrundeliegenden Studien sowie bei Empfehlungen zusätzlich die Stärke der Empfehlung (Empfehlungsgrad) ausgewiesen. Hinsichtlich der Stärke der Empfehlung werden in dieser Leitlinie drei Empfehlungsgrade unterschieden (siehe Tabelle 8), die sich auch in der Formulierung der Empfehlungen jeweils widerspiegeln.

Tabelle 8: Schema der Empfehlungsgraduierung

Empfehlungsgrad	Beschreibung	Syntax
A	Starke Empfehlung	soll
B	Empfehlung	sollte
C	Empfehlung offen	kann

Tabelle 9: Konsensusstärke

Konsenstärke	Prozentuale Zustimmung
Starker Konsens	> 95% der Stimmberechtigten
Konsens	> 75 – 95% der Stimmberechtigten
Mehrheitliche Zustimmung	> 50 – 75% der Stimmberechtigten
Dissens	< 50% der Stimmberechtigten

Statements
Als Statements werden Darlegungen oder Erläuterungen von spezifischen Sachverhalten oder Fragestellungen ohne unmittelbare Handlungsaufforderung bezeichnet. Sie werden entsprechend der Vorgehensweise bei den Empfehlungen im Rahmen eines formalen Konsensusverfahrens verabschiedet und können entweder auf Studienergebnissen oder auf Expertenmeinungen beruhen.

Good Clinical Practice (GCP)
Als 'Good Clinical Practice (GCP)' werden Empfehlungen bezeichnet, zu denen keine Recherche nach Literatur durchgeführt wurde. In der Regel adressieren diese Empfehlungen Vorgehensweisen der guten klinischen Praxis, zu denen keine wissenschaftlichen Studien notwendig sind bzw. erwartet werden können. Für die Graduierung der GCPs wurden keine Symbole verwendet, die Stärke der Empfehlung ergibt sich aus der verwendeten Formulierung (soll/sollte/kann) entsprechend der Abstufung in Tabelle 8.

Empfehlungen zum Staging und Klassifikation

Konsensbasierte Empfehlung:

- Die pTNM-Klassifikation soll als morphologisches Staging eingesetzt werden. Um die Prognose eines HCCs beurteilen zu können, sollte das Staging-System zusätzlich das Tumorstadium, die Leberfunktion und den körperlichen Leistungszustand des Patienten sowie den Effekt der Therapie auf die Lebenserwartung berücksichtigen. Die BCLC-Klassifikation sollte daher als integriertes Staging in der Therapiestratifikation des HCCs eingesetzt werden. [GCP; starker Konsens]

BCLC-Klassifikation aus

BCLC Stadium	Allgemeinzustand	Tumor	Leberfunktion
A1	ECOG 0	1 Herd < 5 cm	Keine portale Hypertension

			normales Bilirubin
A2	ECOG 0	1 Herd < 5 cm	portale Hypertension normales Bilirubin
A3	ECOG 0	1 Herd < 5 cm	portale Hypertension Bilirubin erhöht
A4	ECOG 0	1 Herd < 5 cm	Child-Pugh A oder B
B	ECOG 0	groß multilokulär	Child-Pugh A oder B
C	ECOG 1-2	Gefäßinvasion oder Metastasen	Child-Pugh A oder B
D	ECOG 3-4	egal	Child-Pugh C

Therapieempfehlungen:

3.5.2.2. Patienten mit 1-3 Tumoren < 3 cm

3.40.	Konsensbasierte Empfehlung
GCP	Bei CHILD-A- und CHILD-B-Zirrhose mit adäquater Leberfunktion und nur gering- oder mäßiggradiger portaler Hypertension (Bilirubin < 2 mg/dl; keine Splenomegalie, Thrombozyten > 100.000) sollte bei bis zu 3 HCC-Herden < 3cm eine Radiofrequenz-Ablation (RFA) oder eine Resektion durchgeführt werden starker Konsens

3.5.2.3. Patienten mit 1-3 Tumoren 3-5 cm

3.41.	Konsensbasierte Empfehlung
GCP	Bei CHILD-A- und CHILD-B-Zirrhose mit adäquater Leberfunktion und nur gering- oder mäßiggradiger portaler Hypertension (Bilirubin < 2 mg/dl; keine Splenomegalie, Thrombozyten > 100.000) sollte bei bis zu 3 HCC-Herden > 3 cm und < 5 cm eine individuelle Abwägung zwischen Radiofrequenz-Ablation (RFA) und Resektion interdisziplinär erfolgen.
	starker Konsens

3.42.	Evidenzbasierte Empfehlung
Empfehlungsgrad A	Bei CHILD-A- und CHILD-B-Zirrhose mit adäquater Leberfunktion und nur gering- oder mäßiggradiger portaler Hypertension (Bilirubin < 2 mg/dl; keine Splenomegalie, Thrombozyten > 100.000) soll, wenn bei einem HCC-Herd > 3cm und < 5 cm eine Radiofrequenz-Ablation (RFA) durchgeführt wird, vorher embolisiert werden.
Level of Evidence 1a	De Novo : [215] [216] [217] [218] [219] [220] starker Konsens

3.5.2.4. Patienten mit Tumoren > 5 cm

3.43.	Konsensbasierte Empfehlung
Empfehlungsgrad GCP	Bei CHILD-A- und CHILD-B-Zirrhose mit adäquater Leberfunktion und ohne portale Hypertension, geeigneter Lokalisation und ausreichender Leberreserve kann bei einer Tumorgröße > 5 cm eine Resektion durchgeführt werden. starker Konsens

3.44.	Konsensbasierte Empfehlung
GCP	Die Resektabilität wird bestimmt durch anatomische und funktionelle Kriterien. Die Indikation zur Resektion orientiert sich an der lokalen Resektabilität, den Behandlungsmöglichkeiten eines evtl. extrahepatischen Tumorwachstums und an der allgemeinen Operabilität. Die Resektabilität soll durch einen erfahrenen hepatobiliären Chirurgen festgestellt werden.

Lokal Ablative Verfahren.

3.45.	Empfehlung
Empfehlungsgrad B	Die Radiofrequenz-Ablation (RFA) sollte als Standardmethode der perkutanen Lokalablation des HCCs betrachtet werden.
Level of Evidence 2b	De Novo: [229] [230]
	starker Konsens

Transarterielle Verfahren

Patientenselektion für die Durchführung eines transarteriellen Verfahrens

Evidenzbasierte Empfehlung:

- Die transarterielle Chemoembolisation (TACE) soll bei Patienten durchgeführt werden, bei denen ein kurativ es Verfahren nicht möglich ist und die folgende Kriterien aufweisen: solitäres oder multifokales HCC ohne extrahepatische Metastasierung und ECOG ≤ 2, im Stadium CHILD-Pugh A oder B. [LoE: 1b; GoR: A; starker Konsens]

Konsensbasierte Empfehlung:

- Die Indikation zur transarteriellen Chemoembolisation (TACE) soll in einem interdisziplinären Tumorboard gestellt werden. [GCP; starker Konsens]
- Im Einzelfall kann die transarterielle Chemoembolisation (TACE) bei nicht führender systemischer Metastasierung erwogen werden. [GCP; starker Konsens]
- Die transarterielle Chemoembolisation (TACE) kann bei Patienten mit segmentaler Pfortaderthrombose erwogen werden. [GCP; starker Konsens]

Systemische bzw. nicht auf die Leber beschränkte Verfahren
Patientenselektion für eine systemische Therapie:

Evidenzbasierte Empfehlung:

- Bei HCC-Patienten im Stadium Child-Pugh A mit Fernmetastasen oder einer hepatischen Tumormanifestation, die lokoregionär nicht kontrolliert

	werden kann, mit einem ECOG-Status 0-2 und einer Lebenserwartung von > 3 Monaten, soll eine Systemtherapie mit Sorafenib angeboten werden. [LoE: 1a; GoR: A; starker Konsens] Leitlinienadaption [1] • Außer Sorafenib sollte eine Systemtherapie mit Einzelsubstanzen, eine Kombinationschemotherapie, eine intraarterielle Chemotherapie oder eine Kombination von Chemotherapie und Strahlentherapie nur im Rahmen von klinischen Studien durchgeführt werden. [LoE: 2a; GoR: B; starker Konsens] Leitlinienadaption [1] *Konsensbasierte Empfehlung:* • Die palliative Therapie mit Sorafenib sollte nicht über einen symptomatischen und radiologischen Progress hinaus fortgesetzt werden. Die Toxizität der Therapie soll engmaschig überwacht und berücksichtigt werden. [GCP; starker Konsens] *Evidenzbasiertes Statement:* • Bei HCC-Patienten im Stadium Child-Pugh B konnte für eine Sorafenibtherapie bisher kein Überlebensvorteil nachgewiesen werden. [LoE: 3b; staker Konsens] *Evidenzbasierte Empfehlung:* • Bei HCC-Patienten im Stadium Child-Pugh B sollte keine Therapie mit Sorafenib durchgeführt werden. [LoE: 3b; GoR: B; Konsens] *Konsensbasierte Empfehlung:* Bei HCC-Patienten im Stadium Child-Pugh C soll keine Therapie mit Sorafenib durchgeführt werden. [GCP; starker Konsens] **3.6.4. Indikation für eine Zweitlinientherapie** **3.74. Konsensbasierte Empfehlung** **GCP** Nach Progress unter einer Sorafenibtherapie soll eine bestmögliche supportive Therapie erfolgen. Andere medikamentöse Tumortherapien sollen nur im Rahmen klinischer Studien erfolgen. starker Konsens
NCCN, 2017 [13]. Hepatobiliary Cancers (Version 3.2017)	Fragestellung/Zielsetzung: Empfehlungen zur Diagnostik und Therapie von hepatobiliären Krebserkrankungen
	Methodik Grundlage der Leitlinie

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines for Hepatobiliary Cancers, an electronic search of the PubMed database was performed to obtain key literature in the field of hepatobiliary cancers published between August 26, 2015 and August 25, 2016, using the following search terms: (hepatocellular carcinoma) OR (liver cancer) OR (biliary tract cancer) OR (gallbladder cancer) OR (cholangiocarcinoma). The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.[3]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Practice Guideline; Guidelines; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The PubMed search resulted in 130 citations, and their potential relevance was examined. The data from key PubMed articles and articles from additional sources deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN website (www.NCCN.org).

LoE/GoR

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

Empfehlungen

	Treatment Options All patients with HCC should be carefully evaluated for the many available treatment options. It is important to reiterate that the management of patients with HCC is complicated by the presence of underlying liver disease. Furthermore, it is possible that the different etiologies of HCC and their effects on the host liver may impact treatment response and outcome. The treatment of patients with HCC often necessitates multidisciplinary care with the involvement of hepatologists, cross-sectional radiologists, interventional radiologists, transplant surgeons, pathologists, medical oncologists, and surgical oncologists, thereby requiring careful coordination of care.[31] **→ Siehe Anhang!**

Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

NICE, 2017 [14]. Sorafenib for treating advanced hepatocellular carcinoma	Recommendations 1.1 Sorafenib is recommended as an option for treating advanced hepatocellular carcinoma only for people with Child-Pugh grade A liver impairment, only if the company provides sorafenib within the agreed commercial access arrangement. 1.2 This recommendation is not intended to affect treatment with sorafenib thatwas started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop. Evidence: 3.1 The appraisal committee (section 6) considered evidence submitted by Bayer and a review of this submission by the evidence review group. This appraisal was a Cancer Drugs Fund reconsideration of the published NICE technology appraisal guidance on sorafenib for treating advanced hepatocellular carcinoma. 3.2 The company's original submission presented clinical effectiveness data from the SHARP study. SHARP was a multicentre, double-blind, placebo-controlled, randomised trial in patients with advanced hepatocellular carcinoma who had not received previous systemic treatment. The study included 602 patients and assessed the effect of sorafenib plus best supportive care (n=299) compared with placebo plus best supportive care (n=303). The primary outcomes in SHARP were overall survival and time to symptomatic progression.

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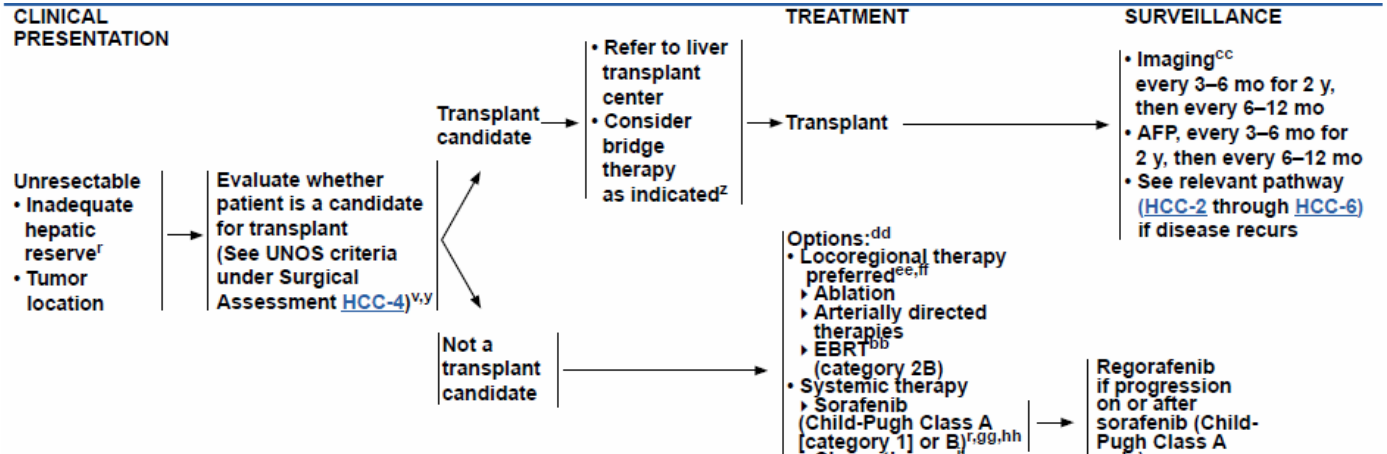
Anhang

NCCN, 2017 [13]



[r]See Child-Pugh Score (HCC-C).
[v]See Principles of Surgery (HCC-D).
[y]Mazzaferro V, Regalia E, Doci, R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334(11):693-700.
[z]Many transplant centers consider bridge therapy for transplant candidates. (See Discussion).
[bb]Case series and single-arm studies suggest safety and possible efficacy of radiation therapy in selected cases. (See Principles of Locoregional Therapy (HCC-E).
[cc]Multiphasic abdominal MRI or multi-phase CT scans for liver assessment are recommended. Consider chest CT. See Principles of Imaging (HCC-A).
[dd]Order does not indicate preference. The choice of treatment modality may depend on extent/location of disease, hepatic reserve, and institutional capabilities.
[ee]See Principles of Locoregional Therapy (HCC-E).
[ff]Use of chemoembolization has also been supported by randomized controlled trials in selected populations over best supportive care. (Lo CM, Ngan H, Tso WK, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology 2002;35:1164-1171) and (Llovet JM, Real MI, Montaña X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomized controlled trial. Lancet 2002;359:1734-1739).
[gg]For selected patients, two randomized phase 3 clinical trials have demonstrated survival benefits. (Llovet J, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma New Engl J Med 2008;359(4):378-390) and (Cheng A, Kang Y, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia Pacific region with advanced hepatocellular carcinoma: a phase III randomized,double-blind, placebo-controlled trial. Lancet Oncol 2009;10:25-34).
[hh]Caution: There are limited safety data available for Child-Pugh Class B or C patients and dosing is uncertain. Use with extreme caution in patients with elevated bilirubin levels. (Miller AA, Murry K, Owzar DR, et al. Phase I and pharmacokinetic study of sorafenib in patients with hepatic or renal dysfunction:CALGB 60301. J Clin Oncol 2009;27:1800-1805).The impact of sorafenib on patients potentially eligible for transplant is unknown.
[ii]There are limited data supporting the use of chemotherapy, and its use in the context of a clinical trial is preferred.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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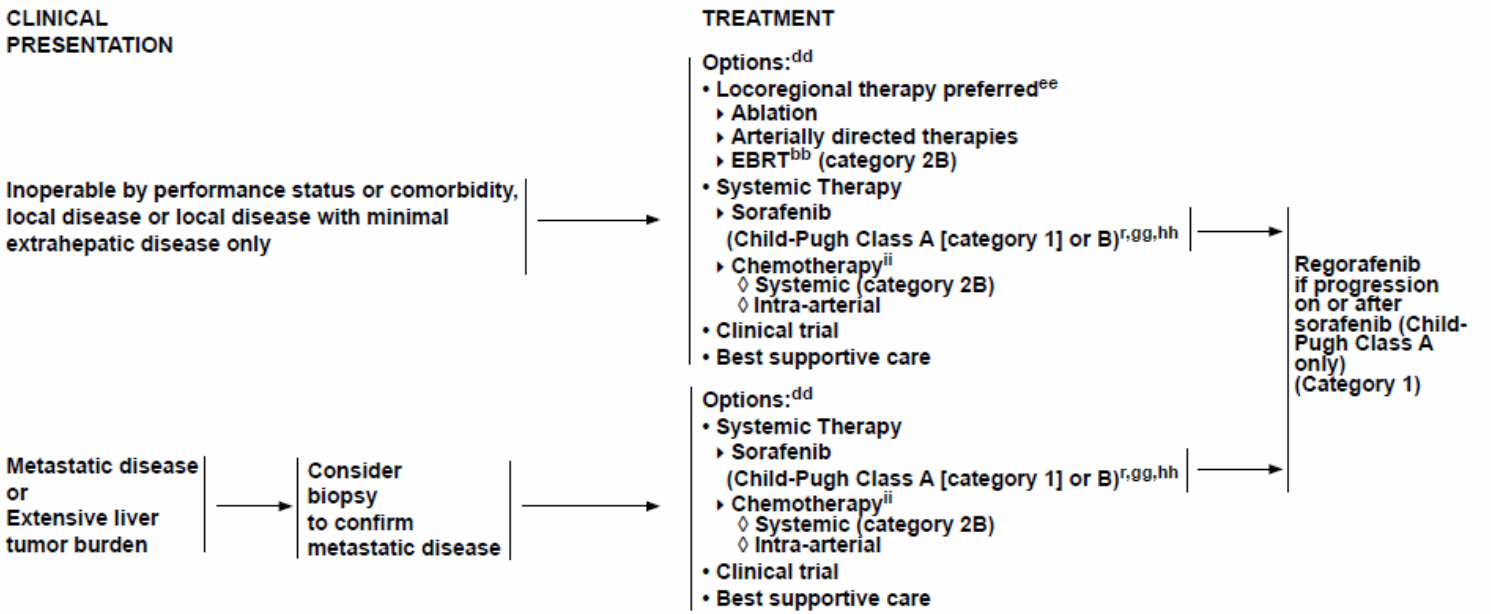
HCC-5



[r] See Child-Pugh Score (HCC-C).

[bb] Case series and single-arm studies suggest safety and possible efficacy of radiation therapy in selected cases. (See Principles of Locoregional Therapy (HCC-E)).

[dd] Order does not indicate preference. The choice of treatment modality may depend on extent/location of disease, hepatic reserve, and institutional capabilities.

[ee] See Principles of Locoregional Therapy (HCC-E).

[gg] For selected patients, two randomized phase 3 clinical trials have demonstrated survival benefits. (Llovet J, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. New Engl J Med 2008;359(4):378-390) and (Cheng A, Kang Y, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009;10:25-34).

[hh] Caution: There are limited safety data available for Child-Pugh Class B or C patients and dosing is uncertain. Use with extreme caution in patients with elevated bilirubin levels. (Miller AA, Murry K, Owzar DR, et al. Phase I and pharmacokinetic study of sorafenib in patients with hepatic or renal dysfunction: CALGB 60301. J Clin Onc 2009;27:1800-1805). The impact of sorafenib on patients potentially eligible for transplant is unknown.

[ii] There are limited data supporting the use of chemotherapy, and its use in the context of a clinical trial is preferred.

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Detaillierte Darstellung der Recherchestrategie

Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) am 02.10.2017

#	Suchfrage
#1	MeSH descriptor: [Carcinoma, Hepatocellular] explode all trees
#2	MeSH descriptor: [Liver Neoplasms] explode all trees
#3	hepatoma*:ti,ab,kw or HCC:ti,ab,kw or hepatocarcinoma*:ti,ab,kw or hepatocellular next carcinom*:ti,ab,kw or liver cell carcinoma*:ti,ab,kw
#4	liver:ti or "hepatic":ti or "hepatocellular":ti or "hepatobiliary":ti
#5	cancer*:ti or tumor* or tumour*:ti or neoplas*:ti or carcinoma* or adenocarcinoma*:ti or malignan*:ti
#6	#4 and #5
#7	#1 or #2 or #3 or #6
#8	#7 Publication Year from 2012 to 2017, in Cochrane Reviews (Reviews only) and Technology Assessments

SR, HTAs in Medline (PubMed) am 02.10.2017

#	Suchfrage
#1	Carcinoma, Hepatocellular[MeSH Terms]
#2	Liver Neoplasms[mh:noexp]
#3	((hepatocarcinoma*[Title]) OR hepatoma*[Title]) OR HCC[Title]
#4	(liver[Title] OR hepatic[Title] OR hepatocellular[Title] OR hepatobiliary[Title])
#5	(((((((cancer*[Title]) OR tumor[Title]) OR tumors[Title]) OR tumour*[Title]) OR neoplasm*[Title]) OR carcinoma*[Title]) OR adenocarcinoma*[Title]) OR malignan*[Title]
#6	#4 AND #5
#7	#1 OR #2 OR #3 OR #6
#8	((((((((((treatment*[Title/Abstract]) OR therapy[Title/Abstract]) OR therapies[Title/Abstract]) OR therapeutic[Title/Abstract]) OR monotherap*[Title/Abstract]) OR polytherap*[Title/Abstract]) OR pharmacotherap*[Title/Abstract]) OR effect*[Title/Abstract]) OR efficacy[Title/Abstract]) OR treating[Title/Abstract]) OR treated[Title/Abstract]) OR management[Title/Abstract]) OR drug*[Title/Abstract]
#9	#7 AND #8
#10	carcinoma, hepatocellular/therapy[MeSH Terms]
#11	liver neoplasms/therapy[mh:noexp]
#12	#9 OR #10 OR #11
#13	(#12) AND ((Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp]) OR (((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR

	(systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))
#14	(#13) AND ("2012/10/01"[PDAT] : "2017/10/02"[PDAT])
#15	(#14) NOT "The Cochrane database of systematic reviews"[Journal]

Leitlinien in Medline (PubMed) am 02.10.2017

#	**Suchfrage**
#1	Carcinoma, Hepatocellular[MeSH Terms]
#2	Liver Neoplasms[mh:noexp]
#3	((hepatocarcinoma*[Title]) OR hepatoma*[Title]) OR HCC[Title]
#4	(liver[Title] OR hepatic[Title] OR hepatocellular[Title] OR hepatobiliary[Title])
#5	(((((((cancer*[Title]) OR tumor[Title]) OR tumors[Title]) OR tumour*[Title]) OR neoplasm*[Title]) OR carcinoma*[Title]) OR adenocarcinoma*[Title]) OR malignan*[Title]
#6	#4 AND #5
#7	#1 OR #2 OR #3 OR #6
#8	#7 AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[Title]))
#9	#8 ("2012/10/01"[PDAT] : "2017/10/02"[PDAT]))))

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