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Clinical features and outcomes of hepatocellular carcinoma in Caucasian cirrhotic patients on long-term analogue therapy for hepatitis B

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Background

- Patients with Hepatitis-B-Virus (HBV) infection are at high risk of progression of cirrhosis and decompensation, hepatocellular carcinoma (HCC) and liver-related death

- Studies with long-term administration of third-generation nucleotide analogues (NUCs) have clearly shown to stabilize liver disease → reverse and prevent clinical decompensation

- Chemoprevention of HCC under HBV therapy is still a matter of debate

- Prospective studies to assess the outcome of patients developing HCC during anti-HBV therapy are lacking

Antiviral therapy in HBV patients

- Indications: **presence of cirrhosis, serum ALT level, serum HBV DNA level** and additional indications (e.g. malignancy and pregnancy)

Clinical Practice Guidelines

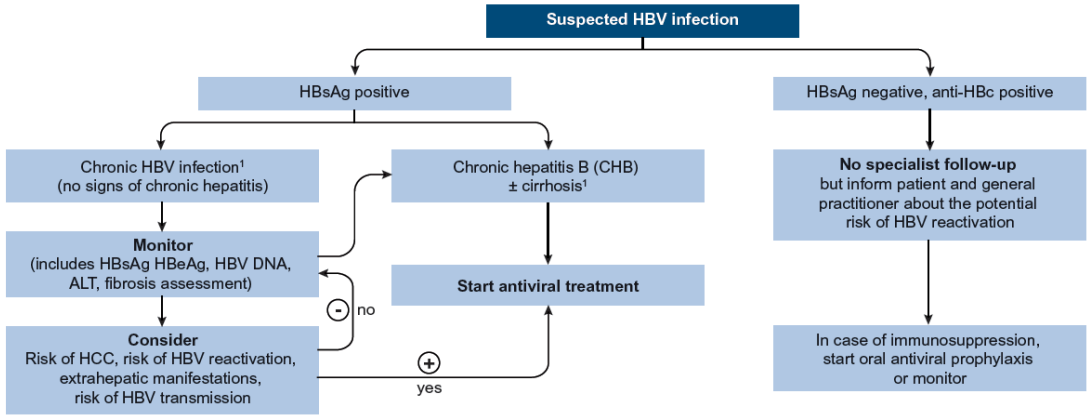

Fig. 2. Algorithm for the management of HBV infection. [1]see definitions in text and Fig. 1.

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Antiviral therapy in HBV patients

- Main Goal: Improve survival by **preventing disease progression and HCC development**
  + prevention of mother to child transmission and hepatitis B reactivation

- Endpoints: Long-term suppression of HBV DNA, loss of HBeAg (when initially HBeAg-positive), ALT normalisation, and loss of HBsAg

Aim of the study

To define the clinical features and outcomes of HCC in long-term NUC-treated HBV patients

Primary endpoints: Clinical features of HCC and Alpha-fetoprotein (AFP) pattern

Secondary endpoints: Response to treatments, development of early and late recurrence after therapy for HCC, and survival

Material and Methods

Design:
- Retroprospective study

Setting:
- HCC Surveillance among NUC-treated HBV patients in 2 different hospitals in Milan, Italy

Patients:
- 76 de novo HCCs diagnosed between 2005 and 2016 enrolled
- All patients treated with NUC therapy for HBV-related liver disease
- Exclusion criteria: HCC detected at baseline or occurring within 6 months after starting treatment; HIV and HDV coinfections; autoimmune hepatitis

HBV therapy:

- Initial: Lamivudine or Entecavir (ETV) or Tenofovir disoproxil fumarate (TDF) as monotherapy
- For lamivudine-resistant patients Adefovir was added (from 2003) switched to TDF from 2008

Surveillance:

- Abdominal ultrasound and serum AFP levels every 6 months in cirrhotic patients
- AFP monitoring every 6 months for patients with advanced fibrosis (Ishak score 4-5)

HCC diagnosis:

- Per 2005 American Association for the Study of the Liver Diseases criteria (AASLD) until 2010
- From 2010 per updated criteria using contrast imaging techniques (CEUS, CT, MRI)
- Ultrasound-guided fine-needle biopsy in nodules escaping radiological diagnosis
- Staging at enrollment (MRI or CT - chest-CT, bone scintigraphy when clinically required)
- HCC stage according to Barcelona Clinic Liver Cancer (BCLC) classification

Treatment for HCC:

- Evaluated by multidisciplinary clinical team
- Management changing in line with the updating of clinical guidelines
- Treatment selection according to the specific expertise of each Centre and the general condition of each patient; and other factors as tumor site
- Response to therapy defined by EASL and modified RECIST criteria (CT or MRI)

Statistical analysis:

- Fisher`s exact or chi-square for quantitative and qualitative variables
- Kaplan-Meier to estimate outcome rates
- Log-rank test to compare curves between patient groups
- Kalbfleisch-Prentice method for competing risk framework

Results: Demographical and Clinical features of study population (n=76)

TABLE 1 Demographical, clinical and virological characteristics of the 76 patients with HBV-related hepatocellular carcinoma developed during long-term treatment with nucleos(t)ide analogues

Variable	N = 76
Age, y[a]	67 (40-83)
Males	64 (84%)
Ethnicity	
Caucasian	73 (96%)
Asian	2 (3%)
Indian Americans	1 (1%)
Family history of hepatocellular carcinoma	2 (3%)
Alcohol abuse	3 (4%)
Smoking habits	19 (25%)
Overweight (BMI 25-29.9 kg/m^2)	29 (38%)
Obesity (BMI >30 kg/m^2)	10 (13%)
Class I	9
Class II	1
Diabetes	12 (16%)
Cirrhosis[b]	70 (92%)
Child-Pugh Turcotte score	
A	64 (91%)
B	5 (8%)
C	1 (1%)
Transient elastography value >12 kPa[c]	15 (38%)
Oesophageal varices	13 (17%)
Small-sized varices	10 (13%)
Medium/large-sized varices	3 (4%)
qHBsAg, IU/mL[d]	644 (2-10 650)
HBeAg negative	72 (95%)
HBV DNA undetectable	73 (96%)
Genotype D[e]	40 (89%)
Nucleos(t)ide analogues	
ETV or TDF ± Lamivudine	57 (75%)
Lamivudine	10 (13%)
Lamivudine+Adefovir	9 (12%)
Duration of Nucleos(t)ide analogues treatment, mo[a]	81 (6-190)
ALT <41 IU/L	63 (83%)

BMI, body mass index; ETV, entecavir; TDF, tenofovir; ALT, alanine aminotransferase; qHBsAg, quantitative hepatitis B surface antigen; HBeAg, hepatitis B e antigen.
[a]Median (range); [b]at NUC start; [c]available in 55 patients (72%) and performed within 6 mo before diagnosis; [d]available in 41 patients (54%); [e]available in 45 patients (59%) at NUC start. Obesity grade I: BMI 30-34.9 kg/m^2; obesity grade II: BMI ≥35 kg/m^2.

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Results: Characteristics of tumours

Variable	N = 76
Single tumour node	59 (78%)
Node size, mm[a]	20 (6-57)
In "Milan criteria"	71 (93%)
In "Up to 7 criteria"	71 (93%)
Extra-hepatic disease[b]	2 (3%)
BCLC staging system	
0	17 (22%)
A	53 (70%)
B	2 (3%)
C	3 (4%)
D	1 (1%)
AFP levels, ng/mL[a]	4 (1-3615)
>7	27 (36%)
>200	4 (5%)

BCLC, Barcelona Clinic for Liver Cancer; AFP, alpha-fetoprotein.
[a]Median (range); [b]Macrovascular portal vein invasion in 2 and lymph-node metastasis in 1.

→ Among 5 patients with advanced stage: no difference in co-factors compared to patients ealier stage

→ AFP in 64% < 7ng/mL

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Treatment algorithm

First-line treatment: curative treatment in **59 (78%) patients**

- 30 (58%) Radio-frequency thermal ablation (RFTA)
- 21 (41%) surgical resection
- 8 patients were listed for Liver Transplant (LT) (in 5 patients bridge therapy)

Non curative approaches: **17 (22%) patients**

- 13 (76%) Transarterial Chemoembolization (TACE)
- 2 (12%) Radioembolization
- 2 (12%) Systemic medical treatment

Response

- **Complete response in 40 (59%) patients after first treatment** (excluding 8 LT)
  - 24 (60%) maintained complete response during 45.4 months of FUP
  - 16 (40%) experienced recurrence in 20.2 months → resection (1)/ RFTA (5) / TACE (8)/ Sorafenib (2)

- **Partial response in 13 (19%) patients**
  → Second-line treatment: LT (5), RFTA (7), TACE (1)

- **Stable disease in 2 (3%) patients** (treated with sorafenib)

- **Disease progression in 13 (9%) patients**
  - LT (3), RFTA (2), TACE (3) , Sorafenib (2), best supportive care (3)

→ Overall complete response in 45 (58%) patients

Survival

- **19 (25%) patients died** during 45 months after HCC diagnosis:
  - **15 (79%)** due to HCC progression
  - 4 (21%) for extra-hepatic reasons

  (no patients died for end-stage liver disease)

- Median overall survival (OS): **45 months**, 5-year OS: **69%**; 5-year OS in LF patients: **62%**

- Median liver-related survival: **45 months**, corresponding 5-year OS: **74%**

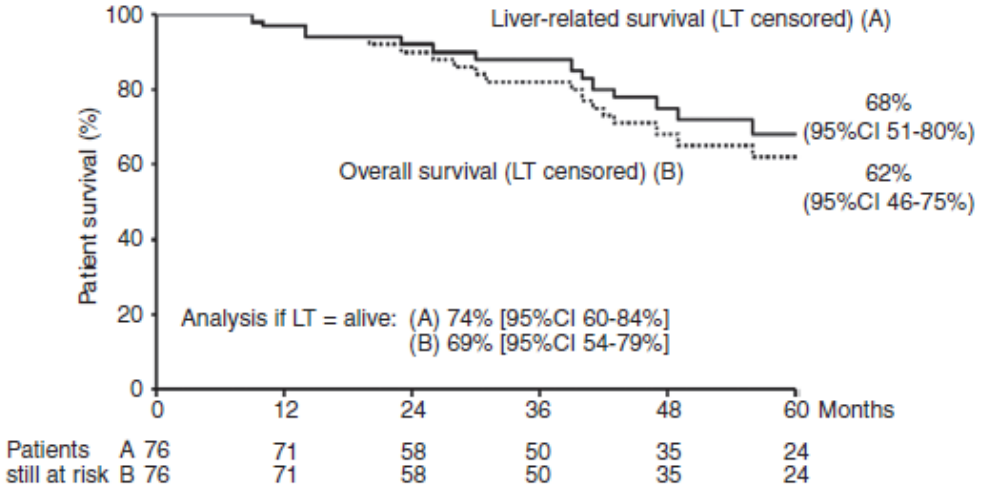

FIGURE 2 Cumulative 5-year overall and liver-related survival in 76 patients with hepatocellular carcinoma included in the study

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Discussion

1. Clinical and biological features of HCC occuring in long term NUC-therapy: small nodules, amenable for curative treatment– compared to previous studies

2. Excellent 5-year overall survival of patients of 69%

3. Limitation of diagnostic accurancy of AFP levels

Discussion

1. Clinical and biological features of HCC occuring in long term NUC-therapy:

   - Majority of cases presented with early, small, single HCC

Literature:

- Previous studies in untreated cirrhotics showed that HBV related HCC are aggressive
- Previous studies in NUC-treated patients, but from different geographical areas and smaller in size

Explanations:

Logistic:

- Compliance optimised by recall policies and frequent visits due to the need of NUC
- HCC surveillance is free in Italy (Europe) → access easier

Biological:

- Reduced inflammation and fibrosis, ; modification of adaptive immune reactions, effective control of HBV DNA → reduction of cytokines and growth factors

- Lower turnover of hepatocytes → reduces riks of host DNA mutations

Other:

- Finding of limited number of HCC detected in advanced stages more likely due to the limited sensibility of ultrasound

Discussion

2. Most important finding: **Excellent 5-year overall survival of patients of 69%; low risk of reccurence: 39% after 3 years**

Literature:

- Pooling data from studies in Asia: compared treated and untreated patients
  → showed better OS in treated patients and lower risk of death (statistical significance not reached ← small sample size and short FUP)

- In Asian studies 5-year survival of patients with HCC developed during treatment with NUC varied between 16% and 40%
  → might be due to more advance stage of HCC; no access to transplantation

- Many studies included patients treated with NUC only after HCC treatments (different study design)

Explanations:

- Possible Explanation: Strict adherence to surveillance protocol → identification of small treatable tumours

- Multiple anti-tumour procedures could been offered with well-preserved liver function (due to prolonged suppression of HBV infection)

Discussion

3. Diagnostic accurancy of AFP levels was limited: 64% serum levels < 7ng/mL

- In line with other data (Korea): patients with current NUC therapy showed poorer performance of AFP

Explanation:

- HBV replication might directly induce AFP expression in HCC

→ decreased sensitivity?

- Contrast: 2 Asian studies showed high positive predictive value for HCC development
- All studies showed a high specificity of AFP increase during NUC therapy (when ALT levels normal)

Limitations

- Lack of an untreated control group
  - unethical to offer cirrhotic patients no treatment
  - hard to compare data to old cohorts (progress in treatment)
- Sample Size
- Academic centre with large expertise
  - limit applicability of finding in other regions

Strengths

- Largest cohort study to date
- Management according to international updated criteria
- Patients were homogeneous and managed by a single centre unit

Conclusion

- Majority of HCC developing in Caucasian compensated cirrhosis patients on long-term NUC **are small (BCLC 0/A lesions), amenable to potentially curative treatments** with **survival benefits**

- NUC therapy can be associated to **low risk of HCC recurrence** among patients with HBV related HCC

- This study sheds new **light on the topic that HCC is almost the only complication in patients with HBV permanently suppressed by NUC**
  → **Identification and strict adherence to surveillance protocol is of importance**

→ Data must be confirmed in other independent cohorts

Gastroenterology 2018

Compliance With Hepatocellular Carcinoma Surveillance Guidelines Associated With Increased Lead-Time Adjusted Survival of Patients With Compensated Viral Cirrhosis

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C. Riebensahm, Journal Club 02.08.2018

Compliance with HCC surveillance guidelines

- Evidence of survival benefit associated with HCC surveillance remains controversial
- Previous studies limited

Aim of the study: Asses impact of complicance with surveillance guidelines on tumor burden, allocation of curative treatment, survival in patients with viral cirrhosis

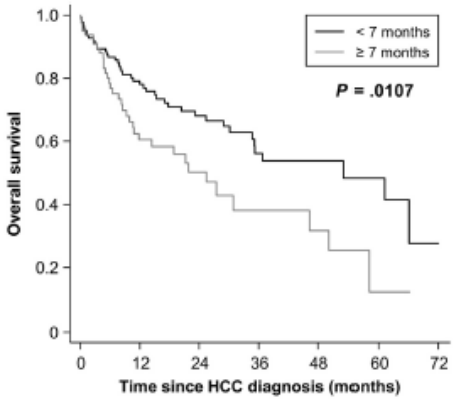
Setting:

- Large, prospective, multicenter ANRS CO12 CirVir cohort in France
- Patients were considered complicanct if time were <7 months ; noncompliant if > 7 months

Results

- Diagnosis of HCC in 216 patients (5-year cumulative incidence of HCC in cohort: 12.9%)
  - Compliance with guidelines: 129 patients **(60%)**
  - Patients **who were complied had a lower tumor burden** and **better access to curative treatments**

→ Median OS rate in compliant patients **57.8 months vs. 30 months** in noncompliant patients
→ After lead-time adjustment, this difference remained significant



Timeframe	Number at risk (events)												
< 7 months	128	(25)	75	(8)	46	(6)	24	(1)	12	(1)	7	(2)	1
≥ 7 months	86	(25)	32	(4)	17	(3)	6	(1)	5	(2)	1	(0)	0

Figure 1. Lead-time–adjusted survival as a function of compliance with HCC surveillance guidelines (sojourn time [*k*] 140 d): <7 months median overall survival, 53.2 mo (95% CI, 30.2–NA) vs ≥7 months median overall survival, 25.4 mo (95% CI, 10.8–46.4 mo).

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Conclusion

→ Survival advantage associated with compliance with HCC –screening guidelines

→ **Even a moderate deviation from screening guidelines had a dramatic impact on survival** (OS compliant patients twice as long as OS noncompliant patients)

→Improving compliance with surveillance guidelines should translated into a significant improvement in the prognosis

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Thank you for your attention !

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