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Hepatocellular carcinoma in central Slovakia – tertiary referral centre experience with 207 patients

Hepatocelulárny karcinóm na strednom Slovensku – analýza kohorty 207 pacientov v nemocnici 3. stupňa

L. Skladany[1], S. Adamcova-Selcanova[1], V. Malec[2], J. Badinkova[1], E. Pritzova[2], J. Janek[3], S. Okapec[4]

[1] HEGITO (Division of Hepatology, Gastroenterology and Liver Transplantation), Department of Internal Medicine II, Slovak Medical University, F. D. Roosevelt University Hospital, Banska Bystrica, Slovak Republic
[2] Department of Oncology, F. D. Roosevelt University Hospital, Banska Bystrica, Slovak Republic
[3] Department of Surgery, F. D. Roosevelt University Hospital, Banska Bystrica, Slovak Republic
[4] Department of Radiology, F. D. Roosevelt University Hospital, Banska Bystrica, Slovak Republic

Summary: **Introduction:** The features of hepatocellular carcinoma (HCC) differ between geographical regions. **Aim:** To analyze a cohort from a tertiary referral centre. **Methodology:** The study employed a retrospective analysis of consecutive outpatients. The inclusion criterion was patients with HCC and the exclusion criterion was insufficient data. The study interval was 2007–2016. **Results:** Cohort 207 patients, 95% with cirrhosis, 76% men; age 62 years. Etiology of liver disease: Alcoholic 106 (48%), hepatitis C 17%, hepatitis B 13%, non-alcoholic steatohepatitis 10%, cryptogenic 7%, non-cirrhotic 4%, other 1%. Diagnosis by surveillance 24%, otherwise 67%, unknown 9%. Diameter if diagnosis by SUR--HCC 5 cm, otherwise 8.6 cm (p = 0,001). BCLC stages: A – 30 patients (15%), B – 29%, C – 36%, D – 20%; BCLC according to diagnosis (SUR-HCC vs. otherwise): A – 15/49 (31%) vs. 12/140 (9%), B – 43 vs. 27%, C – 16 vs. 39%, D – 10 vs. 25%. Treatment: Surgical resection in 17 patients (7%); liver transplantation 14 (6%); radiofrequency ablation 20 (8%); transarterial chemoembolization 60 (24%); sorafenib 88 (35%); best of supportive care 46 (19%), 3 patients were awaiting liver transplantation. Mean survival 17 (0.06–112) months; survival according to BCLC: A – 37 (2–112), B – 21 (0.6–86), C – 14 (0.06–92), D – 3 (0.06–24). **Conclusion:** The demographics in our cohort resembled those of Western Europe and North America. Alcoholic liver disease was the most common etiology for underlying liver disease; 95% of patients had cirrhosis. Only 24% of cases were detected by SUR-HCC; therefore, a marked shift to the right in the BCLC stage distribution was seen, what resulted in a suboptimal allocation of curative treatments and subsequently to worse survival. The treatment results and the management of HCC in our region are comparable with standard of care in West Europe and North America.

Key words: hepatocellular carcinoma – cohort – diagnosis – treatment – survival – surveillance

Súhrn: **Úvod:** Vlastnosti hepatocelulárneho karcinómu (HCC) z rôznych geografických oblastí sú odlišné. **Cieľ:** Analyzovať kohortu pacientov v nemocnici 3. stupňa. **Metodológia:** Retrospektívna analýza za sebou idúcich pacientov. Vstupné kritériá: HCC; vylučovacie kritériá: nedostatok dát; interval: roky 2007–2016. **Výsledky:** Súbor 207 pacientov, 95 % s cirhózou, 76 % mužov; vek 62 rokov. Etiológia hepatálneho ochorenia: Alkohol (ALD) 106 (48 %), hepatitída C 17 %, hepatitída B 13 %, nealkoholová steatohepatitída 10 %, kryptogénna 7 %, necirhotická 4 %, iná 1 %. Diagnóza prostredníctvom surveillance 24 %, bez surveillance 67 %, neznámy spôsob diagnózy 9 %. Priemer ložiska pri diagnóze SUR-HCC 5 cm, bez SUR-HCC 8,6 cm (p = 0,001). BCLC štádium: A – 30 pacientov (15 %), B – 29 %, C – 36 %, D – 20 %; BCLC podľa diagnózy (SUR-HCC vs. non-SUR--HCC): A – 15/49 (31 %) vs. 12/140 (9 %), B 43 vs. 27 %, C – 16 vs. 39 %, D – 10 vs. 25 %. Terapia: Chirurgická resekcia 17 pacientov (7 %), transplantácia pečene 14 (6 %), rádiofrekvenčná ablácia 20 (8 %), transarteriálna chemoembolizácia 60 (24 %), sorafenib 88 (35 %), suportívna starostlivosť 46 (19 %), 3 pacienti sú čakateľmi na transplantaci pečene. Priemerné prežívanie 17 (0,06–112) mesiacov, prežívanie podľa BCLC: A – 37 (2–112), B – 21 (0,6–86), C – 14 (0,06–92), D – 3 (0,06–24) mesiacov. **Záver:** Demografické údaje v našej kohorte sú porovnateľné s krajinami západnej Európy a Severnej Ameriky. ALD bola najčastejšou etiológiou základného ochorenia pečene, 95 % pacientov malo cirhózu. Len 24 % pacientov bolo zachytených prostredníctvom SUR-HCC, preto bol zaznamenaný výrazný posun doprava v BCLC štádiách, čo viedlo k suboptimálnej alokácii radikálnej liečby a následne aj k horšiemu prežívaniu. Súhrnne sú tieto výsledky porovnateľné s údajmi z Európy a Severnej Ameriky.

Kľúčové slová: hepatocelulárny karcinóm – kohorta – diagnóza – liečba – prežívanie – surveillance

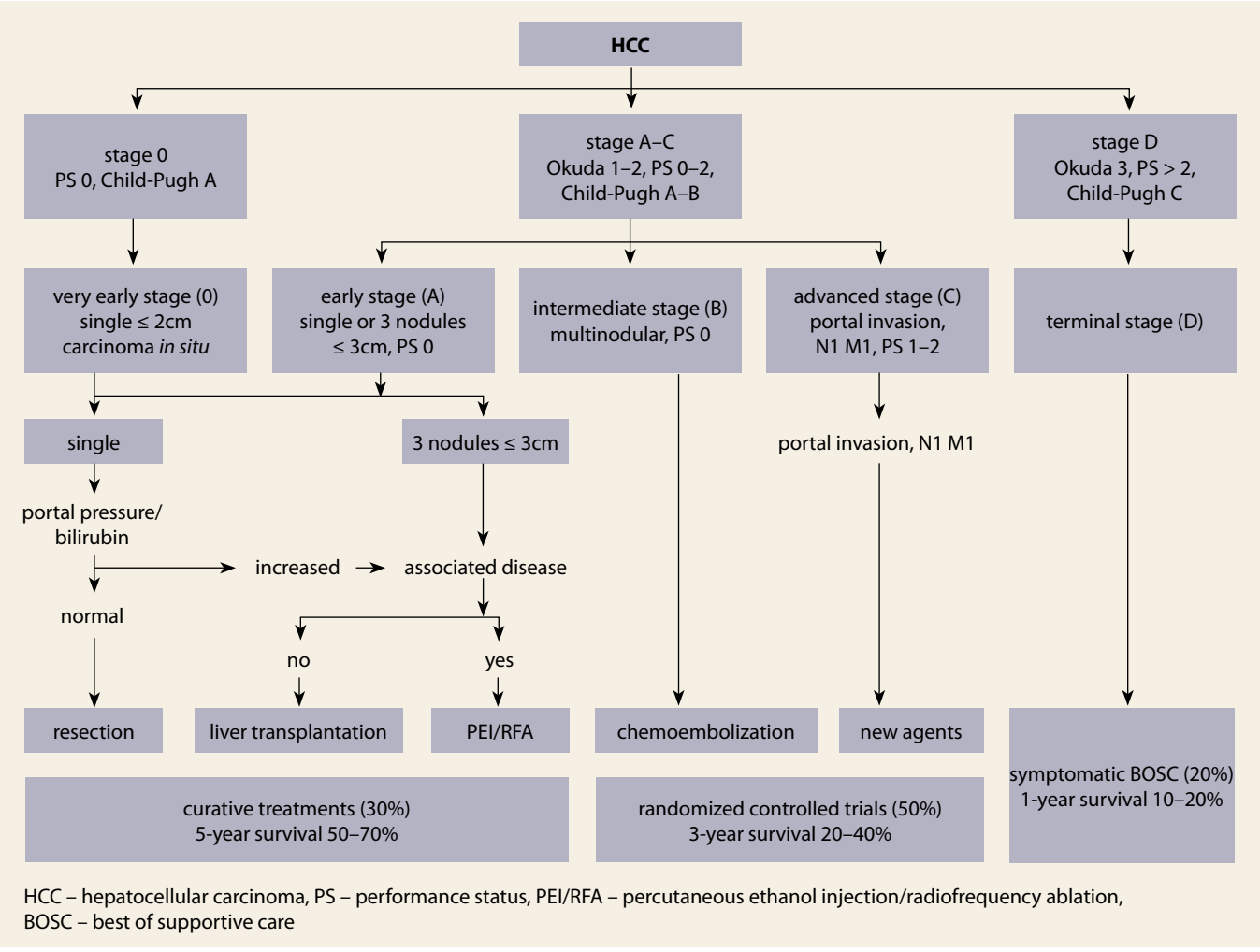
Introduction

Hepatocellular carcinoma (HCC) is the seventh most common cancer and the third leading cause of cancer-related death worldwide, with an estimated 748,000 new liver cancer cases and 696,000 liver cancer deaths caused in 2008 [1]. Its incidence ranks from the fifth most common cancer in men to the nineth most common cancer in women, and it is the fastest increasing cause of cancer-related death. The main causes of HCC are alcoholic liver disease (ALD), non-alcoholic steatohepatitis (NASH) and hepatitis C virus (HCV) [2–9].

Slovakia is one of the countries with low-to-medium incidence, with 3 to 30 new cases per 100,000 inhabitants; these countries are typical by the rise of incidence of HCC [1,7,10–25]. HCC is becoming the most frequent decompensating event in patients with previously compensated advanced chronic liver disease (ACLD), and in Slovakia it is one of the leading causes of liver transplantation (LTx; 10% of all LTx) [26,27]. Thanks to cross-sectional studies it is now possible to better detect demographic and clinical characteristics of HCC, which allows better planning of effective treatment strategies [19]. The expenses to society per patient with HCC are enormous – 32,907 USD; 89% of them are healthcare-related and 11% related to loss of productivity [14,28].

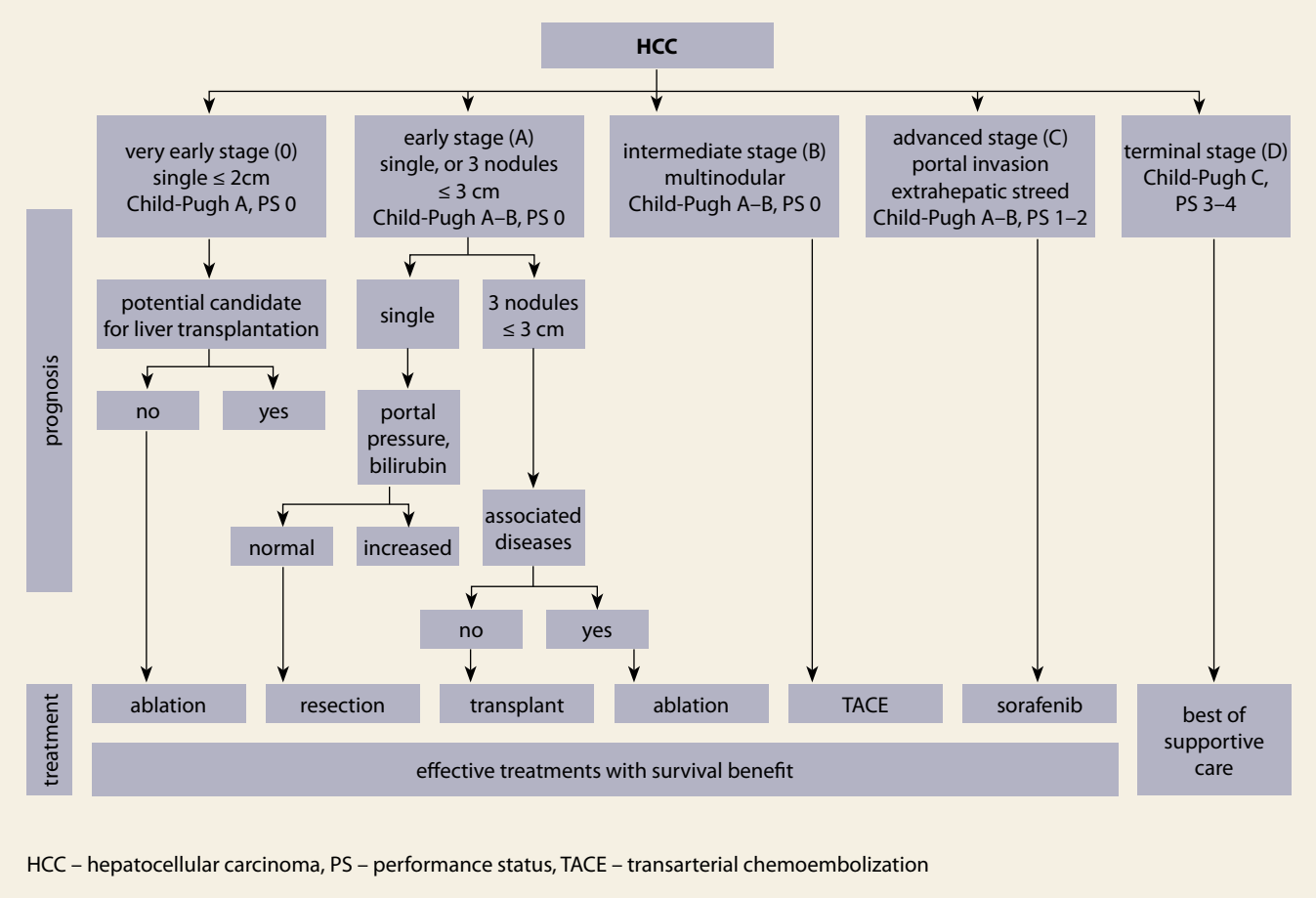
Risk factors of HCC

Most of the HCC cases (80–90%) arise in the context of liver cirrhosis, nowadays termed ACLD [10]. Other risk factors are usually intertwined so that their individual impacts over ACLD is quite difficult to quantify [29–31]. There are region-dependent risk factors, such as HBV, HCV, alcohol consumption and obesity; and region-independent (or at least less dependent) risk factors such as male gender, and being over 65 years of age. The structure of these factors should be known and considered. For example, there is recent evidence to suggest that there is increase in the incidence of HCC cases without underlying cirrhosis, especially in the association with non-alcoholic fatty liver disease (NAFLD), and the signal (small and questioned) of the increase in the incidence of HCC after the (successful) HCV infection therapy with interferon-free regimens [29,31–33].



HCC – hepatocellular carcinoma, PS – performance status, PEI/RFA – percutaneous ethanol injection/radiofrequency ablation, BOSC – best of supportive care

Scheme 1. BCLC classification 2001 according to [37].
Schéma 1. BCLC klasifikácia 2001 podľa [37].



HCC – hepatocellular carcinoma, PS – performance status, TACE – transarterial chemoembolization

Scheme 2. BCLC classification 2016 according to [55].
Schéma 2. BCLC klasifikácia 2016 podľa [55].

Surveillance of HCC

When HCC manifests, the size of the tumour is usually > 5 cm, and the possibility of curative treatments and prognosis are poor. On the other hand, if at the time of diagnosis the tumour diameter is < 5 cm, curative modalities can be applied (radiofrequency catheter ablation – RFA, surgical resection – SR and LTx), and the probability of 5-year survival > 50% can be expected [34,35]. The most effective method of early diagnosis is SUR-HCC [36–39]. Guidelines-endorsed SUR-HCC modality is abdominal ultrasonography (USG), performed by an experienced physician every 6 months [5,30,31,40–42]. The effectiveness of SUR-HCC varies in dependence on region and etiology of ACLD – from 43 to 86% [32,43]. An average diameter of lesions detected by SUR-HCC as well as linkage to care can be considered as the quality control measures which are recommended by guidelines [32,40,44–51].

Recall policy

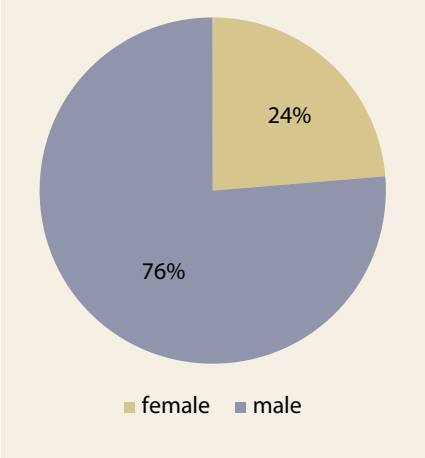
The next step after detecting a new lesion by SUR-HCC is either computed tomography, or magnetic resonance imaging, or both [36–39,52]. The biopsy of tumour is usually performed in case of diagnostic uncertainty, or (in our region) for research; in this case, a biopsy of surrounding parenchyma could be considered in order to appreciate the so-called field effect [53]. After the publication of guidelines permitting non-invasive diagnosis of HCC, the use of liver biopsy had fallen to around 20% [54].

Prognostic classification

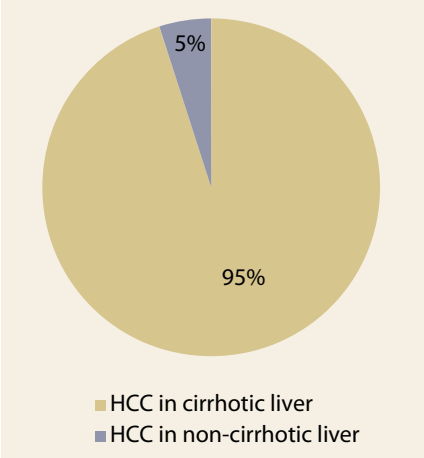
Prognostic classification (staging) is the main instrument of the effective management of HCC. Comparative studies showed that the best staging offers BCLC system (Scheme 1 – BCLC classification 2001; Scheme 2 – BCLC classification 2016) [37,55]. The main advantages of this system are that it takes into account all three domains decisive for prognosis (the tumour, the liver, and the patient), its prognostic accuracy across the stages, and the possibility to allocate treatment according to the stage [37,55–62].

Therapy

The so-called curative therapeutic modalities (RFA, SR, LTx) defined by the > 50% possibility of 5-year survival, can be used only in early-stage HCC (BCLC A); however, patients in this stage represent less than one third of all cases [42,61–63]. The other two thirds are divided to three groups with different recommended

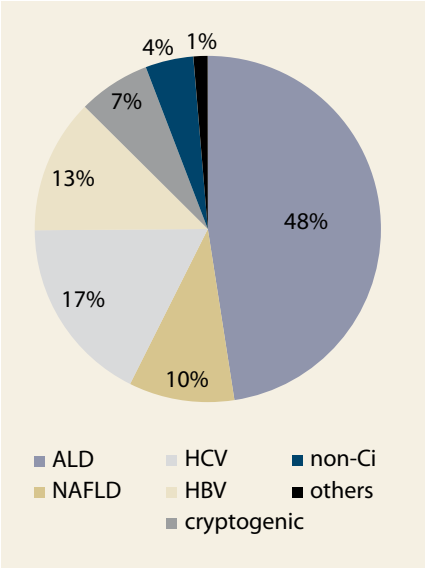


Graph 1. Gender of HCC patients in the cohort (N = 207).
Graf 1. Pohlavie pacientov s HCC v sledovanej kohorte (n = 207).

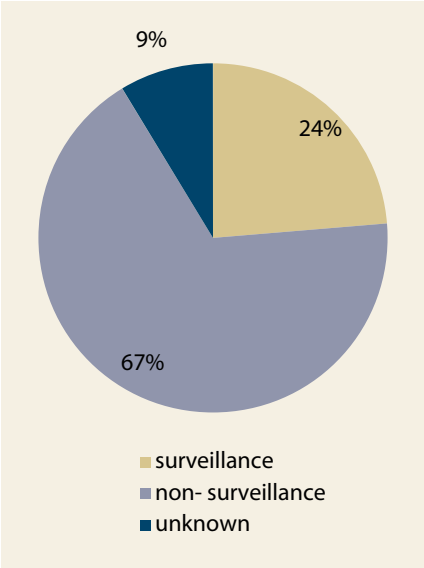


Graph 2. HCC in cirrhotic and non-cirrhotic liver in the cohort.
Graf 2. HCC v teréne cirhózy a v necirhotickom teréne v sledovanej kohorte.

HCC – hepatocellular carcinoma, ALD – alcoholic liver disease, NAFLD – non-alcoholic fatty liver disease, HCV – hepatitis C virus infection, HBV – hepatitis B virus infection, non-Ci – non-cirrhotic patients



Graph 3. Aetiology of liver diseases (N = 207).
Graf 3. Etiológia hepatálneho ochorenia (n = 207).



Graph 4. Surveillance vs. other modes of diagnosis (N = 207).
Graf 4. Surveillance vs. iný spôsob diagnostiky (n = 207).

treatment approaches: 1. intermediate stage HCC – BCLC stage B (median survival 17–37 months), with recommended treatment by one of locoregional (liver-directed) modalities; 2. advanced stage – C (median survival 5.5 months) [64], treated by sorafenib; and 3. terminal stage – D (median survival 3 months), best of supportive care (BOSC) [65–69]. These simple-to-use allocation rules are not rigid due to the possibility of implementing a stage-migration strategy and an imperative of HCC management – multidisciplinary team discussions [70–73].

The aims of the study

The aims of the study are the following: 1. To determine the demographic and clinical characteristics of patients with HCC in a single-centre cohort; 2. to determine the proportion and characteristics of diagnosis of cases by the SUR-HCC; 3. to determine the distribution of BCLC stages at the time of diagnosis; 4. to determine allocation of therapy and 5. to determine prognosis in respect to the BCLC classes.

Patients and methods

In this retrospective study the analysis proceeded according to the following steps: The search of the Hospital Information System „Care Center®" for the key Diagnosis „HCC" (SAS). Retrieved medical records were subsequently compared to the database of The Liver Unit and scrutinized for details with members of MDT. Patients seen between July 2007 and November 2016 were analysed.

1. Inclusion criterion – diagnosis of HCC according to the guidelines operating during the study interval [7,36–39,59].

2. Exclusion criterion – impossibility to retrieve sufficient data for final analysis.

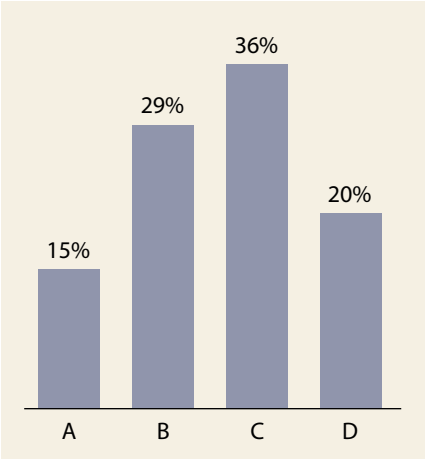
3. Recorded variables – age, gender, presence/absence of liver cirrhosis as a stage of ACLD, etiology of ACLD, the means of diagnosis (by means of SUR-HCC, or otherwise), BCLC stage at diagnosis, diameter of lesions at diagnosis, treatment modality, survival.

4. Definitions – ACLD was diagnosed according to the accepted guidelines [59]; SUR-HCC was defined as the finding of at least two negative USG examinations 6-months apart, before determination of the HCC Diagnosis; the BCLC stages were determined using two consecutive sets of BCLC criteria (Scheme 1 and 2).

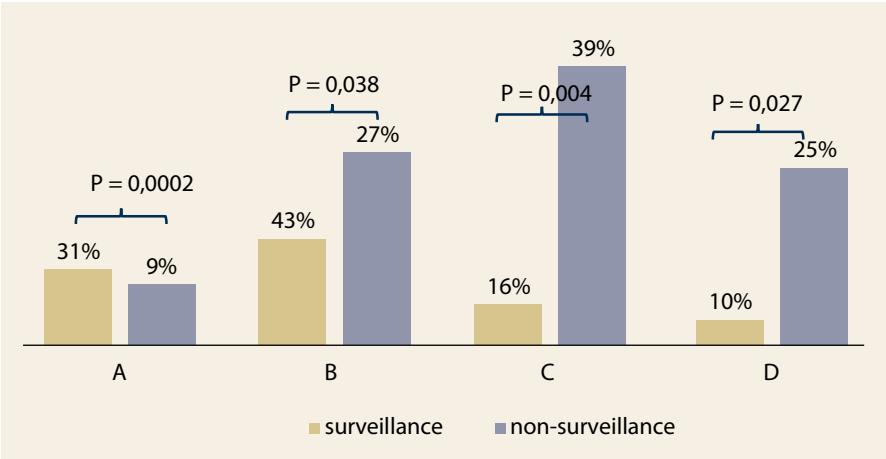
5. Treatment – the management was decided by the MDT according to allocation principles based on the BCLC system. The therapeutic armamentarium at the Liver Unit consisted of all the modalities endorsed by the Guidelines of the study interval, including LTx.

Results

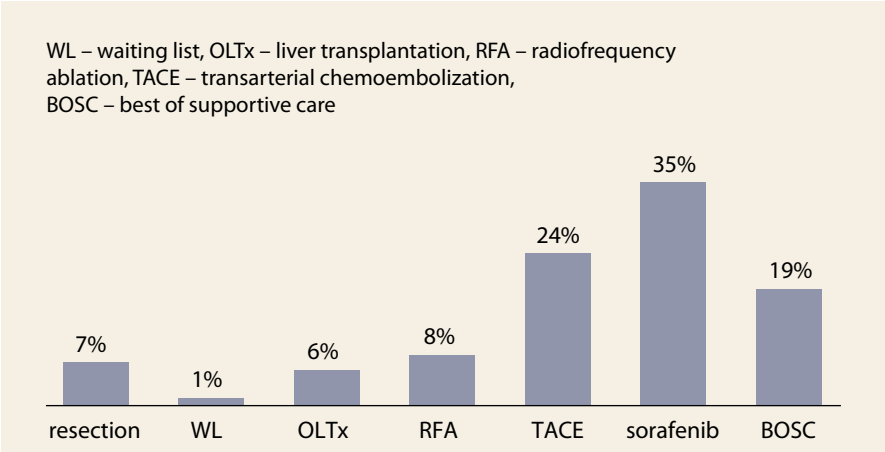
Cohort consisted of 207 patients, 197 with liver cirrhosis (95%), 158 men



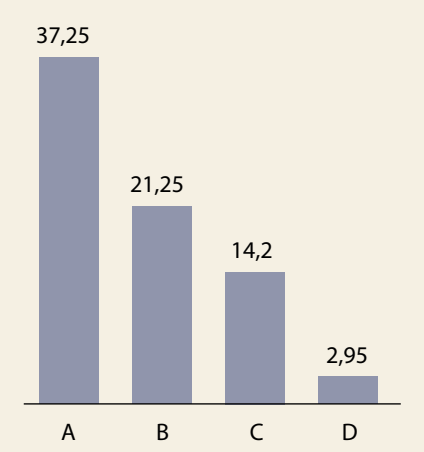
Graph 5. BCLC stages at the time of HCC diagnosis of HCC (N = 207).
Graf 5. BCLC štádiá v čase diagnózy HCC (n = 207).



Graph 6. HCC diagnosed by surveillance vs. non-surveillance according to BCLC stages (N = 189).
Graf 6. Diagnóza HCC v rámci surveillance vs. non-surveilance podľa BCLC štádií (n = 189).



Graph 7. Treatment modalities in the whole cohort (N = 248 modalities in 207 patients).
Graf 7. Terapeutické modality v sledovanej kohorte (n = 248 modalít u 207 pacientov).



Graph 8. Survival in months according to BCLC stages (N = 207).
Graf 8. Prežívanie v mesiacoch podľa BCLC štádií (n = 207).

(76%), with median age of 65.9 (25–94) years (men vs. women = non-significant) (Graph 1 and 2).

Etiology

Etiology of underlying ACLD (and supposedly also the main etiology behind HCC): ALD – 106 patients (48%), HCV – 39 (17%), HBV – 28 (13%), NASH – 22 (10%), cryptogenic – 15 (7%), without cirrhosis – 10 (4%), others (primary biliary cholangitis, morbus Wilson, hereditary hemochromatosis) – 3 (1%) (Graph 3). In 49 cases (24%) the HCC was diagnosed by SUR-HCC, in 67% by other way, in remaining 9% the way of diagnosis was unknown (Graph 4). The average diameter of lesions at the time of diagnosis in SUR-HCC subgroup was 5.05 (0.75–20) cm, as compared to 8.6 (1–27.9) cm in patients without SUR-HCC (p = 0.001).

BCLC stages at admission

1. the whole cohort: BCLC A – 30 patients (15%), B – 61 patients (29%), C – 74 patients (36%), D – 42 patients (20%) (Graph 5); 2. according to the diagnosis modality (SUR-HCC vs. otherwise): A – 31% (15/49 patients) vs. 9% (12/140 patients) (p = 0.0002); B – 43% (21/49 patients) vs. 27% (38/140 patients) (p = 0.038); C – 16% (8/49 patients) vs. 39% (55/140 patients) (p = 0.004); D – 10% (5/49 patients) vs. 25% (35/140 patients) (p = 0.027) (Graph 6).

Treatment

RFA 20 patients (8%), SR 17 patients (7%); LTx 14 patients (6%); DEB-TACE 60 patients (24%); sorafenib 88 patients (35%); BOSC 46 patients (19%), 3 patients were awaiting LTx (Graph 7).

Survival

Mean survival in 1. the whole cohort was 17,34 (0,06–111.6) months; 2. according to BCLC stages: A – 37.25 (2.2–111.6)

months; B – 21.25 (0.56–85.6) months; C – 14.2 (0.06–91.9) months; D – 2.95 (0.06–23.8) months (Graph 8).

Discussion

This analysis has several limitations in its retrospective and single-centre design, limited number of patients, and impossibility of subdividing early stage HCC to BCLC 0 (very early) and BCLC A. These drawbacks do not preclude it to be a reflection of characteristics and management of the HCC in this Central European region. Male predominance and the age of patients are comparable to other cohorts from Western Europe and North America, apart from the lack of age difference between genders; whether it is the signal of relevance will be seen over time [74,75].

As for the risk factors, liver cirrhosis was present in 95% of patients which falls well into the range of 98.3–56% found in the six studies from Germany, Netherlands, Italy, Denmark and Norway [76–79]. It is noticeable considering the trend of HCC to arise more and more in livers without cirrhosis (e. g. in 54% in the recent paper by Piscaglia) [32]. One possible explanation is an overestimation of the stage of ACLD in our cohort, since the liver biopsy was not a prerequisite for the diagnosis of cirrhosis; against this notion is the cumulative number of liver resecates in SR, liver explants in LTx, and hepatic venous pressure gradient measurements with no signal of over diagnosing the stage of ACLD. The other possibility is that the hit of the most renowned etiology of HCC without cirrhosis – NAFLD – has not yet been full-blown in this region [75,80]. Unfortunately, we were not able to ascertain the roles of the other common protective and risk factors – i.e. diet, smoking, obesity, type 2 diabetes mellitus (T2DM) and metabolic syndrome (MS). One can derive some information from their prevalence in the general population of Slovakia: Mediterranean diet (22.9%), smoking (41.2%), obesity (27.5%), T2DM (8.5%), and MS (10–84%) [81–85]. The etiology of underlying ACLD lends support to the "addictive" rather than "viral" pattern of the HCC in this region [86]. In nearly half the cases of HCC (48%), the main etiology was ALD. This is more than in several other studies from Europe (20–37%), but similar to the French prospective study [39,72,87,88]. The figure for ALD is considered to truly reflect the real-world influence of alcohol intake on health in Slovakia [89–94]. Another etiology attesting to the propensity of HCC in Slovakia to be of an "addictive" origin was the NAFLD/NASH. With 10% as the sole cause of LTx and another 40% as the possible co-factor, it can well be considered the second most important target for intervention. The roles of HCV and HBV, as well as the autoimmune syndromes were comparable to the figures from the other countries of this region [18,45,51,75]. Notably, none of the HCCs developed in the setting of HCV treatment with directly-acting antivirals.

Of concern is the low rate of diagnosis by SUR-HCC (24%). Authors consider it to be a true reflection of the situation in Slovakia [95]. Comparable rates of SUR-HCC uptake seen in the literature is no reason for complacency [40,96–98]; on the contrary, it is taken as the cause of serious concern. In fact, this finding is considered to be the most important result of the analysis and the starting point for the optimization of SUR-HCC process in Slovakia. The second most important finding is the large diameter of the lesions detected by SUR-HCC (5.05 cm); although still significantly lower than that from diagnosis by other means (8.63 cm), it is also the cause of concern. It means that SUR-HCC was not only used at the suboptimal rate, but that it was also performed at the low level of quality.

Suboptimal quality notwithstanding, SUR-HCC was still associated with significantly less advanced BCLC stage at the diagnosis. The right-sided distribution of BCLC stages further illuminates the reserves of early diagnosis: only 15% of the cases fell into class A as compared to up to 42% elsewhere [99,100]. The results lend support to the value of SUR-HCC which has been supported by only one Asian randomized controlled trial (with several limitations) and therefore is still a matter of controversy: when we split our cohort according to diagnosis modality, the results have shown significantly more BCLC A + B cases with-, and significantly more C + D cases without SUR-HCC (Graph 3). Overall survival (17 months), and the survival according to the BCLC classes (37 months in BCLC A to 3 months in BCLC D) (Graph 4), were comparable to the results from the literature [99]. The possibility of curative treatment was low (RFA 8%, SR 7%, LTx 6%), which is probably the result of a trend to right-sided BCLC stage distribution at diagnosis. Even though the need for improvement is indisputable, a comparison of the results to those of El-Serag from the U.S. is somewhat relieving (RFA 4.1%, SR 8.2%, LTx 0.9%) [101]. Last but not least is the finding of the availability of all the recommended treatment modalities and their standard performance regarding survival.

Conclusions

1. Demographics in this cohort resemble those of HCC in the Western Europe and North America; 2. ALD was the most common etiology of ACLD; 3. Liver cirrhosis was diagnosed in 95% of the cases; 4. Only 24% of cases were detected via SUR-HCC; 5. Therefore the marked shift to the right in the BCLC stage distribution (A + B < C + D), leading to 6. Sub-optimal allocation of curative treatments and 7. Survival. According to these results, the management of HCC in our catchment area is full of reserves but still comparable to the standard of health care in Western Europe and North America.

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Svetlana Adamcova-Selcanova, MD
HEGITO (Division of Hepatology, Gastroenterology and Liver Transplantation)
Department of Internal Medicine II
Slovak Medical University
F. D. Roosevelt University Hospital
Nam. L. Svobodu 1
974 01 Banska Bystrica
Slovak Republic
sselcanova@gmail.com

MUDr. Ľubomír Skladaný, PhD.

MUDr. Ľubomír Skladaný, PhD., absolvoval v roce 1988 LF UK v Bratislavě. Od té doby doposud pracuje na II. interní klinice Slovenské zdravotnické univerzity (SZU) ve FN s poliklinikou F. D. Roosevelta v Banské Bystrici. Získal atestace z vnitřního lékařství I (1991) a II (1995), z gastroenterologie (1999), hepatologie (2002), PhD. o hepatitidě C u hemodialyzovaných pacientů (2002), a post hostujícího docenta SZU (2006). V roce 2010 založil a vede HEGITO – Hepatologické, gastroenterologické a transplantační oddělení II. interní kliniky SZU; program transplantací jater byl spuštěn pod vedením IKEM Praha v roce 2008. V roce 2012 se stal přednostou II. interní kliniky SZU. Je prezidentem Slovenské hepatologické společnosti a členem výboru Slovenské transplantační společnosti. Zabývá se klinickým výzkumem v hepatologii, v současnosti především v oblasti selhání jater.
Od 1. února 2018 přijal MUDr. Skládaný v časopise Gastroenterologie a hepatologie pozici koeditora sekce klinická a experimentální gastroenterologie pro Slovenskou republiku. Redakce časopisu se těší na spolupráci s ním a přeje mnoho pracovních úspěchů.

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Složení: Acidum ursodeoxycholicum (UDCA) 500 mg v 1 potahované tabletě. **Indikace:** Disoluce cholesterolových žlučových kamenů ve žlučníku, jejichž průměr nemá přesahovat 15 mm při současně zachované funkci žlučníku. Symptomatická léčba primární biliární cholangitidy (PBC) za předpokladu nepřítomnosti dekompenzované cirhózy jater. Hepatobiliární porucha při cystické fibróze u dětí od 6–18 let. **Dávkování a způsob podání:** Přípravek URSOSAN FORTE je vhodný pro pacienty s tělesnou hmotností 47 kg a vyšší. *Disoluce cholesterolových žlučových kamenů:* 10 mg/kg/den pravidelně večer před spaním, obvykle 6 až 24 měsíců. *Symptomatická léčba primární biliární cholangitidy (PBC):* 14 ± 2 mg/kg/den. Během prvních třech měsíců se tablety užívají ve třech denních dávkách, po zlepšení hodnot jaterních testů se může denní dávka užívat jednou denně, večer, neomezeně dlouhou dobu. *Děti s cystickou fibrózou od 6 do méně než 18 let:* 20–30 mg/kg/den ve 2–3 dávkách. Tablety se polykají celé a nerozkousané. **Kontraindikace:** Přecitlivělost na žlučové kyseliny a pomocné látky; akutní zánět žlučníku a žlučových cest; obstrukce žlučových cest; kalcifikované žlučové kameny; porušená kontraktilita žlučníku; časté biliární koliky; děti po neúspěšné portoenterostomii nebo děti s biliární atrézií bez zajištění dobrého průtoku žluči. **Nežádoucí účinky:** Průjem, urtika, bolesti v nadbřišku. **Interakce:** Cholestyramin, kolestipol, antacida obsahující hydroxid hlinitý nebo oxid hlinitý snižují vstřebávání a účinnost UDCA. Tyto přípravky doporučujeme užít 2 hodiny před, nebo 2 hodiny po podání UDCA. Současné podávání s ciprofloxacinem, dapsonem, nitrendipinem může vést ke snížení jejich účinku; s cyklosporinem může vést k ovlivnění jeho absorpce. Hypolipidemika (klofibrát) a estrogeny zvyšují sekreci cholesterolu do žluče, mohou podporovat tvorbu žlučových kamenů a tím zhoršují vyhlídky na úspěch léčení. **Upozornění:** V průběhu léčby je třeba kontrolovat jaterní enzymy: v prvních 3 měsících ve čtyřtýdenních intervalech, později 1× za čtvrt roku. Neužívat během těhotenství, pokud to není jednoznačně nezbytné. **Uchovávání:** Tento léčivý přípravek nevyžaduje žádné zvláštní podmínky uchovávání. **Balení:** Velikost balení: 10, 20, 30, 50, 60, 90 nebo 100 tablet. Na trhu nemusí být všechny velikosti balení. **Datum revize textu:** 10. 11. 2017. S podrobnějšími informacemi o přípravku se seznamte v SPC. Přípravek je vázán na lékařský předpis. **Výrobce a držitel rozhodnutí o registraci:** PRO.MED.CS Praha a. s., Telčská 377/1, Michle, 140 00 Praha 4, Česká republika.

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