**APENDIX 1.**

This guideline was performed by a team-working board of experienced hepatologists, oncologists, liver surgeons, liver transplant surgeons, pathologists and radiologists, experienced on the management of patients with HCC from Argentina. The A.A.E.E.H proposed this guideline for the best diagnostic and treatment care for HCC patients in our country.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study Design** | **Initial quality of the evidence** | **If RCT decreases if** | **In observational studies, increases if:** | **Final quality of the evidence** |
| Randomized clinical trial (RCT) | High | 1-Limitation in the design and development;2-Inconsistency of results;3-Uncertainty that the evidence is plausible.4-Imprecision of results (confidence intervals). |  | HighModerateLowVery Low |
| Observational studies | Low |  | Strength of the association:-Strong-Dose-gradient dependent.Adjustment for confounding variables that:-Could reduce the effect.-Suggest spurious effect. |

Each working team was organized in groups, in whom specific clinical research questions were submitted to be answered based on their experience and the best available evidence. An independent committee reviewed this synthesis and approached each recommendation according the the level and quality of the evidence according to GRADE, as follows:

[1] Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. Bmj 2008;336:924–6. doi:10.1136/bmj.39489.470347.AD.

[2] Guyatt GH, Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, Liberati A, et al. Going from evidence to recommendations. Bmj 2008;336:1049–51. doi:10.1136/bmj.39493.646875.AE.

[3] Moher, Schulz, Altman. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. Lancet 2001;357:4–4. doi:10.1016/S0140-6736(00)04337-3.

[4] Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 2009;62:1006–12. doi:10.1016/j.jclinepi.2009.06.005.

[5] Elm von E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007;370:1453–7. doi:10.1016/S0140-6736(07)61602-X.

***General organization of the clinical practice guideline:***

*a. General coordination:* Federico Piñero, Mario Tanno y Gabriel Aballay Soteras.

*b. AAEEH Board:* Beatriz Ameigieras, Diana Krasniasky, Fernando Cairo.

*c. Hepatology committee experts:* Eduardo Fassio, Silvia Mengarelli, Andrés Ruf, Adrián Gadano, Melisa Dirchwolf, Nora Fernández, Federico Villamil, Ezequiel Ridruejo, Valeria Descalzi, Margarita Anders, Guillermo Mazzolini, Silvia Borzi, Fernando Cairo, Virginia Reggiardo, Marcelo Silva, Sebastián Marciano.

*d. Oncology committee experts:* Gonzalo Recondo, Florencia Perazzo.

*d. Imaging committee experts:* Mariano Volpachio, Juan Pablo Perotti, Federico Diaz Telli, Juan Carlos Spina.

*e. Surgery committee experts:* Gustavo Podestá, Eduardo de Santibañes, Lucas McCormack, Martín Maraschio.

*f. Pathology committee experts:* Cecilia Lagues, Marcelo Amante, María Teresa Davila.

*g. Radiology intervention committee experts:* Ricardo García Mónaco, Guillermo Eiselle.

*h. Evaluation of quality of the evidence:* Matías Tisi Baña –consultant-, Federico Piñero, Ariel Izcovich –consultant-.

***Clinical research questions of interest.***

1. *Which is the epidemiology of HCC in Latin America and in Argentina? Which are the main risk factors for HCC development? Is there any specific population at risk for HCC?*
2. *What are the primary, secondary and tertiary preventive measures to be performed?*
3. *What is the rationale for HCC surveillance and is the evidence strongly enough to be recommended? Who to be screened and with which method? Are surveillance and screening failure the same? How we can improve adherence to surveillance policies?*
4. *Is there any flow or algorithm to assess liver nodules? How can we improve and avoid screening failure in our country?*
5. *Is HCC imaging diagnosis feasible and robust? Are the imaging criteria applicable in Argentina? Can we apply the LIRADS in our country?*
6. *In nodules without imaging hallmarks, how can you further diagnose HCC? Are biliary contrast agents accurate? Are they cost-effective in our country?*
7. *Is there any role in biomarkers for HCC diagnosis? Which biomarkers can we recommend in our country?*
8. *What is the role of pathology in HCC diagnosis or prognostic issues? Is there any hallmark to specifically perform HCC diagnosis?*
9. *What is the best-evidence based staging algorithm? Is it applicable in our country? Are there any “grey zones” to be addressed? What is the effect of adherence or non-adherence to its recommendations?*
10. *Who are the best candidates for locoregional therapies including RFA, PEI or MWA? Are there other novel therapies?*
11. *Who are the best candidates for liver resection? Are there other “non-ideal” candidates?*
12. *Is there any adyuvant or neo-adyuvant therapy for curative treatments?*
13. *How to manage HCC recurrence after curative therapies? What are the best options in our country?*
14. *Who are the best liver transplant candidates? Is it feasible to expand beyond Milan criteria? Are composite criteria better than Milan? Should we include composite criteria in our country?*
15. *How to avoid tumour progression while on the waiting list? Are there any limits for “down-staging? Are they applicable in Argentina?*
16. *Who are the best candidates for trans-arterial chemoembolization (TACE)? Are conventional TACE or with drug-eluting beads (DEB) cost-effective in our country?*
17. *Who are the best candidates for trans-arterial radioembolization (TARE)? Is TARE superior to TACE? What is the role (if any) of TARE for the treatment of HCC patients?*
18. *Which imaging criteria should we use to assess tumour response? With that imaging method?*
19. *How to assess progressive disease and when to start systemic therapy in intermediate stage?*
20. *Who are the best candidates for first line systemic therapies? With which agents? How we can manage adverse events? When to start second line therapies (if available in our country?*
21. *Who are the best candidates for second line systemic therapies? With which agents? How to manage adverse events?*
22. *Areas of uncertainty. What is the effect of viral eradication (HBV or HCV) on the natural history of HCC? Is it worth treating these patients at each HCC stage?*
23. *What is the role of hepatologists? Are multidisciplinary teams necessary?*