Appendix 2. Histological Subtypes of Hepatocellular Carcinoma – Relative Frequency, Histological Molecular and Clinical Features and Prognostic Implications (based on WHO 2019 Classification)

HCC Subtype	Relative Frequency	Histological Features	Molecular Features	Clinical Features	Prognosis (compared with conventional HCC)
Steatohepatitic	5–20%	>50% of tumour shows histological features of steatohepatitis including steatosis, ballooning, Mallory–Denk bodies, intra-tumoural inflammation and pericellular fibrosis	IL-6/JAK/STAT activation; lower frequency of *CTNNB1, TP53* and *TERT* promoter mutations	Frequently arises in background of fatty liver disease (metabolic or alcohol related); non-lesional liver often also show features of fatty liver disease	Similar
Clear cell	3–7%	>80% of the tumour has a clear cell morphology due to intracytoplasmic glycogen; may also have focal steatosis	No definite association recognised	None recognised	Better
Macrotrabecular-massive	5%	>50% of the tumour has macrotrabecular growth pattern with trabeculae typically >10 cells thick: vascular invasion common	*TP53* mutations and *FGF19* amplifications	High serum AFP levels	Worse
Scirrhous	4%	>50% of the tumour shows dense intratumoural fibrosis	*TSC1/2* mutations; TGF-beta signalling activation	May mimic cholangiocarcinoma radiologically	Variable
Chromophobe	3%	Neoplastic cells have light or clear cytoplasm; generally mild nuclear pleomorphism with focal areas of marked nuclear atypia; scattered microscopic pseudocysts	Alternative lengthening of telomeres (ALT)	None recognised	Similar

Fibrolamellar	1%	Large neoplastic cells with granular eosinophilic cytoplasm, large vesicular nuclei and prominent nucleoli; usually numerous intracytoplasmic pale and/or hyaline bodies; neoplastic cells stain positively for K7 and CD68; dense lamellar intratumoural fibrosis; non-cirrhotic background liver	Activation of protein kinase A (PKA) via *DNAJB1-PRKACA* fusion gene	Young median age (25 years); no underlying liver disease;	Similar to conventional HCC arising in non-cirrhotic liver
Neutrophil-rich	<1%	Numerous neutrophils diffusely infiltrating within the tumour; may have focal sarcomatoid morphology	Tumour cells produce granulocyte-colony-stimulating-factor (GCSF)	Elevated peripheral white blood cell count, IL-6 levels and C-reactive protein	Worse
Lymphocyte-rich	<1%	Dense intratumoral lymphoid cell infiltrates; lymphocytes outnumber neoplastic cells in most areas	No definite association recognised; not EBV-related	None recognised	Better