

Vascular invasion (Required)

Reason/Evidentiary Support

Hepatocellular carcinoma

Vascular invasion (VI) is an independent prognostic factor in HCC after resection¹⁻⁸ as well as after transplantation.⁹⁻¹⁴ VI affects survival also in early HCC.¹⁵ For the TNM staging system, vascular invasion is a component of the pT stage.¹⁶

VI is classified as macroscopic or microscopic (MiVI). Macroscopic VI is defined as invasion of tumour into a major vessel that can be identified during macroscopic examination or radiological imaging and is part of established staging systems, such as Barcelona Clinic Liver Cancer classification (BCLC).

For the pathological classification in the 8th edition of TNM,¹⁶ involvement of major branch of portal vein or hepatic vein is classified as pT4. This refers to the main right or left branch of the vein, as distinct from macroscopic vascular invasion which relates to macroscopically visible involvement of any vessel – the width of the vessel is not helpful as intravascular tumour may distend the calibre of the vein.

MiVI is usually defined as tumour within a vascular space lined by endothelium, visible only on microscopy, identified in the liver tissue surrounding the tumour and venous vessels in the tumour capsule and/or non-capsular fibrous septa. However, there is a lack of consensus for the definition of MiVI.¹⁷ Inter-observer and intra-observer variability in the evaluation of MiVI in HCC has been reported.¹⁸

MiVI can be assessed in Haematoxylin-Eosin stained sections, following strict criteria to avoid misinterpretation (i.e. presence of tumour cells in a space lined by endothelial cells, attachment of tumour cells to the vascular wall, or identification of muscular wall or elastic lamina for larger blood vessels). In challenging cases, the use of immunohistochemical staining specific for smooth muscle (such as h-caldesmon) may be helpful to confirm the vascular nature of the suspicious lesions. Special stains for elastic fibres (e.g. Victoria blue, Orcein, E-VG) also can be useful.¹⁷ When appearances are suspicious for vascular invasion, but the criteria above are not met, this can be recorded as 'indeterminate'; this would not be regarded as miVI for staging purposes.

There are several studies that sub-classify miVI according to distance of vessels from the HCC, number of vascular channels involved and/or number of cancer cells identified within the vessel, which are able to demonstrate prognostic significance for survival.^{19,20, 21, 22} However, these studies have not been validated by prospective studies and/or independent groups, and therefore sub classification of MiVI is not a required item at this stage.

Cholangiocarcinoma

Vascular invasion is an important prognostic factor for ICC.²³⁻²⁷ Macroscopic vascular invasion is a strong predictor of survival: 5-year survival has been reported to be 0% for patients with macroscopic vascular invasion.^{23,24}

For TNM staging system, vascular invasion is a component of the pT stage.

References

- 1 Okada S, Shimada K, Yamamoto J, Takayama T, Kosuge T, Yamasaki S, Sakamoto M and Hirohashi S (1994). Predictive factors for postoperative recurrence of hepatocellular carcinoma. *Gastroenterology* 106(6):1618-1624.
- 2 Lauwers GY, Terris B, Balis UJ, Batts KP, Regimbeau JM, Chang Y, Graeme-Cook F, Yamabe H, Ikai I, Cleary KR, Fujita S, Flejou JF, Zukerberg LR, Nagorney DM, Belghiti J, Yamaoka Y and Vauthey JN (2002). Prognostic histologic indicators of curatively resected hepatocellular carcinomas: a multi-institutional analysis of 425 patients with definition of a histologic prognostic index. *Am J Surg Pathol* 26(1):25-34.

- 3 Imamura H, Matsuyama Y, Tanaka E, Ohkubo T, Hasegawa K, Miyagawa S, Sugawara Y, Minagawa M, Takayama T, Kawasaki S and Makuuchi M (2003). Risk factors contributing to early and late phase intrahepatic recurrence of hepatocellular carcinoma after hepatectomy. *J Hepatol* 38(2):200-207.
- 4 Portolani N, Coniglio A, Ghidoni S, Giovanelli M, Benetti A, Tiberio GA and Giulini SM (2006). Early and late recurrence after liver resection for hepatocellular carcinoma: prognostic and therapeutic implications. *Ann Surg* 243(2):229-235.
- 5 Sumie S, Kuromatsu R, Okuda K, Ando E, Takata A, Fukushima N, Watanabe Y, Kojiro M and Sata M (2008). Microvascular invasion in patients with hepatocellular carcinoma and its predictable clinicopathological factors. *Ann Surg Oncol* 15(5):1375-1382.
- 6 Wang CC, Iyer SG, Low JK, Lin CY, Wang SH, Lu SN and Chen CL (2009). Perioperative factors affecting long-term outcomes of 473 consecutive patients undergoing hepatectomy for hepatocellular carcinoma. *Ann Surg Oncol* 16(7):1832-1842.
- 7 Lim KC, Chow PK, Allen JC, Chia GS, Lim M, Cheow PC, Chung AY, Ooi LL and Tan SB (2011). Microvascular invasion is a better predictor of tumor recurrence and overall survival following surgical resection for hepatocellular carcinoma compared to the Milan criteria. *Ann Surg* 254(1):108-113.
- 8 Jonas S, Bechstein WO, Steinmuller T, Herrmann M, Radke C and Berg T et al (2001). Vascular invasion and histopathologic grading determine outcome after liver transplantation for hepatocellular carcinoma in cirrhosis. *Hepatology* 33:1080-1086.
- 9 Duffy JP, Vardanian A, Benjamin E, Watson M, Farmer DG, Ghobrial RM, Lipshutz G, Yersiz H, Lu DS, Lassman C, Tong MJ, Hiatt JR and Busuttil RW (2007). Liver transplantation criteria for hepatocellular carcinoma should be expanded: a 22-year experience with 467 patients at UCLA. *Ann Surg* 246(3):502-509; discussion 509-511.
- 10 Parfitt JR, Marotta P, Alghamdi M, Wall W, Khakhar A, Suskin NG, Quan D, McAllister V, Ghent C, Levstik M, McLean C, Chakrabarti S, Garcia B and Driman DK (2007). Recurrent hepatocellular carcinoma after transplantation: use of a pathological score on explanted livers to predict recurrence. *Liver Transpl* 13(4):543-551.
- 11 Mazzaferro V, Llovet JM, Miceli R, Bhoori S, Schiavo M, Mariani L, Camerini T, Roayaie S, Schwartz ME, Grazi GL, Adam R, Neuhaus P, Salizzoni M, Bruix J, Forner A, De Carlis L, Cillo U, Burroughs AK, Troisi R, Rossi M, Gerunda GE, Lerut J, Belghiti J, Boin I, Gugenheim J, Rochling F, Van Hoek B and Majno P (2009). Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. *Lancet Oncol* 10(1):35-43.
- 12 D'Amico F, Schwartz M, Vitale A, Tabrizian P, Roayaie S, Thung S, Guido M, del Rio Martin J, Schiano T and Cillo U (2009). Predicting recurrence after liver transplantation in patients with hepatocellular carcinoma exceeding the up-to-seven criteria. *Liver Transpl* 15(10):1278-1287.
- 13 Bhangui P, Vibert E, Majno P, Salloum C, Andreani P, Zocrato J, Ichai P, Saliba F, Adam R, Castaing D and Azoulay D (2011). Intention-to-treat analysis of liver transplantation for hepatocellular carcinoma: living versus deceased donor transplantation. *Hepatology* 53(5):1570-1579.
- 14 Hsieh CH, Wei CK, Yin WY, Chang CM, Tsai SJ, Wang LY, Chiou WY, Lee MS, Lin HY and Hung SK (2015). Vascular invasion affects survival in early hepatocellular carcinoma. *Mol Clin Oncol* 3(1):252-256.
- 15 Rodriguez-Peralvarez M, Luong TV, Andreana L, Meyer T, Dhillon AP and Burroughs AK (2013). A systematic review of microvascular invasion in hepatocellular carcinoma: diagnostic and prognostic variability. *Ann Surg Oncol* 20(1):325-339.

- 16 Brierley JD, Gospodarowicz MK and Wittekind C (eds) (2016). *UICC TNM Classification of Malignant Tumours, 8th Edition*, Wiley-Blackwell.
- 17 Fan L, Mac MT, Frishberg DP, Fan X, Dhall D, Balzer BL, Geller SA and Wang HL (2010). Interobserver and intraobserver variability in evaluating vascular invasion in hepatocellular carcinoma. *J Gastroenterol Hepatol* 25(9):1556-1561.
- 18 Roayaie S, Blume IN, Thung SN, Guido M, Fiel MI, Hiotis S, Labow DM, Llovet JM and Schwartz ME (2009). A system of classifying microvascular invasion to predict outcome after resection in patients with hepatocellular carcinoma. *Gastroenterology* 137(3):850-855.
- 19 Guglielmi A, Ruzzenente A, Campagnaro T, Pachera S, Valdegamberi A, Nicoli P, Cappellani A, Malfermoni G and Iacono C (2009). Intrahepatic cholangiocarcinoma: prognostic factors after surgical resection. *World J Surg* 33(6):1247-1254.
- 20 Fujita N, Aishima S, Iguchi T, Mano Y, Taketomi A, Shirabe K, Honda H, Tsuneyoshi M and Oda Y (2011). Histologic classification of microscopic portal venous invasion to predict prognosis in hepatocellular carcinoma. *Hum Pathol* 42(10):1531-1538.
- 21 Sumie S, Nakashima O, Okuda K, Kuromatsu R, Kawaguchi A, Nakano M, Satani M, Yamada S, Okamura S, Hori M, Kakuma T, Torimura T and Sata M (2014). The significance of classifying microvascular invasion in patients with hepatocellular carcinoma. *Ann Surg Oncol* 21(3):1002-1009.
- 22 Iguchi T, Shirabe K, Aishima S, Wang H, Fujita N, Ninomiya M, Yamashita YI, Ikegami T, Uchiyama H, Yoshizumi T, Oda Y and Maehara Y (2014). New Pathologic Stratification of Microvascular Invasion in Hepatocellular Carcinoma: Predicting Prognosis After Living-Donor Liver Transplantation. *Transplantation*.
- 23 Suzuki S, Sakaguchi T, Yokoi Y, Okamoto K, Kurachi K, Tsuchiya Y, Okumura T, Konno H, Baba S and Nakamura S (2002). Clinicopathological prognostic factors and impact of surgical treatment of mass-forming intrahepatic cholangiocarcinoma. *World J Surg* 26(6):687-693.
- 24 Fisher SB, Patel SH, Kooby DA, Weber S, Bloomston M, Cho C, Hatzaras I, Schmidt C, Winslow E, Staley CA, 3rd and Maithel SK (2012). Lymphovascular and perineural invasion as selection criteria for adjuvant therapy in intrahepatic cholangiocarcinoma: a multi-institution analysis. *HPB (Oxford)* 14(8):514-522.
- 25 Wang Y, Li J, Xia Y, Gong R, Wang K, Yan Z, Wan X, Liu G, Wu D, Shi L, Lau W, Wu M and Shen F (2013). Prognostic nomogram for intrahepatic cholangiocarcinoma after partial hepatectomy. *J Clin Oncol* 31(9):1188-1195.
- 26 Li T, Qin LX, Zhou J, Sun HC, Qiu SJ, Ye QH, Wang L, Tang ZY and Fan J (2014). Staging, prognostic factors and adjuvant therapy of intrahepatic cholangiocarcinoma after curative resection. *Liver Int* 34(6):953-960.
- 27 Mavros MN, Economopoulos KP, Alexiou VG and Pawlik TM (2014). Treatment and Prognosis for Patients With Intrahepatic Cholangiocarcinoma: Systematic Review and Meta-analysis. *JAMA Surg* 149(6):565-574.