Margin status (Core and Non-core)

Margin assessment is based on combined macroscopic and microscopic measurement. Because margin involvement may be a focal, macroscopically indiscernible finding, extensive sampling is important for accurate assessment of the margin status.[1] The need for extensive tissue sampling to detect microscopic margin involvement is also supported by molecular studies.[2]

"R1" is defined by Union for International Cancer Control (UICC)[3]/American Joint Committee on Cancer (AJCC)[4] TNM as *microscopic residual disease,* i.e., irrespective of whether tumour is left behind at a surgical resection margin or at a non-surgical tissue plane. Assessment of the R-status should therefore be based on evaluation of all surfaces of the resection specimen, including the anterior pancreatic surface and the surface of the superior mesenteric vein groove (Figure 1). Involvement of these surfaces increases the risk of local tumour recurrence and is therefore of prognostic relevance.[5] Studies based on a fully standardised, detailed pathology examination protocol that includes evaluation of all surfaces report on a high R1-rate (>70%) that correlates with survival.[6-8]

Currently, a margin is considered positive if the tumour is at or within 1 millimetre (mm) of the margin (R1). This definition was originally adopted from the protocols for the assessment of rectal cancer, for which a clearance of ≤1 mm was found to be predictive of local recurrence and poor survival. Based on the dispersed growth pattern that is characteristic of pancreatic ductal adenocarcinoma and more pronounced than in rectal cancer,[9] a definition based on larger clearances (e.g., 1.5 mm) was proposed and found to be prognostically significant in some studies,[10,11] but has not been implemented in diagnostic practice. Because the anterior surface of the pancreas is a peritonealised anatomical surface, involvement of that surface is defined by breaching of the surface, i.e., a clearance of 0 mm. While further evidence is awaited, assessment of the margin status based on R1 defined as 1 mm clearance (0 mm for the anterior surface) is now also recommended by the AJCC and other professional bodies.[4,12-14]

An appropriate definition of microscopic margin involvement (R1) following neoadjuvant treatment has not been established yet.[15] Because a clearance of >1 mm does not necessarily reflect absence of microscopic residual disease, it is recommended to record the minimum distance to the relevant margins.

The definition of R1 based on 1 mm clearance applies to ductal adenocarcinoma of the pancreas only. There is no evidence that this definition is also appropriate for acinar cell carcinoma, which has a different, often less dispersed growth pattern. It is therefore recommended to record the minimum distance to the closest margin(s).

By consensus, diagnosing macroscopic residual disease (R2) is the surgeon's responsibility, and therefore this data item is not included in the pathology reporting document.

The distance of a carcinoma to some of the margins may be large, such that this information is of limited clinical relevance. However, it is recommended to record the clearance to the margins that are closest to, but not involved by, the tumour (non-core).

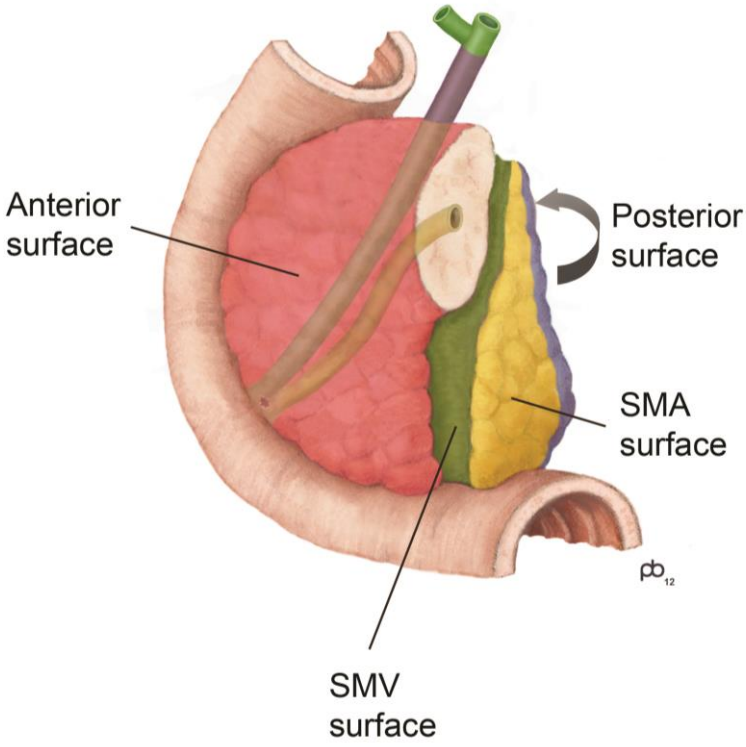

Figure 1: Circumferential surfaces of a pancreatoduodenectomy specimen to be included in the assessment of the margin status: anterior pancreatic surface (red), superior mesenteric vein (SMV) dissection margin (green), superior mesenteric artery (SMA) dissection margin (yellow), posterior dissection margin (blue). Permission courtesy of Mr Paul Brown.[16]

References

1 Verbeke CS, Leitch D, Menon KV, McMahon MJ, Guillou PJ and Anthoney A (2006). Redefining the R1 resection in pancreatic cancer. *Br J Surg* 93(10):1232-1237.

2 Kim J, Reber HA, Dry SM, Elashoff D, Chen SL, Umetani N, Kitago M, Hines OJ, Kazanjian KK, Hiramatsu S, Bilchik AJ, Yong S, Shoup M and Hoon DS (2006). Unfavourable prognosis associated with K-ras gene mutation in pancreatic cancer surgical margins. *Gut* 55(11):1598-1605.

3 Brierley JD, Gospodarowicz MK and Wittekind C (eds) (2016). *UICC TNM Classification of Malignant Tumours, 8th Edition*, Wiley-Blackwell.

4 Amin MB, Edge SB, Greene FL, Byrd DR, Brookland RK, Washington MK, Gershenwald JE, Compton CC, Hess KR, Sullivan DC, Jessup JM, Brierley JD, Gaspar LE, Schilsky RL, Balch CM, Winchester DP, Asare EA, Madera M, Gress DM and Meyer LR (eds) (2017). *AJCC Cancer Staging Manual. 8th ed.*, Springer, New York.

5 Nagakawa T, Sanada H, Inagaki M, Sugama J, Ueno K, Konishi I, Ohta T, Kayahara M and Kitagawa H (2004). Long-term survivors after resection of carcinoma of the head of the pancreas: significance of histologically curative resection. *J Hepatobiliary Pancreat Surg* 11(6):402-408.

6 Menon KV, Gomez D, Smith AM, Anthoney A and Verbeke CS (2009). Impact of margin status on survival following pancreatoduodenectomy for cancer: the Leeds Pathology Protocol (LEEPP). *HPB (Oxford)* 11(1):18-24.

7 Campbell F, Smith RA, Whelan P, Sutton R, Raraty M, Neoptolemos JP and Ghaneh P (2009). Classification of R1 resections for pancreatic cancer: the prognostic relevance of tumour involvement within 1 mm of a resection margin. *Histopathology* 55(3):277-283.

8 Esposito I, Kleeff J, Bergmann F, Reiser C, Herpel E, Friess H, Schirmacher P and Buchler MW (2008). Most pancreatic cancer resections are R1 resections. *Ann Surg Oncol* 15(6):1651-1660.

9 Verbeke CS, Knapp J and Gladhaug IP (2011). Tumour growth is more dispersed in pancreatic head cancers than in rectal cancer: implications for resection margin assessment. *Histopathology* 59(6):1111-1121.

10 Jamieson NB, Chan NI, Foulis AK, Dickson EJ, McKay CJ and Carter CR (2013). The prognostic influence of resection margin clearance following pancreaticoduodenectomy for pancreatic ductal adenocarcinoma. *J Gastrointest Surg* 17(3):511-521.

11 Chang DK, Johns AL, Merrett ND, Gill AJ, Colvin EK, Scarlett CJ, Nguyen NQ, Leong RW, Cosman PH, Kelly MI, Sutherland RL, Henshall SM, Kench JG and Biankin AV (2009). Margin clearance and outcome in resected pancreatic cancer. *J Clin Oncol* 27(17):2855-2862.

12 College of American Pathologists (CAP) (2017). *Protocol for the examination of specimens from patients with carcinoma of the pancreas*. Available from: https://documents.cap.org/protocols/cp-gihepatobiliary-pancreas-exocrine-17protocol-4001.pdf (Accessed 1st November 2019).

13 The Royal College of Pathologists of Australasia (RCPA) (2014). *Cancer of the exocrine pancreas, ampulla of Vater and distal common bile duct Structured reporting protocol*. Available from: https://www.rcpa.edu.au/Library/Practising-Pathology/Structured-Pathology-Reporting-of-Cancer/Cancer-Protocols (Accessed 1st October 2019).

14 The Royal College of Pathologists (RCPath) (2017). *Dataset for the histopathological reporting of carcinoma of the pancreas, ampulla of Vater and common bile duct*. Available from: www.rcpath.org. (Accessed 1st October 2019).

15 Verbeke C, Lohr M, Karlsson JS and Del Chiaro M (2015). Pathology reporting of pancreatic cancer following neoadjuvant therapy: challenges and uncertainties. *Cancer Treat Rev* 41(1):17-26.

16 Campbell F and Verbeke C (2013). *Pathology of the Pancreas - A Practical Approach.* Springer, London.