Extent of invasion (Core and Non-core)

The Union for International Cancer Control[1]/American Joint Committee on Cancer (AJCC)[2] 8th edition Staging Manuals divide T stage into T1a and T1b. T1a refers to invasion into lamina propria or muscularis mucosae whereas T1b involves the submucosa. Thus, the depth of invasion, which is the T staging criteria, needs be recorded accurately.

In addition, the extent of invasion has been associated with lymph node metastases, lymphovascular invasion and cancer recurrence. For both glandular and squamous malignancies, there are efforts to further subdivide the level of invasion. However, there is lack of multicentred studies to confirm the need of these subdivisions and to evaluate the best system to use.

The following systems are commonly employed and are provided as reference for optional use:

<u>For adenocarcinoma and high grade Barrett dysplasia</u>

In these malignancies, the Barrett muscularis mucosae is often duplicated (Figures 4 and 6; Table 2).[2-5]

There are two systems for assessing the depth of invasion (Figure 6). One is recommended by the AJCC, as described by Westerterp et al (2005).[5] It divides high grade Barrett dysplasia and intramucosal carcinoma into M1 to M3. The second system, proposed by the groups of Vieth et al (2005)[3] and Stolte et al (2010),[6] divides the invasion into M1 to M4. The difference between the two systems is that Westerterp et al (2005)[5] defines M3 as invasion of the original (deep) muscularis mucosae, whereas the second system[3,6] subdivides muscularis mucosa invasion into inner layer invasion (M3) and outer layer invasion (M4). However, the second system[3,6] is used less often as it requires larger specimens (for example, endoscopic submucosal dissection specimens) to be able to assess the division between M3 and M4.

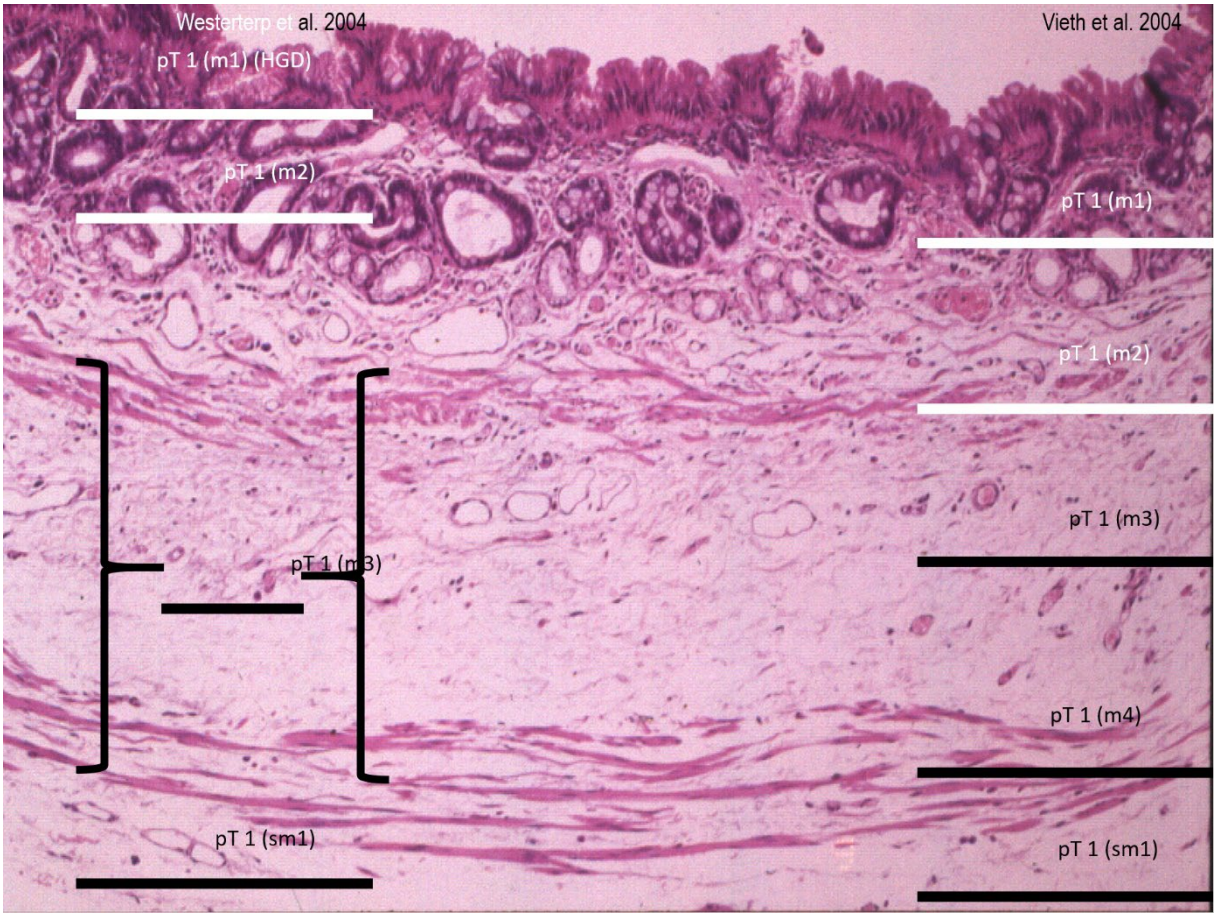

Figure 4: Subdivision of mucosal Barrett layer. Reproduced with permission from Vieth et al (2012). Barrett oesophagus. Practical issues for daily routine diagnosis. *Pathology - Research and Practice* 208(5):261-268.[7]

Table 2: Intramucosal carcinoma (T1a) subclassification schemes.[2-5]

Depth of invasion	Vieth et al 2005[3]	Westerterp et al 2005[5]	Kaneshiro et al 2011[4]	AJCC 2017[2]
None - Tis, high grade dysplasia (HGD)	HGD	m1	HGD	Tis
Tumour cells invade into lamina propria (LP) beyond the basement membrane	m1	m2	LP	T1a
Tumour cells invade inner duplicated muscularis mucosae (IMM)	m2	m2	IMM	T1a
Tumour cells in the space between the duplicated muscularis mucosae and original muscularis mucosae, i.e., between muscularis mucosae (BMM)	m3	m2	BMM	T1a
Tumour cells into outer original muscularis mucosae (OMM)	m4	m3	OMM	T1a

For squamous cell carcinoma and high grade squamous dysplasia

For these malignancies, Japanese pathologists have proposed a sub-division of levels of invasion as follows:[4]

- T1a-EP
- T1a-LPM
- T1a-MM
- T1b-SM1
- T1b-SM2
- T1b-SM3

pT1 of intramucosal cancer is assessed in the three stages, including pT1a-EP (epithelium), pT1a-LPM (lamina propria mucosae) and pT1a-MM (invasion into muscularis mucosae) (Figures 5 and 6). For cancer that invades the submucosa, the submucosa is divided into three levels depending on the depth of invasion under microscopic observation - the top layer, middle layer, and bottom layer - which are pSM1, pSM2, and pSM3.

In a cancer that invades beyond the muscularis mucosae of an ER case, the entire submucosal layer may not be observed. Therefore, the depth of invasion from the lower end of the muscularis mucosae should be described using measured values. The subclassification of pT1b for squamous cell carcinoma is pT1b-SM1 for cancer cell invasion up to 200 micrometres (µm) and pT1b-SM2 for cancer cell invasion exceeding 200 µm.[8] On the other hand, for adenocarcinoma, SM1 corresponds to infiltration into the submucosa of up to 500 µm; SM2 for invasion exceeding 500 µm and up to 1000 µm; whereas SM3 is for deeper than 1000 µm.[8] One of the rationales for this subdivision is that the risk of lymph node metastasis is shown to be related to the invasive depth for endoscopic resection cases.[9,10]

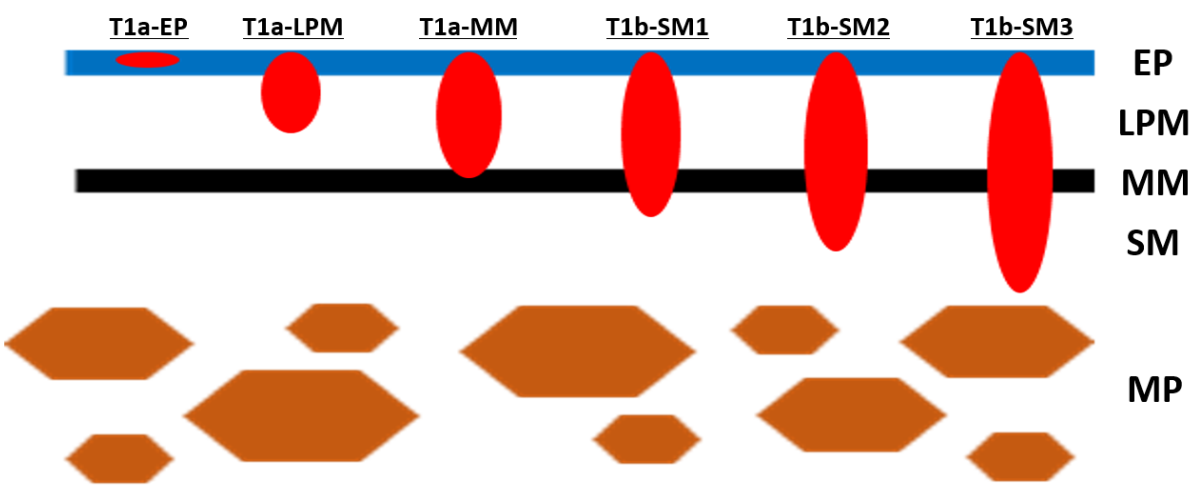

Figure 5: pT1 of intramucosal squamous cancer is assessed in the three stages: pT1-EP (epithelium), pT1a-LPM (lamina propria mucosae) and pT1a-MM (muscularis mucosae). The subclassification of pT1b is: pT1b-SM (submucosa) 1 for cancer cell invasion up to 200 µm and pT1b-SM2 for cancer cell invasion exceeding 200 µm; MP (muscularis propria). Modified with permission from Japan Esophageal Society (2017). Japanese Classification of Esophageal Cancer, 11th Edition: Part I. *Esophagus* 14:1–36.[11]

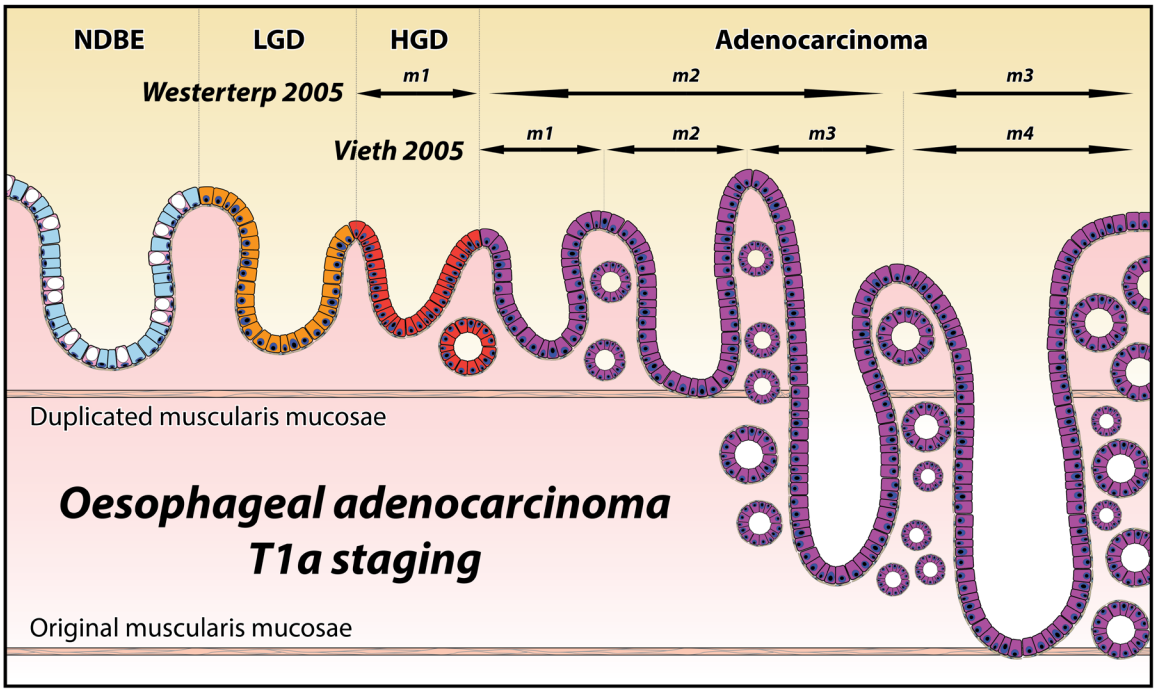

Figure 6: The two different systems of classification of the level of invasion of pT1a oesophageal adenocarcinoma). Permission courtesy of Dr Marnix Jansen.

References

1 Brierley JD, Gospodarowicz MK and Wittekind C (eds) (2016). *Union for International Cancer Control. TNM Classification of Malignant Tumours, 8th Edition*, Wiley, USA.

2 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 Edition*, Springer, New York.

3 Vieth M and Stolte M (2005). Pathology of early upper GI cancers. *Best Pract Res Clin Gastroenterol* 19(6):857-869.

4 Kaneshiro DK, Post JC, Rybicki L, Rice TW and Goldblum JR (2011). Clinical significance of the duplicated muscularis mucosae in Barrett esophagus-related superficial adenocarcinoma. *Am J Surg Pathol* 35(5):697-700.

5 Westerterp M, Koppert LB, Buskens CJ, Tilanus HW, ten Kate FJ, Bergman JJ, Siersema PD, van Dekken H and van Lanschot JJ (2005). Outcome of surgical treatment for early adenocarcinoma of the esophagus or gastro-esophageal junction. *Virchows Arch* 446(5):497-504.

6 Stolte M, Kirtil T, Oellig F, Vogel C, Mueller H, May A, Ell C and Wittenberg R (2010). The pattern of invasion of early carcinomas in Barrett's esophagus is dependent on the depth of infiltration. *Pathol Res Pract* 206(5):300-304.

7 Vieth M, Langner C, Neumann H and Takubo K (2012). Barrett's esophagus. Practical issues for daily routine diagnosis. *Pathol Res Pract* 208(5):261-268.

8 Manner H and Pech O (2015). Measurement of the tumor invasion depth into the submucosa in early adenocarcinoma of the esophagus (pT1b): Can microns be the new standard for the endoscopist? *United European Gastroenterol J* 3(6):501-504.

9 Yamashina T, Ishihara R, Nagai K, Matsuura N, Matsui F, Ito T, Fujii M, Yamamoto S, Hanaoka N, Takeuchi Y, Higashino K, Uedo N and Iishi H (2013). Long-term outcome and metastatic risk after endoscopic resection of superficial esophageal squamous cell carcinoma. *Am J Gastroenterol* 108(4):544-551.

10 Katada C, Muto M, Momma K, Arima M, Tajiri H, Kanamaru C, Ooyanagi H, Endo H, Michida T, Hasuike N, Oda I, Fujii T and Saito D (2007). Clinical outcome after endoscopic mucosal resection for esophageal squamous cell carcinoma invading the muscularis mucosae--a multicenter retrospective cohort study. *Endoscopy* 39(9):779-783.

11 Japan Esophageal Society (2017). Japanese Classification of Esophageal Cancer, 11th Edition: part I. *Esophagus* 14(1):1-36.