Please provide us with a reasonable definition for curative R0 resection in Barrett's esophagus neoplasia; which one should we choose?

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A resection is considered to be R0 when the pathological examination confirms that the edges of the resected specimen are free of disease. A resection is curative when the patient is cured by the endoscopic treatment without need for further surgery or chemoradiation therapy. In the colon for example, the definition of the curative R0 resection is quite simple: a strict R0 is defined by an 'en bloc' specimen with normal mucosa on the edges when examined histologically. The treatment is considered to be curative if the resection is R0 with an invasion depth less than 1000 µm in the submucosa, without lymphatic or venous emboli, without budding, and with a differentiated carcinoma. The situation is far more complex in the neoplasia developed on Barrett's esophagus (BE) since different degrees of neoplasia are possible with different prognosis and treatment strategies. At present, we do not have any consensus on the definition of R0 and curative resections for BE neoplasia (**Fig. 1 a**). This editorial aims to discuss various definitions of the R0 resection and their clinical impact. We shall also discuss the literature available to choose the best criteria to define resection curativeness.

Different definitions of the R0 resection (**Fig. 1**)

The simplest definition is the strict "colon-like R0" (**Fig. 1 b**) defined by a normal mucosa on the edges of the resection. Nevertheless, choosing such a standard for BE conduct to resect all of the BE to avoid both the presence of the precancerous condition represented by the intestinal metaplasia. This full resection strategy is technically difficult for a long segment of BE and very risky in terms of adverse events per procedure (perforations) and post procedure (stenosis). Furthermore, radiofrequency ablation (RFA) is the reference method to treat flat BE neoplasia in order to reduce the adverse events with an effective homogeneous ablation [1–4]. BSG guidelines clearly recommend the combined strategy with endoscopic resection of the visible components and RFA for the flat ones to prevent recurrences [5].

But what degree of Barrett neoplasia is acceptable on the margins of our resections? Intestinal metaplasia (IM)? Low grade dysplasia (LGD)? High grade dysplasia (HGD)? Intramucosal carcinoma (IMC)? …

Intestinal metaplasia (IM) has a very low risk of progression (0.1–0.9%) to the next stages of BE neoplasia and follow-up is clearly recommended for these patients. A resection of all of the neoplastic tissue including low grade dysplasia seems to be the best option from a carcinologic point of view since it removes all of the neoplastic risk. This "intestinal metaplasia-R0" (**Fig. 1 c**) choice is attractive but probably not effective for two reasons. First, endoscopic diagnosis of LGD is actually not possible even with magnified chromoendoscopy in expert hands [6–9]. Furthermore, the pathological diagnosis of LGD is difficult with low inter-observer concordance between pathologists [10,11]. Second, the resected area including all neoplastic lesions will be very large and complicated by stenosis that could have been avoided by using a combined strategy with resection and RFA of the flat BE components.

Low grade dysplasia (LGD) has a clear potential to progress to the next stages of cancer when confirmed by two different pathologists. Although neoplastic potential has been discussed in some reports as having a very low risk of progression (0.54%) to HGD [12], a recent report with pathological consensus for the diagnosis of LGD has demonstrated a potential risk of 25% to progress to HGD and 8.8% for adenocarcinoma during a 3-year follow-up [13]. This last trial advised to treat patients with LGD using RFA, but surveillance is currently the recommended approach. LGD treat-

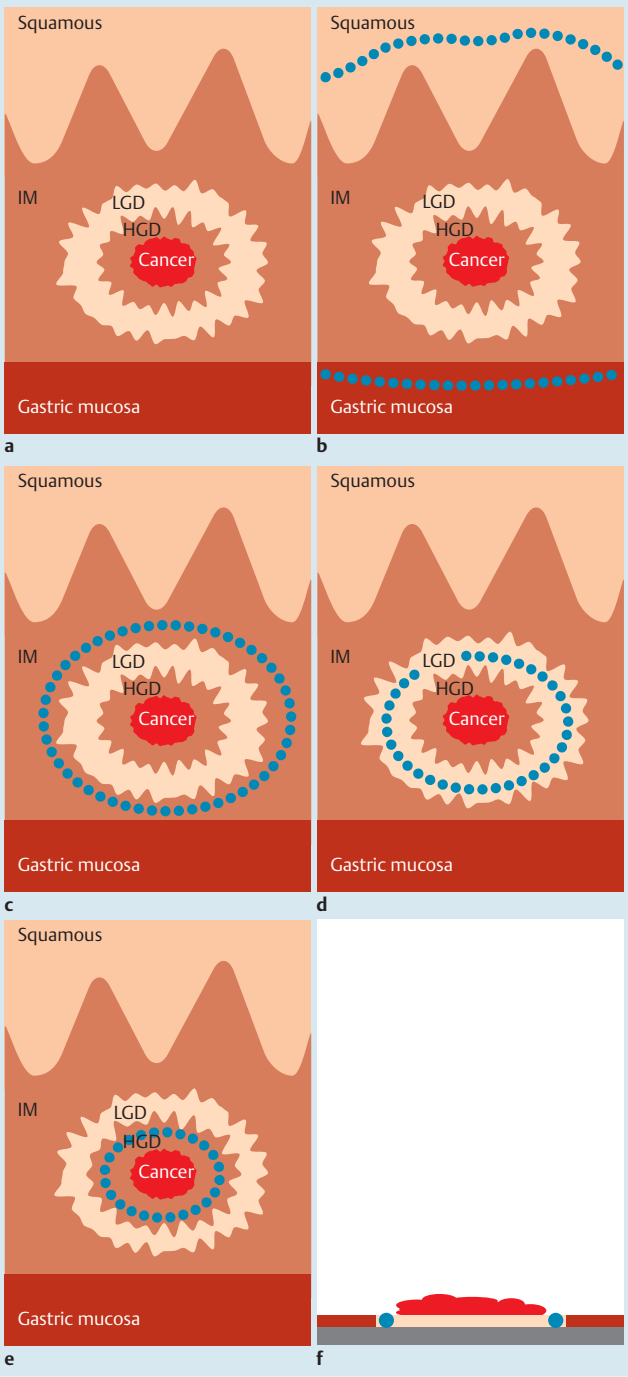

Fig. 1 Schematic representation of the different R0 resections. **a** Neoplasia representation; **b** Colon-like R0; **c** Intestinal metaplasia R0; **d** LGD or less R0; **e** HGD or less R0; **f** Flat components R0. IM, intestinal metaplasia; LGD, low grade dysplasia; HGD, high grade dysplasia.

ment by RFA is still being evaluated in different trials to determine the benefits and cost effectiveness of such a therapeutic strategy versus surveillance. According to those elements, the "LGD or less-R0" (**Fig. 1 d**) definition with LGD or intestinal metaplasia on the margins of our BE resections could be considered to be a satisfactory solution since the patient will continue surveillance but without any residual HGD or cancer component. In this definition, the resection is theoretically curative without any further treatment but with only the surveillance of remaining LGD.

The most popular definition is to define R0 by complete resection of the carcinoma regardless of the presence of HGD on the margins (**Fig. 1 e**). This last definition was chosen in a recent report evaluating ESD for BE neoplasia [14] in Belgium. In this case, HGD on the margins would be treated by further RFA to ablate the remaining neoplasia. This strategy could be justified to reduce the resected area as much as possible with a small resection concerning only the carcinoma component and a large RFA to treat the remaining flat BE. However, some arguments run against this radical strategy. First, differential diagnosis between high grade dysplasia and intramucosal carcinoma is far from easy either endoscopically or pathologically. Furthermore, the presence of HGD on the margins does not guarantee that the remaining BE is free from an intramucosal or invasive component. Thus, it is dangerous to cut into an HGD area as we cannot be perfectly sure of the pure intramucosal extent of this lesion before resection.

If we consider this last definition, why do we not go even further considering R0 resection if all of the invasive carcinoma is resected completely but with intramucosal carcinoma on the edges? In fact, if the intramucosal carcinoma is flat (**Fig. 1 f**), RFA is theoretically possible, but cutting into intramucosal carcinoma does not provide a complete piece so we cannot be sure of the non-invasiveness in the remaining component outside of the resected area. Furthermore, the characterization of invasiveness for BE neoplasia is difficult. If HGD is well recognized and delineated by endoscopy with narrow band imaging with or without magnification, the characterization of the invasion depth is not well established. Second, large resections are sometimes associated with severe suspected stenosis (recurrence, inflammation, etc) that could compromise further treatment by RFA and therefore the curative issue for the patient.

According to these different possible definitions, we need a consensus so we can all talk about the same thing. But we already understand that the definition of R0 resection will not be directly linked to the curative issue of the endoscopic treatment.

In a second part, we shall discuss the curativeness of the resection.

Curative resection of BE neoplasia

First, from a locally carcinologic point of view, the definition depends on the treatment strategy. If a combined strategy is used, RFA could be a curative option after all of the resections have completely removed the invasive and non-flat components without delayed stenosis. Indeed, for non-flat lesions and invasive components, RFA is not very homogeneous or effective, ablation is not deep enough and may delay the diagnosis of a potential lymph node risk. Finally, if a stenosis has occurred, RFA becomes very difficult and non-homogeneous. According to those elements, we could consider the resection to be curative if the margins are positive with flat HGD or intramucosal carcinoma.

From a lymph node invasion point of view, the maximal depth acceptable to consider the resection as a curative one has not been clearly defined. First, by analogy with gastric cancer or with glandular mucosa, the sm1 stage is defined by an invasion depth less than 500 µm in the submucosa. On the other hand, for squamous neoplasia, a different level is used with only 200 µm for sm1 invasion. At the Paris classification workshop in 2002, this difference was defined arbitrary based on the stomach conditions. The literature is not very rich to help clarify this point since

we do not know exactly whether the submucosal thickness is the same all along the BE. The situation could be different for short and long BE.

The lymph node risk associated with the presence of submucosal lymphatic or venous emboli has been clearly demonstrated. In a meta-analysis of more than 1800 patients, the risk of unexpected lymph node metastases for patients with mucosal neoplasms in BE was in the range 1 – 2 % [15]. Nevertheless, according to the lesions invading the muscularis mucosae (m3), this risk increased to 4.7 % for 170 patients [15]. Esophagectomy has a mortality rate that often exceeds 2 %, with substantial morbidity and no guarantee of curing metastatic disease. Therefore, the risk of lymph node metastases alone does not warrant the choice of esophagectomy over endoscopic therapy for HGD and intramucosal carcinoma in Barrett's esophagus [15] but should be discussed on a case-by-case basis for m3 lesions. Submucosal lesions with only sm1 invasion are associated with a lymph node risk between 13 % [16] and 22 % [17]. In some surgical series, the risk of lymph node metastasis in sm1 cancer did not differ between squamous cell and adenocarcinoma. These last reports indicate that sm1 lesions should be treated by further surgery or chemoradiation therapy. Nevertheless, endoscopic series selecting "low risk" sm1 lesions with invasion of the upper submucosal third (sm1), absence of infiltration into lymph vessels/veins, histological grade G1 /2, and macroscopic type I/II showed better outcomes without any metastatic recurrences for 21 patients treated by endoscopic resection [18]. In another prospective work, the same team demonstrated a low risk of 2 % to lymph nodes for those selected low risk sm1 versus 9 % (P=0.24) in the high risk group (undifferentiated G3, emboli) [19]. Unfortunately, the depth used to define sm1 was not clarified for patients only treated endoscopically and we do not know if the authors chose 200 or 500 µm. In the latter study, there was no significant difference between long and short segment BE according to the lymph node rate in low risk sm1 lesions but further prospective studies are required.

To summarize, the situation in BE is not as simple and clear as it is in the colon and we need to standardize the definitions for R0 and curative resections. Should we adapt the R0 definition to the BE or should we change the curative one according to the treatment strategy with both endoscopic resection and RFA?

A reasonable R0 definition could be a complete resection of HGD and carcinoma components irrespective of the presence of IM or LGD on the margins. This definition seems effective to resect all of the high risk mucosa with a complete analysis but avoiding stenosis.

On the other hand, some elements are clear for the definition of curativeness: lymphatic or venous emboli, deep submucosal invasion, and undifferentiated types (G3) are associated with a high risk of lymph node metastases and should be treated by further surgical or chemo-radiation therapies. However, there is still a lack of data on the safe depth between 200 µm ("esophagus like") and 500 µm ("stomach like") that should be adopted to define sm1. Thus, we need large scale evaluations to know precisely the outcomes of endoscopic resections for intramucosal and sm1 lesions with a low and high risk of lymph node metastases so as to manage patients safely and to propose to them the better option between a risky curative surgery and a hazardous risk of recurrence during surveillance.

Competing interests: None

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