Is it justified to ablate flat-type esophageal squamous cancer? An analysis of endoscopic submucosal dissection specimens of lesions meeting the selection criteria of radiofrequency studies

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Background: Endoscopic radiofrequency ablation (RFA) appears to be a safe and effective treatment for flat-type noninvasive squamous neoplasia of the esophagus. However, if RFA is applied to lesions containing invasive cancer (esophageal squamous cell carcinoma [ESCC]), histological features associated with lymph node metastases may remain undetected. In addition, extension of neoplasia down the ducts of esophageal submucosal glands (SMGs) may create a sheltered "niche" beyond the reach of ablation.

Objective: To determine the RFA eligibility of flat-type ESCC.

Design: Retrospective analysis of prospectively collected data of ESCC patients.

Setting: National Cancer Center Hospital, Tokyo, Japan.

Patients: Patients with flat-type ESCC larger than 3 cm removed by endoscopic submucosal dissection (ESD).

Interventions: Three endoscopists involved in RFA studies in China reviewed endoscopic images to select lesions eligible for RFA. Corresponding ESD resection specimens were histologically examined.

Main Outcome Measurements: The presence of poor histological features (ie, invasion in m3 or deeper, poor tumor differentiation, or lymphovascular invasion) and the number of involved esophageal SMGs and ducts.

Results: Sixty-five lesions were included, 17 (26%) of which qualified as RFA eligible by RFA endoscopists. Interobserver agreement for this assessment was poor ($\kappa = 0.09$). Six of the 17 specimens (35%) showed relevant disease: 4 lesions invaded in the muscularis mucosae, 1 of which also showed lymphovascular invasion; 2 lesions showed extension of neoplasia into SMGs.

Limitations: Limited number of cases. RFA eligibility status was based on analysis of still images.

Conclusions: One third of flat-type ESCC, deemed eligible for RFA, demonstrated histological features that are considered (relative) contraindications to endoscopic treatment. Because it appears difficult for endoscopists to identify low-risk ESCC, conservative use of RFA for flat-type ESCC is advocated until long-term follow-up data are available. (Gastrointest Endosc 2014;80:995-1002.)

Abbreviations: ESCC, esophageal squamous cell carcinoma; ESD, endoscopic submucosal dissection; IQR, interquartile range; LNM, lymph node metastasis; LVI, lymphovascular invasion; RFA, radiofrequency ablation; SMG, submucosal gland; USL, unstained lesion.

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Although the incidence of esophageal adenocarcinoma is increasing rapidly in the Western world, 80% of esophageal carcinomas occur in other parts of the world, where 90% of cases are esophageal squamous cell carcinoma (ESCC). Especially in South and Eastern Africa, central Asian countries, and parts of China, with regional incidences in excess of 100 per 100,000 person-years, ESCC is far more prevalent than in the West.[1]

When diagnosed at a symptomatic stage, the prognosis of esophageal squamous cell cancer is poor because lymph node metastasis (LNM) and distant metastasis are frequently present. The prognosis is favorable when ESCC or its precursor lesion—intraepithelial neoplasia (IEN)—is detected at an early, generally asymptomatic stage. This early stage can be identified at endoscopy, and detection is enhanced by chromoendoscopy with Lugol's iodine staining. In normal esophageal squamous cell epithelium, iodine reversibly binds to the intracellular glycogen causing a brown stained mucosa. In contrast, squamous neoplastic cells contain little glycogen and therefore appear as unstained lesions (USLs).

The risk of lymph node metastasis (LNM) in ESCC is the key factor determining treatment strategies and is linked to the depth of tumor invasion. In IEN (T1m1) and ESCC limited to the lamina propria (T1m2), the risk of LNM is less than 5%. This marginal risk is deemed acceptable for endoscopic therapy. Lesions invading the muscularis mucosa (T1m3) or superficial submucosa (T1sm1) carry a higher risk of distant LNM and are considered borderline lesions; the choice between endoscopic treatment or surgery should be individualized and discussed in a multidisciplinary setting in centers with a tertiary referral function for esophageal cancer. Lesions infiltrating the deep submucosa (≥T1sm2) are not eligible for curative endoscopic treatment.[2,3] On endoscopy, protruding and excavated lesions (Paris classification type 0-I and 0-III, respectively) harbor a greater than 90% risk of submucosal invasion; in flat-type lesions (Paris types 0-IIa, 0-IIb, or 0-IIc), this risk is estimated to be approximately 15%.[4]

Endoscopic submucosal dissection (ESD) is currently considered the treatment of choice for those cases in which curative endoscopic treatment is attempted. En bloc resection of large neoplastic areas by ESD allows accurate histopathological staging and grading, but is technically demanding and has a long learning curve.[5] In Japan and Korea, en bloc resection of large neoplastic areas with ESD is well established, but the same level of expertise is not widely available elsewhere. Furthermore, esophageal ESD is associated with a significant risk of perforation, and stricture formation occurs in cases of larger resections (ie, >75% of esophageal circumference).[6] Radiofrequency ablation (RFA) is a safe and effective treatment of Barrett's esophagus with or without dysplasia.[7,8] RFA is potentially a less demanding alternative for ESD in the treatment of flat squamous cell neoplasia. This is particularly attractive in those regions (such as Sub-Saharan Africa and the Far East) that have high incidences of early squamous neoplasia, but lack a high level of ESD expertise. Recent studies on RFA in these patients suggest that this technique is safe and effective for flat-type squamous neoplasia, although studies are small and have T1m1 lesions mainly included, and follow-up remains short.[9,10]

The main drawback of RFA is that it precludes histopathological examination of the ablated lesion. RFA appears therefore most efficacious in patients at low risk (ie, <5%) of LNM in whom the benefits of ESD do not outweigh its risks. At this point, however, the exact rate of poor histological features lost to pathology workup by ablative treatment of flat-type early ESCC is not known. In addition, extension of neoplastic disease along mucosal surfaces into gland orifices and ducts of esophageal submucosal glands has previously been reported in ESCC.[11,12] However, this has only been done in esophagectomy specimens and not for early lesions. Extension of neoplastic epithelium along pre-existing ductal linings into the submucosa may create a "niche" for neoplastic epithelium beyond the reach of ablative treatment.

In this study, we therefore set out to define the occurrence of poor histological features in patients with extensive (>3 cm), flat-type ESCC deemed eligible for ablative treatment. Second, we recorded the pattern of neoplastic ductal extension in ESD specimens of lesions considered eligible for ablative therapy and related the extent of ductal involvement to stage of disease.

METHODS

Patient selection

Study patients were identified from a prospectively collected database containing all consecutive patients with esophageal cancer discussed at the multidisciplinary meeting at the National Cancer Center Hospital in Tokyo, Japan. We selected all patients in the database who had undergone ESD for flat or slightly depressed ESCC (Paris type 0-IIb or 0-IIc, respectively, as scored by local endoscopists). Lesions showing partly elevated or excavated features were not included in the study. Only en bloc resections with a minimum diameter of 3 cm (as measured on the fixed specimen in the pathology department) were included in this analysis. All consecutive lesions meeting these inclusion criteria between January 2008 and December 2012 were included. The institutional review board granted exemption from approval for this study.

Endoscopic resection and histology processing

All ESD procedures and previous mapping endoscopies were performed according to local protocol with GIF-H260, GIF-H260Z, or GIF-Q260J endoscopes (Olympus Medical Systems, Tokyo, Japan) by using a standard videoendoscopy processor (EVIS Lucera; Olympus Medical Systems). First, the lesion was demarcated by placing