Submucosal tumor appearance is a useful endoscopic predictor of early primary-site recurrence after definitive chemoradiotherapy for esophageal squamous cell carcinoma

Author/s:

Chia-Hung Tu M.D.[1], Manabu Muto M.D. PhD.[2], Takahiro Horimatsu M.D.[2], Keisei Taku M.D.[3], Tomonori Yano M.D.[4], Keiko Minashi M.D.[4], Masakatsu Onozawa M.D.[5], Keiji Nihei M.D.[5], Satoshi Ishikura M.D., PhD.[5], Atsushi Ohtsu M.D. PhD.[4], Shigeaki Yoshida M.D.[4]

Affiliation/s:

1. Division of Gastroenterology and Hepatology, Department of Internal Medicine, Far Eastern Memorial Hospital, Taipei, Taiwan

2. Department of Gastroenterology and Hepatology, Kyoto University, Kyoto, Japan

3. Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Shizuoka, Japan

4. Division of Digestive Endoscopy and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan

5. Division of Radiation Oncology, National Cancer Center Hospital East, Kashiwa, Japan

Corresponding author:

Manabu Muto, MD. PhD.

Department of Gastroenterology and Hepatology, Kyoto University, Kyoto, Japan.

Mailing address: 54 Kawaharacho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan.

TEL: +81-75-751-4319

FAX: +81-75-751-4303

Email : mmuto@kuhp.kyoto-u.ac.jp

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ABSTRACT

Background:

Chemoradiotherapy (CRT) for esophageal cancer is disadvantageous because of a high locoregional failure rate. Detecting early small recurrent cancers at the primary site is necessary for potential salvage treatment. However, most endoscopists are inexperienced and therefore a role for surveillance endoscopy after complete remission (CR) has not been established. We retrospectively evaluated serial surveillance endoscopic images from patients eventually proved to have primary-site recurrence in order to identify useful endoscopic features for early diagnosis.

Methods:

From January 2000 to December 2004, 303 patients with esophageal squamous cell carcinoma underwent definitive CRT and 133 of them achieved CR. The surveillance endoscopic images stored at intervals of 1–3 months for the 16 patients with recurrence only at the primary tumor site and the 61 patients with no recurrence were collected for reexamination.

Results:

Among 133 patients who achieved CR, 16 (12%) developed only local recurrence at the primary site. Thirteen of the 16 primary-site recurrent tumors (81%) appeared as submucosal tumors (SMT), with the remaining appearing as erosions or mild strictures. Eighty-one percent of biopsy-proved recurrences were preceded by newly developed lesions such as SMT, erosions, or mild strictures detected by earlier surveillance endoscopies. For all 77

patients achieving CR with no metastasis, 86% of the evolving SMT with negative biopsies were eventually confirmed as cancer at later endoscopies. Thirteen of the 21 evolving lesions were subsequently confirmed as recurrent cancer.

Conclusions:

Early primary-site recurrence of esophageal cancer after a complete response to CRT is detectable with frequent endoscopic surveillance. SMT appearance is a useful endoscopic sign of early recurrence, as well as a predictor of subsequent diagnosis of recurrence.

KEY WORDS: esophageal cancer, chemoradiotherapy, surveillance, recurrence.

INTRODUCTION

Definitive chemoradiotherapy (CRT) is widely accepted as a standard treatment option in the management of locally advanced esophageal cancer because of its high response rate and significant survival benefit.[1,2] A major drawback to this nonsurgical approach is locoregional treatment failure. At least 40% of patients undergoing CRT experienced local failure, some of whom did not develop distant metastases.[1,3–5]

These primary-site recurrence patients are traditionally managed with salvage esophagectomy for a chance of long-term survival, particularly in those with an earlier pathological stage (T1N0 and T2N0).[6,7] However, high perisurgical mortality and morbidity rates are major concerns.[7,8] Recently developed nonsurgical techniques, such as salvage endoscopic mucosal resection and photodynamic therapy, have the advantages of greater safety and fewer treatment-related sequelae, while conferring promising survival benefits for local failures after definitive CRT.[9,10] Technically, endoscopic mucosal resection and photodynamic therapy are feasible only when the volume of the locally recurrent tumor is small enough to be amenable to these endoscopy-based procedures. Therefore, the application of these newer treatments depends crucially on the ability to identify early recurrent tumors by endoscopy.

A strategy of frequent surveillance endoscopy initiated early after remission of the cancer should theoretically improve the chances of detecting primary-site recurrent tumors in their early stages. This requires the prompt recognition of minute tumors arising from the former neoplastic bed, instead of from the uninvolved normal esophageal mucosa. However,

the complete regression of cancer cells results in residual fibrosis, radiation-induced tissue injury, and the distortion of normal microstructures,[11,12] which may render relapsing neoplastic growth morphologically different from typical primary tumors. Apparently, most endoscopists are inexperienced in hunting for these difficult lesions. To our knowledge, no study of the skills in endoscopic detection of such lesions has been published. Not surprisingly, a follow-up endoscopy after the completion of CRT is considered "optional" in the National Comprehensive Cancer Network clinical practice guidelines for esophageal cancer.[13] We believe that a reliable endoscopic diagnostic technique is necessary to support a strategy of intense endoscopic follow-ups.

As a cancer referral and research hospital, our institute is unique in its implementation of a vigorous endoscopic follow-up program after primary treatment for all patients with esophageal cancer. Therefore, it is possible to analyze the filed imaging data of endoscopic monitoring on the post-CRT mucosa. In the present study, we aimed to identify useful endoscopic findings through reviewing the image data pool to predict recurrent esophageal cancers limited to the primary site after complete remission (CR) is achieved by CRT.

MATERIALS AND METHODS

Patient population

Between January 2000 and December 2004, 303 patients with esophageal squamous cell carcinoma underwent definitive CRT at the National Cancer Center Hospital East, Kashiwa, Japan. The CRT consisted of 50.4–60 Gy irradiation, together with two cycles of continuous infusion with 5-fluorouracil (5FU) and cisplatin. Up to four courses of CRT were

added for those patients who showed a good initial response to treatment.[9]

Response to treatment was assessed at the completion of CRT. CR was defined when all the following criteria were met: (1) the disappearance of the tumor lesion or ulcer at the primary site, with negative biopsies; (2) no esophageal stricture or any condition that prevented a thorough endoscopic examination of the whole esophagus; (3) no remaining measurable disease or distant metastasis on computer tomography and chest roentgenography; and (4) these criteria were met for at least four weeks.

Of the 303 patients, 133 (43.9%) were defined as being in CR at the completion of CRT. Of these 133 patients, 110 were men, with a median age of 62 years. Pretreatment staging of their esophageal cancers was determined with the tumor-node-metastasis classification of the International Union Against Cancer.[14] Seventy (52.6%) patients had T3 tumors; most patients had N1 (65.4%) or M0 (92.5%) disease. Forty-five (33.8%) and 62 (46.6%) patients were classified as clinical stages II and III, respectively (Table 1).

Study design

After achieving CR, initial follow-up endoscopy to confirm CR was scheduled within at most 1–2 months for each patient, accompanied with other necessary studies for the assessment of metastases. After the confirmation of CR, follow-up endoscopy was scheduled every 2–3 months for the first year and every 4–6 months for two years thereafter. Lugol staining and multiple biopsies at the primary site were routinely required.[15] The diagnosis of local recurrence was determined by a positive biopsy.

Of the 133 CR patients, 61 had no recurrence, 56 developed lymph node or distant

metastases, and the remaining 16 developed local recurrence at the primary tumor site with no evidence of metastasis. We excluded the 56 patients with lymph node or distant metastases from this study because for them, evaluation of the primary site was not important and only those patients eligible for salvage treatment on local tumors were of interest. Therefore, the endoscopic images of the remaining 77 patients were retrospectively enrolled. This population comprised patients with esophageal squamous cell carcinoma who achieved CR after the initial CRT and developed no metastasis during follow-up, regardless of local recurrence. All of the filed endoscopic images stored after achieving CR, both conventional endoscopy and Lugol-stained chromoendoscopy, were retrospectively collected for reexamination. The stored endoscopic images were evaluated by consensus among three endoscopists experienced in upper gastrointestinal cancer diagnosis (K. T., M. M., K. M.).

RESULTS

Upon the diagnosis of primary-site recurrence for the 16 patients, 13 (81%) had endoscopic findings resembling SMT, typically a focal bulge mostly covered by normal-appearing mucosa (Fig. 1A).[16] Eleven of the 13 tumors contained central eroded areas recognized as ulcers or erosions (Fig. 1B, 1C). The remaining three tumors were detected as flat erosions without features of SMT (Table 2).

Images of surveillance endoscopies performed at intervals between CR and the diagnosis of recurrence in the 16 patients were sequentially examined. Newly developed gross lesions at the primary site with negative biopsies were interpreted as recurrent lesions. Evolving lesions were discovered in 13 (81%) patients, including six (38% of the 16 patients)

SMT, five (31%) erosions, and two (12%) mild luminal strictures (Table 3).

For all 77 patients achieving CR and free of metastasis, lesions newly developed between CR and the most recent endoscopic surveillance were considered evolving lesions. Therefore, an evolving lesion may be eventually proven to be a recurrence or remain biopsy-negative at the most recent endoscopy. Six of the seven (86%) evolving SMT were subsequently confirmed as recurrent cancer by follow-up endoscopic biopsies. Similarly, five of eight (63%) evolving erosions and two of six (33%) evolving mild strictures were finally confirmed as recurrence. Fifty-six patients were never found to have evolving lesions throughout the follow-up, including three (5%) who were confirmed as recurrence upon the first appearance of an endoscopic lesion. In total, eight of the 21 (38%) patients who developed evolving lesions remained biopsy-negative at their most recent endoscopic follow-up (Table 4).

DISCUSSION

We discovered that the most frequent (81%) endoscopic indicator of primary-site recurrence at its earliest possible stage for a histological diagnosis is SMT. Eighty-one percent of biopsy-proved recurrences were preceded by newly developed lesions such as SMT, erosions, or mild strictures detectable with surveillance endoscopies. Most (86%) evolving SMT with negative biopsies were eventually confirmed as cancer at later endoscopies, but the proportions were lower for other evolving lesions such as erosions (63%) and strictures (33%). This is the first study to describe the morphological changes of early recurring tumors by serial endoscopic observations at short intervals. Our findings will be

helpful for improving the skills to detect potentially treatable primary-site recurrence after definitive CRT for esophageal squamous cell carcinoma.

For the endoscopic diagnosis of primary esophageal cancer, several features have been previously described to detect early stage squamous cell carcinoma: localized mucosal erosions in contrast to normal surrounding mucosa; circumscribed mucosal protuberances with irregular configurations; focal areas of mucosal coarsening and congestion; and, rarely, white mucosal plaques.[16] However, these features are not reliable when applied to early recurrent tumors arising from the mucosal bed of a former primary cancer that regressed after CRT. The original esophageal layering and vascular structures have been disrupted by the primary tumor. Furthermore, the expansion and arrangement of recurring neoplastic cells are disrupted by tissue reactions to previous chemotherapy and radiotherapy, as well as by subsequent repair processes. Tumor necrosis, foam cell formation, vascular granulation, inflammatory exudation and fibrosis are frequent histological sequelae of CRT.[17,18] The minute foci of the initial neoplastic growth may arise from scattered residual cancer cells in deeper tissues, rather than from the superficial mucosal layer, as does the primary cancer.[11] These factors have largely precluded endoscopic ultrasound as a feasible tool in the assessment of residual or recurrent esophageal cancers.[19,20] For the same reason, the endoscopic diagnostic features for recurrent tumors are likely to be different from those for primary tumors.

We speculate that most of the SMT lesions discovered in our study were formed by expanding tumor cells in the submucosal layers, but barely reached the luminal surface because of their depth and constraining fibrosis. Although the overlying mucosa appeared

normal, they manifest their first sign by bulging outward. Malignant cells can be captured by biopsy forceps only when they reach the surface in sufficient numbers, or more efficiently, destroy the surface to make an erosion. This might explain why all of the six newly developed SMT yielded negative results at their first biopsies but eventually proved to be recurrences (Table 3).

Several previous studies have aimed to improve the detection of local recurrence by measures other than endoscopy. In addition to pretreatment staging, F-18-fluorodeoxyglucose–positron emission tomography (FDG–PET) is highly sensitive (up to 96%) in detecting recurrent esophageal cancer, but with somewhat lower specificity (68%–82%).[21–23] However, its utility in detecting locoregional recurrence is limited by its low specificity (57%–75%) for postesophagectomy patients. Postsurgical inflammation and anatomical changes are largely responsible for the false positivity. Detecting small residual or early recurrent cancers is even more challenging because low tumor volume could greatly reduce the sensitivity of FDG–PET. Moreover, such lesions are not distinguishable from post-CRT inflammation or regional lymph-node metastasis.[24,25]

The results of our study disagree with the conventional belief that endoscopy is of limited utility in the management of esophageal cancer after CRT.[13,26] We believe that routine endoscopy, particularly focused on the primary tumor site, is advisable for all patients with esophageal squamous cell carcinoma after the completion of CRT. We also suggest regular endoscopic surveillance at least every three months for those who have achieved CR. The occurrence of SMT-like lesions after CR is an alarming sign that deserves intensive investigation and follow-up if a modality of salvage treatment is available. Any evolving

lesion at the primary site with negative biopsy should be followed closely.

Our retrospective study design has introduced a knowledge bias because the evaluating endoscopists were not totally blinded to the outcomes. Therefore, a randomized controlled trial comparing the clinical outcomes is necessary to establish the role of surveillance endoscopy after definitive CRT for esophageal squamous cell carcinoma.

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Table 1   Clinical data of 133 patients achieving CR with definitive CRT

Characteristic		No. patients	%
Sex			
Male		110	82.7
Female		23	17.3
Age (years)			
Mean	62		
Range	39–76		
T stage			
T1		30	22.6
T2		21	15.8
T3		70	52.6
T4		12	9.0
N stage			
N0		46	34.6
N1		87	65.4
M stage			
M0		123	92.5
M1		10	7.5
Clinical stage			
I		16	12.0
II		45	33.8
III		62	46.6
IV		10	7.5

Macroscopic classification

Type 0	30	22.6
Type 1	19	14.3
Type 2	60	45.1
Type 3	24	18.0

Table 2 Endoscopic findings at primary-site with biopsy-proven recurrence

Endoscopic finding	No. patients	%
SMT	13	81
SMT with erosion or ulceration	11	
SMT without erosion or ulceration	2	
Erosion	3	19
Total	16	100

SMT, submucosal tumor.

Table 3 Endoscopic findings of newly developed lesion for primary-site recurrent tumors

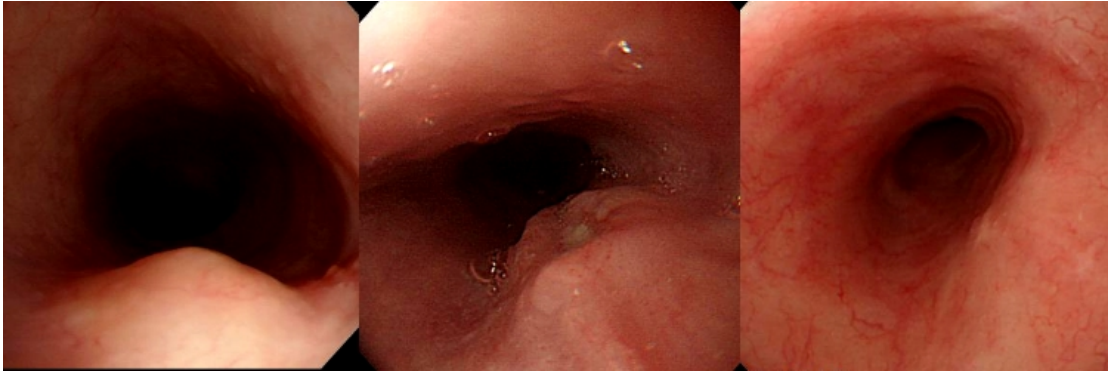| Preceding newly developed lesions with negative biopsies	Findings at diagnosis of recurrence	No. patients
SMT	SMT	6
Erosion	SMT	4
Erosion	Erosion	1
Mild stricture	SMT	2
No newly developed lesion	SMT	1
No newly developed lesion	Erosion	2
Total		16

SMT, submucosal tumor.

Table 4 Primary-site biopsy result of the latest surveillance endoscopy for patients who achieved CR and remained free of metastasis

Evolving lesion found at preceding endoscopies	No. patients	Biopsy result of the latest endoscopy	No. patients
SMT	7 (9%)	Recurrence	6 (86%)
		Negative	1 (14%)
Erosion	8 (10%)	Recurrence	5 (63%)
		Negative	3 (37%)
Mild stricture	6 (8%)	Recurrence	2 (33%)
		Negative	4 (67%)
No evolving lesion	56 (73%)	Recurrence	3 (5%)
		Negative	53 (95%)
Total	77 (100%)		

CR, complete remission; SMT, submucosal tumor.

FIGURE LEGEND

Fig. 1   Initially growing recurrent esophageal cancer at the primary tumor site after complete remission was achieved with chemoradiotherapy may be detected by endoscopy, with features of a submucosal tumor (A), a submucosal tumor with superficial ulcer (B), or a flat erosion (C).

Fig. 1