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# Multiple Early-Stage Malignant Melanoma of the Esophagus with a Long Follow-Up Period After Endoscopic Treatment: Report of a Case and a Literature Review

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## 1. Introduction

Primary malignant melanoma of the esophagus (PMME) accounts for 0.1-0.2% of all malignant disease of the esophagus. Ninety-five percent of all melanomas are found in the derma, and only 0.5% are localized in the esophagus (Bisceglia et al. 2011). The prognosis of PMME is unfavorable because most patients are in the advanced stage at diagnosis and rapidly develop lymph node and distant metastases. Nine cases of early-stage PMME have been reported in eight papers (Minami et al. 2011; Miyatani et al. 2009; Morita et al. 2009; Suzuki et al. 2008; Kimura et al. 2005; Hara et al. 2003; Mikami et al. 2001; Kido et al. 2000). Only two of them were treated curatively by endoscopic mucosal resection (EMR) (Miyatani et al. 2009; Kimura et al. 2005). We now report on a rare case of multiple early-stage PMME, which could obtain prolonged survival for ten years by the combination of systemic chemotherapy, repeated endoscopic treatment, and transarterial chemoembolization.

## 2. Case report

A 75-year-old previously healthy man underwent an esophagogastroduodenoscopy (EGD) for screening. Three black-pigmented flat lesions were detected in the middle and lower thoracic esophagus (Fig. 1), and biopsy specimens revealed features of malignant melanoma. The patient refused esophagectomy, and endoscopic mucosal resection (EMR) was tried in August 2001. The resected specimen revealed that the tumor had invaded the lamina propria (Fig. 2) with no lymphatic or venous invasion and that the horizontal margin was positive. The patient again refused esophagectomy and was followed up closely in the outpatient clinic.

Five months after the first EMR, a recurrence was suspected near the EMR scar. The patient was referred to our hospital. As an alternative treatment to the esophagectomy, six courses of systemic chemotherapy comprising dacarbazine (100 mg/body on day 1, 200 mg/body on days 2-5), nimustine hydrochloride (100 mg/body on day 1), and vincristine (1 mg/body on day 1) were scheduled every four weeks. However, he was forced to discontinue the



Fig. 1. Esophagogastroduodenoscopy showed a black-pigmented flat lesion in the lower esophagus.

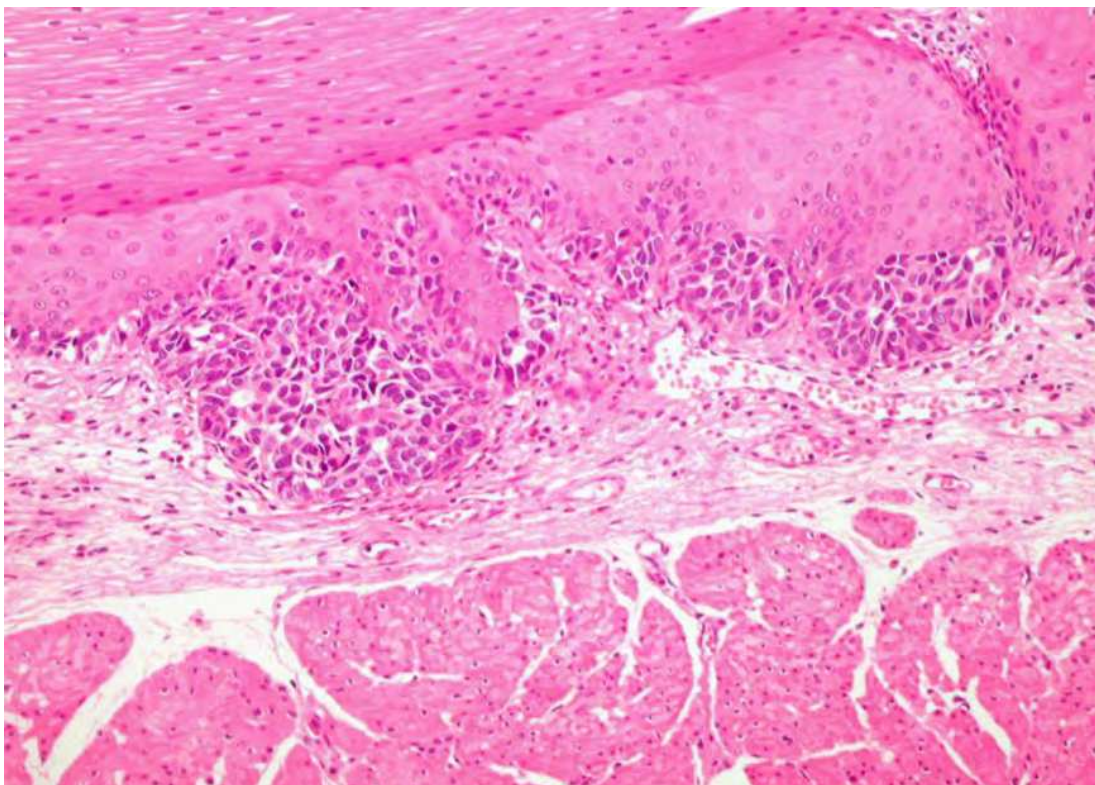


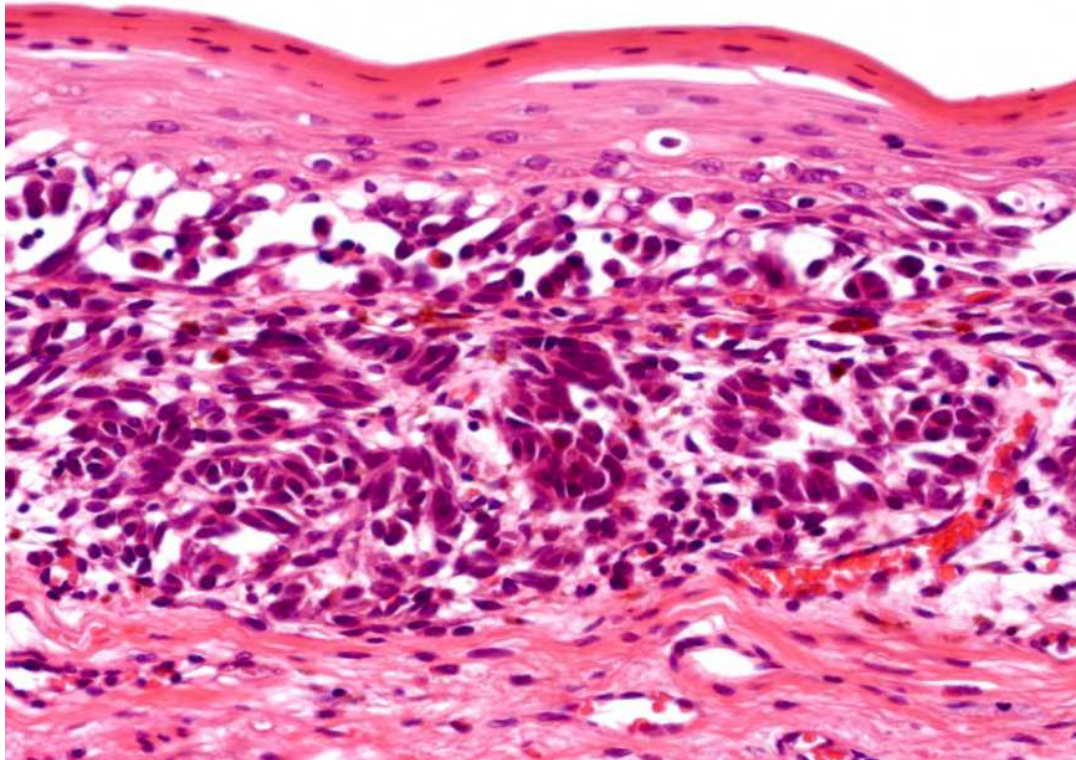
Fig. 2. A specimen from an endoscopic mucosal resection revealed that the melanoma cells had invaded the lamina propria.

treatment after four courses of chemotherapy because of severe thrombocytopenia. He then underwent an EGD every two or three months, and small black-pigmented spots resembling lentigo were detected frequently (Fig. 3). A biopsy specimen revealed the typical histological pattern of melanoma, suggesting metachronous multiple lesions. Because no lymph nodes were involved and no distant metastasis developed, endoscopic treatment including EMR (six times for nine lesions) and tumor ablation using argon plasma coagulation (four times for nine lesions) or bipolar coagulation probe (four times for six lesions) were performed until June 2009. The pathological diagnoses for all EMR specimens were in situ or microinvasive PMME with no lymphatic or venous invasion. Tumor cells were positive for melan A and HMB45 according to immunohistochemistry. A representative case of microinvasive PMME is shown in Fig. 4A and B. Three specimens of nine lesions resected by EMR showed clearly that the black-pigmented area was only part of the whole tumor, and the horizontal margin was positive. A representative horizontal-margin-positive case of PMME is shown in Fig. 5.

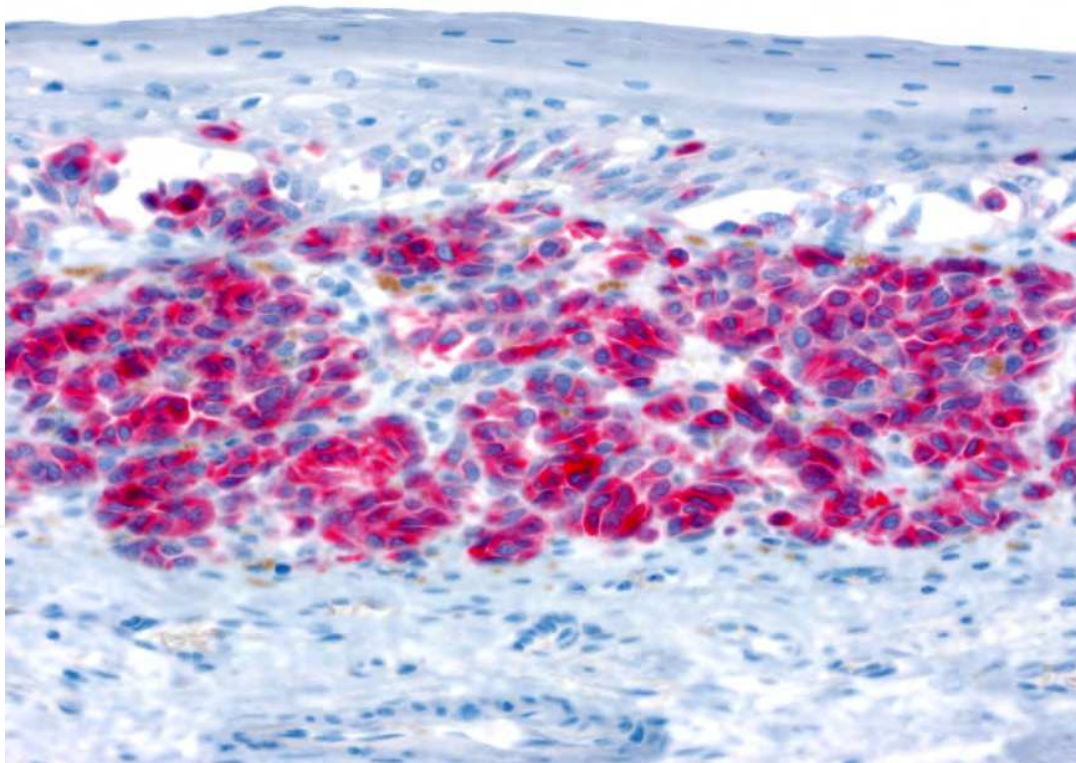


Fig. 3. Small black-pigmented spots resembling lentigo were detected frequently after the initial endoscopic treatment.





(A)



(B)

Fig. 4. A specimen from an endoscopic mucosal resection revealed a histological pattern typical of microinvasive PMME (A) and was immunohistochemically positive for melanin A (B). A chromogenic reaction was developed using alkaline phosphatase.

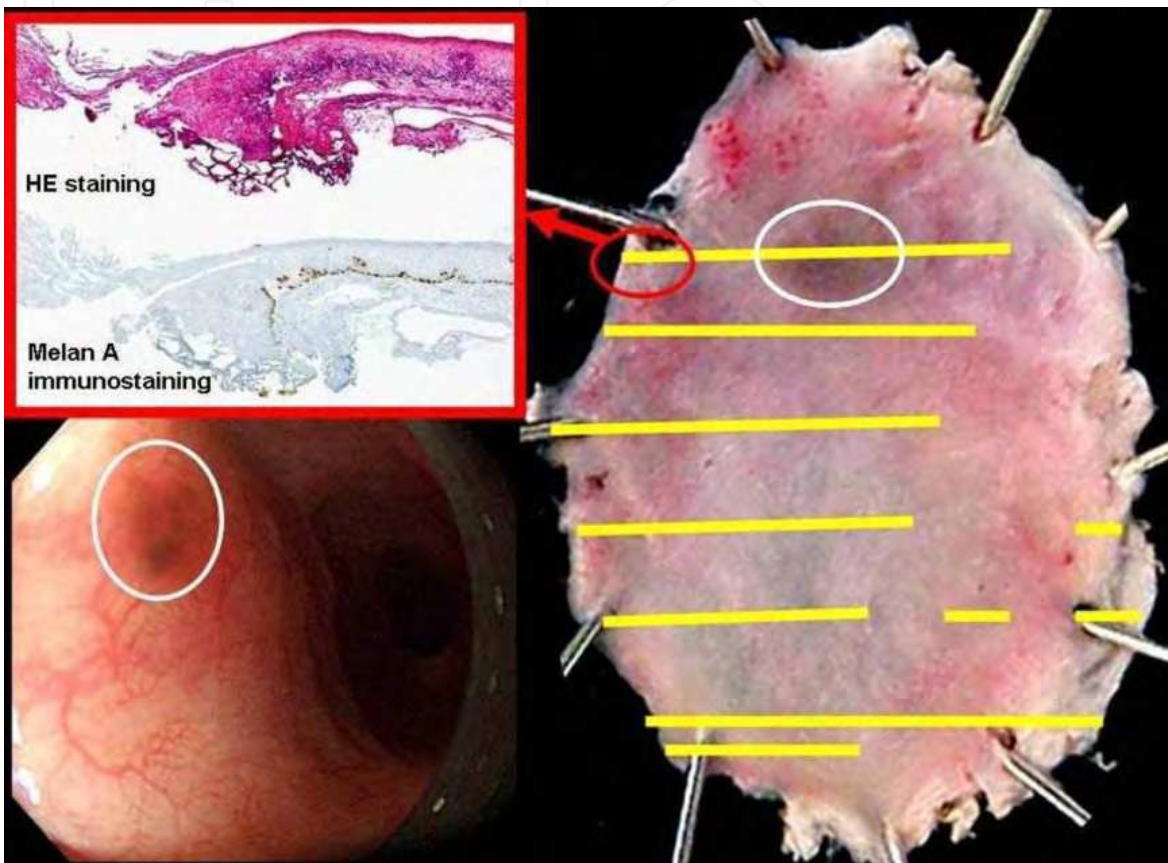


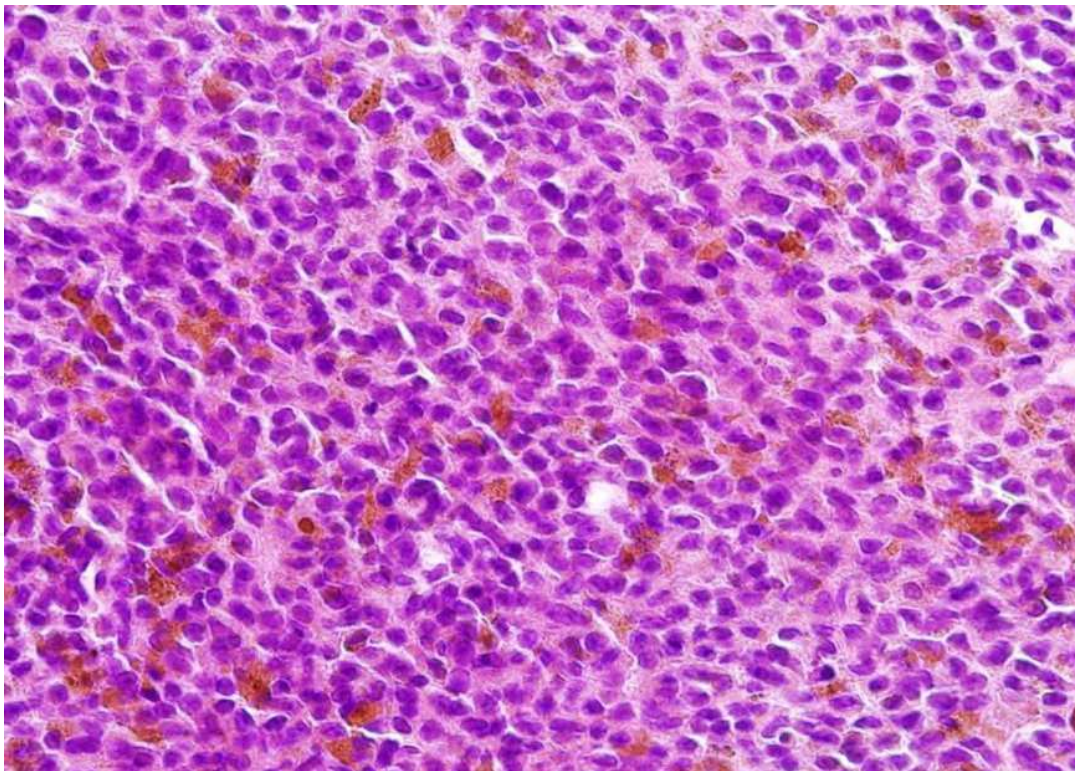
Fig. 5. A specimen from an endoscopic mucosal resection showed that the black-pigmented area was only part of the whole tumor, and the horizontal margin was positive.

Seven years after the first diagnosis of PMME, multiple hepatic tumors (in S4, S6, and S8) were detected by screening abdominal computed tomography (CT) in December 2007 (Fig. 6A). To make a definite diagnosis, a liver needle biopsy was performed in April 2008. The needle biopsy specimens revealed the same histological pattern of PMME (Fig. 6B) and were positive for melan A and HMB45. Then, hepatic metastasis was confirmed. The primary lesion was well controlled, and no other distant metastasis was observed. Because the patient was too old to reintroduce systemic chemotherapy and the dynamic CT image suggested a hypervascular liver tumor, transarterial chemoembolization (TACE) was selected. The hepatic metastases gradually progressed even though he received TACE in June 2008 and April 2010. He died in August 2011 of hepatic failure because of progression of hepatic metastases. The clinical course of this case is summarized in Fig. 7.



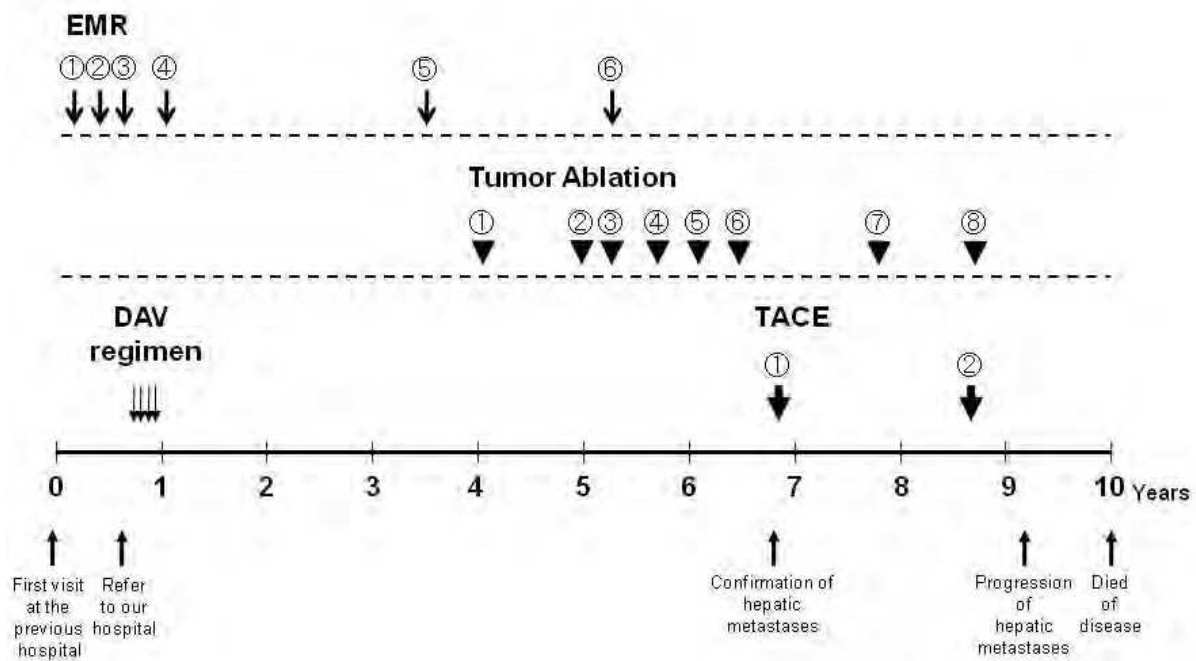


(A)



(B)

Fig. 6. (A) Seven years after the first diagnosis, multiple liver tumors were detected by screening abdominal computed tomography (*arrow in S6*). (B) A needle biopsy specimen from the liver tumor revealed a histological pattern typical of malignant melanoma.



TACE; transarterial chemoembolization

DAV; dacarbazine, nimustine hydrochloride, and vincristine

Fig. 7. Clinical course of this case. Local control of multiple early-stage PMME was achieved mainly by endoscopic treatment (six endoscopic mucosal resections (EMRs) for nine lesions and eight instances of tumor ablation therapy with argon plasma coagulation or a bipolar coagulation probe for 15 lesions).

### 3. Discussion

The following diagnostic histological criteria for PMME have been suggested by Allen and Spitz (Allen & Spitz, 1953): (1) a typical histological pattern of melanoma and the presence of melanin granules within the tumor cells, (2) origin in an area of junctional change within the squamous epithelium, and (3) junctional activity with melanotic cells in the adjacent epithelium. The melanoma cells were immunohistochemically positive for melan A, HMB45, and S-100 protein. These stains are useful for diagnosing amelanotic melanomas in which the tumor cells show no evident melanin granules (Fenoglio-Preiser et al. 2008).

The prognosis of PMME is extremely poor because of its rapid metastatic spread via the lymphatic and blood vessels. Early death from widespread metastases is the usual clinical course. The average overall survival is only 10–13 months, and only one-third of all patients survive for longer than one year after diagnosis (Bisceglia et al. 2011). Surgical resection is considered the best method for treating PMME (Adili & Moning 1997; Kato et al. 1991; Chalkiadakis et al. 1985; Ludwig et al. 1981). Smaller satellite nodules may present around the main tumor, and wider margins of resection are required for treating PMME than with other esophageal tumors. However, even if only the patients whom undergone radical esophageal resection are analyzed, the five-year survival rate is less than 5% (Simpson et al. 1990; Sabanathan et al. 1989). Therapeutic options such as radiotherapy, chemotherapy, and immunotherapy provide limited benefits, even when used in conjunction with surgery.



Table 1 summarizes nine cases of early-stage PMME previously published in the English literature. This table demonstrates that PMME has a relatively good prognosis as long as it is detected early. However, it remains to be fully elucidated whether these minute lesions are true premalignant lesions of advanced PMME.

| Case | Reference                | Age/<br>Gender | Location           | Macroscopic<br>type | Number of<br>lesions | Depth of<br>invasion | Treatment                                   | Survival/<br>Outcome     |
|------|--------------------------|----------------|--------------------|---------------------|----------------------|----------------------|---|--------------------------|
| 1    | Kido,<br>et al. 2000     | 60/male        | lower              | flat                | solitary             | LPM <sup>a</sup>     | surgery                                     | unknown                  |
| 2    | Mikami,<br>et al. 2001   | 42/female      | middle             | polypoid            | solitary             | LPM                  | surgery+che<br>motherapy                    | 2y7m <sup>e</sup> /alive |
| 3    | Hara,<br>et al. 2003     | 52/male        | middle             | flat                | solitary             | EP <sup>b</sup>      | surgery+che<br>motherapy                    | 1 y3m/alive              |
| 4    | Kimura,<br>et al. 2005   | 73/male        | lower              | flat                | solitary             | EP                   | EMR <sup>c</sup>                            | 1y3m/alive               |
| 5    | Suzuki,<br>et al. 2008   | 62/male        | upper to<br>middle | flat                | solitary             | EP                   | surgery                                     | 2y9m/alive               |
| 6    |                          | 67/male        | lower              | flat                | solitary             | LPM                  | surgery                                     | 4y5m/alive               |
| 7*   | Morita,<br>et al. 2009   | 75/male        | lower              | flat                | multiple             | LPM                  | EMR+chemot<br>herapy →<br>TACE <sup>d</sup> | 10y/ dead                |
| 8    | Miyatani,<br>et al. 2009 | 64/female      | lower              | flat                | solitary             | LPM                  | EMR   | 2y6m/alive               |
| 9    | Minami,<br>et al. 2011   | 72/male        | lower              | flat                | solitary             | EP                   | surgery                                     | 2y1m/alive               |

\*The same case of this chapter.

<sup>a</sup>LPM, Tumor invades lamina propria muscle; <sup>b</sup>EP, carcinoma in situ; <sup>c</sup>EMR, endoscopic mucosal resection; <sup>d</sup>TACE, transarterial chemoembolization for hepatic metastases

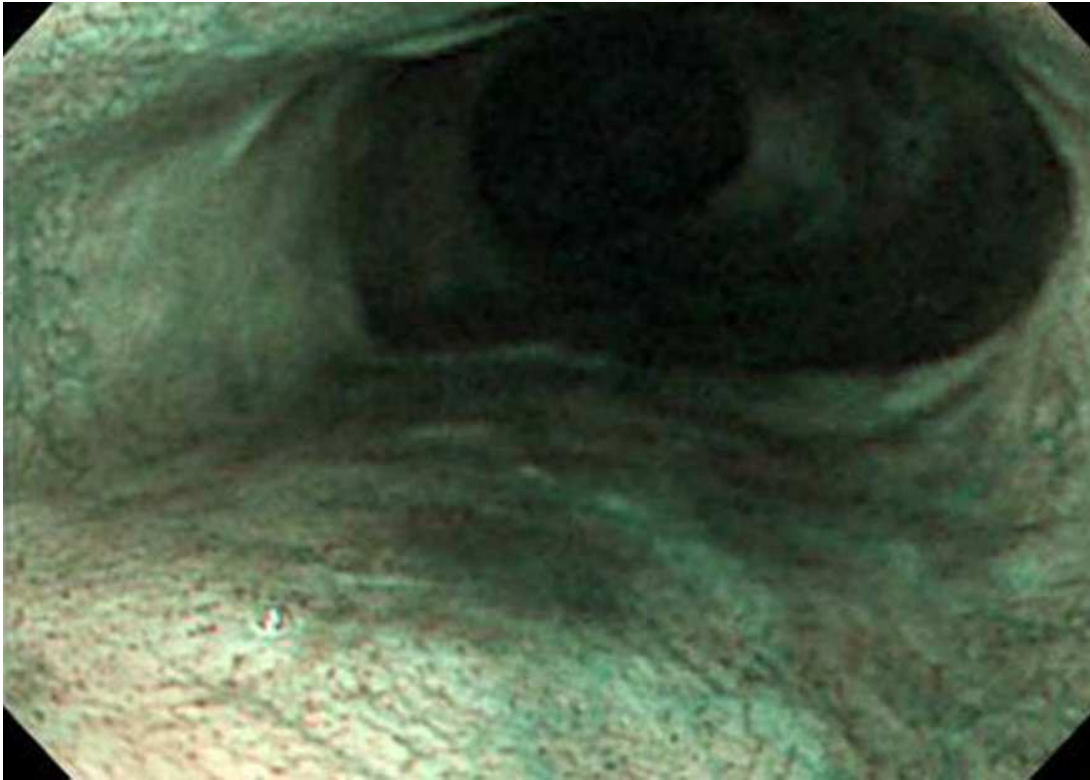
<sup>e</sup>y; year, m; month

Table 1. Features and outcome of early-stage (intramucosal) malignant melanoma of the esophagus published in the literature.

Endoscopically, PMME lesions appear as intraluminal, polypoid, and (usually, but not necessarily) pigmented, irregular masses, which might also be ulcerated. However, only one of nine reported cases of early-stage PMME was the polypoid type (Mikami et al. 2001), and the other eight cases were all the flat type (Minami et al. 2011; Miyatani et al. 2009; Morita et al. 2009; Suzuki et al. 2008; Kimura et al. 2005; Hara et al. 2003; Kido et al. 2000) (Table 1). In contrast, no report is available about the flat-type submucosal invasive PMME. In the present case, many satellite lesions occurred in separate areas, and all lesions were the flat type. In almost 90% of patients, the lesions occur in the middle or distal one-third of the esophagus, usually as a solitary tumor, but multiple lesions have been reported in 12% of patients (Sabanathan et al. 1989; Joob et al. 1995). To our knowledge, present case is the first report of multiple early-stage PMME.

Especially in cases of the flat-type PMME, it is difficult to accurately define the tumor area macroscopically. Because the melanoma cells originated from the basal/deeper layers of the epithelium, it is likely that the size of the black-pigmented area depends on the number and density of the melanoma cells and does not reflect the true size of the tumor. Narrow-band

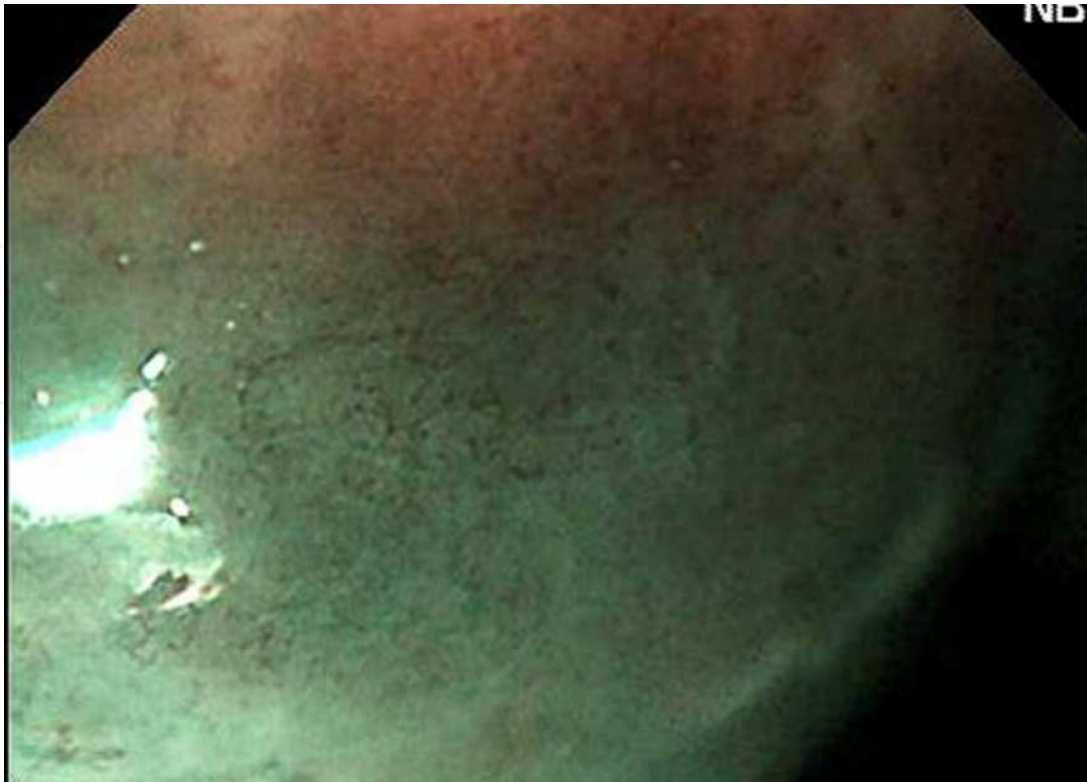
imaging and/or magnifying endoscopy (Cohen, 2007) were not useful for accurately determining the tumor area in the present case (Fig. 8A-C).



(A)



(B)



(C)

Fig. 8. Narrow-band imaging (A), magnifying endoscopy (B), and magnifying endoscopy with narrow-band imaging (C) were not useful for accurately determining the tumor area.

Endoscopic treatment for PMME should be considered for diagnostic purposes (Hirose et al. 2002) and for treatment purposes in limited cases (Miyatani et al. 2009; Morita et al. 2009; Kimura et al. 2005). PMME, especially the polypoid type, can be removed technically by endoscopic treatment (Ho et al. 2007; Herman et al. 2001; Xinopoulos et al. 2001; the depth of the tumor invasion was not mentioned in these three papers); however, indications for local therapy for this disease are still controversial because of the inaccurate diagnosis of the tumor area and the possibility of synchronous multiple lesions (Morita et al. 2009; Ho et al. 2007; Xinopoulos et al. 2001). Further accumulation of early-stage PMME data is required to clarify the tumor behavior of this rare disease.

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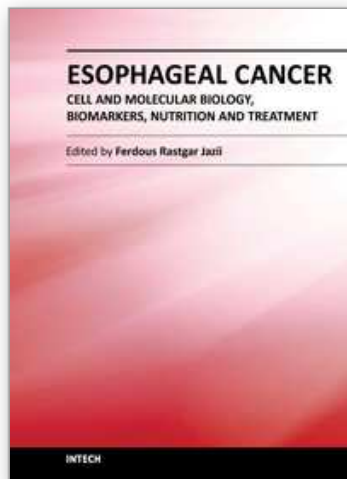
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