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REVIEW ARTICLE

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Nonsurgical treatments for submucosal esophageal squamous cell carcinomas

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Abstract Esophageal cancer is a disease with a poor prognosis. As with superficial esophageal cancers, lymph node metastases are seen rarely if the tumors are limited to the epithelium or lamina propria, but when cancers invade the submucosa, there is a high incidence of lymph node involvement. Surgery with radical lymph node dissection is a standard treatment for treating submucosal esophageal cancers. However, it is usually associated with a reduced level of quality of life for the patients, who are often elderly and have various medical complications making them unfit for aggressive surgery. According to these background indications, various nonsurgical treatments have been developed to preserve the esophagus and to achieve a less invasive cure for such patients. Definitive radiotherapy could be a treatment option for patients with superficial carcinomas, particularly for those with mucosal cancers with an unresectable width by endoscopic mucosal resection (EMR). Although there have been some retrospective analyses with a small number of patients, they could not draw definitive conclusions. Definitive chemoradiotherapy has become one of the treatment options for patients who desire nonsurgical treatment. It has shown similar survival rates with those seen for radical surgery in two retrospective analyses and one multicenter prospective phase II study. The combination of primary EMR and prophylactic chemoradiotherapy has also shown promising results with less invasiveness than surgery. These nonsurgical approaches are now under evaluation in two multi-institutional studies run by the Japan Clinical Oncology Group (JCOG), which will clarify the optimal treatment for this disease.

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Introduction

Esophageal cancer is a disease with a poor prognosis. In Japan, it was the sixth highest ranked cause of death from malignant neoplasms in 2003 [1]. Although most patients have advanced-stage tumors at the time of diagnosis, the number of patients diagnosed with early stages has been increasing in Japan. As with superficial esophageal cancers, lymph node metastases are rarely seen if the tumors are limited to the epithelium and lamina propria, but when cancers invade the submucosa, there is a high incidence of lymph node involvement. Various approaches with curative intent, such as endoscopic mucosal resection (EMR), surgery, definitive radiotherapy, definitive chemoradiotherapy, and their combinations, can be indicated for treating patients with superficial esophageal cancers. In Japan, EMR for mucosal cancer is now the standard treatment because this disease has a very low potential for metastasis and there is sufficient information on its good outcomes. However, various approaches have been indicated for treating submucosal cancers as well as when cancer invades to the lamina muscularis mucosae. Surgery with radical lymph node dissection is a standard treatment for treating submucosal esophageal cancers not only in Japan but also in Physician Data Query from National Cancer Institute [2]. However, it is usually associated with a reduced level of quality of life for the patients, who are often elderly and have various medical complications making them unfit for aggressive surgery. According to these background indications, various nonsurgical treatments have been developed to preserve the esophagus and to achieve a less invasive cure for such patients.

Table 1. Relationship between the depth of tumor infiltration, vascular invasion, and lymph node metastases

Class of tumor	n (+) %[a]	Lymphatic invasion (+) %[b]	Vessel invasion (+) %[b]
m1	0/199 (0.0)	4/381 (1.0)	1/379 (0.3)
m2	5/153 (3.3)	15/231 (6.5)	1/231 (0.4)
m3	28/230 (12.2)	70/303 (23.1)	13/300 (4.3)
sm1	58/219 (26.5)	101/248 (40.7)	32/248 (12.9)
sm2	133/372 (35.8)	209/396 (52.8)	88/397 (22.2)
sm3	260/567 (45.9)	391/581 (67.3)	191/581 (32.9)

m, mucosal; sm, submucosal
[a] Based on operative cases
[b] Based on all cases

Table 2. Relationship between histological cancer invasion and lymph node metastasis with superficial esophageal cancer

First author [Ref.]	Pathological invasion	Number of cases	Lymph node metastasis (+) %
Kodama [3]	m	582	33 (5.6)
	sm	1158	701 (60.5)
Igaki [4]	m	12	1 (8)
	sm	42	17 (41)
Ando [5]	m	33	0 (0)
	sm	82	37 (45)
Gotohda [6]	m	13	0 (0)
	sm	52	23 (44)

m, mucosal; sm, submucosal

The incidence of lymph node metastasis with superficial esophageal cancer

Kodama and Kakegawa [3] have reported the rate of lymph node metastasis for patients in Japan with superficial esophageal cancers between 1990 and 1994 using a nationwide questionnaire. A total of 2418 patients from 143 institutions who had undergone surgical or endoscopic treatment was analyzed. The incidence of lymph node metastasis was examined according to subclasses of the depth of cancer invasion into mucosal (m1–m3) and submucosal regions (sm1–sm3), as defined by the Japanese Society for Esophageal Diseases and described elsewhere in this issue. Both lymphatic vessel involvement and lymph node metastasis became evident when cancers had infiltrated to the lamina muscularis mucosae (subclass m3) and were much higher in patients with submucosal cancers (Table 1). The incidence of lymph node metastasis in patients with mucosal cancers ranged from 0% to 12%, whereas for patients with submucosal cancers it ranged from 26% to 46%. Igaki et al. reported [4] the clinical outcomes of 57 patients who had undergone esophagectomy with three-field lymph node dissection and found pathological lymph node metastases in 19 (33%). Of the 12 patients with mucosal cancers, only 1 (8%) had pathological lymph node metastases, whereas these were seen in 17 of 42 (41%) patients with submucosal cancers. Other reports by Ando et al. [5]. and Gotohda et al. [6] revealed no lymph node involvement in patients with mucosal cancers, whereas incidences of 45% (37/82) and 44% (23/52) pathological lymph node metastases were seen in those with submucosal esophageal cancers. Thus, it is evident that submucosal esophageal cancer has a high potential for metastasis (Table 2), and this should be taken into consideration when choosing treatment and when interpreting any differences in treatment outcomes between surgical and nonsurgical approaches.

Treatments for superficial esophageal cancer

Definitive radiotherapy

It has been reported recently that radiation therapy might be an effective treatment for superficial esophageal cancers, although various treatment methods, planning of target volumes, and doses were used in the reports. Okawa et al. [7] reported the effectiveness of definitive radiation therapy in patients with superficial esophageal cancer from 15 institutions in Japan between 1981 and 1990 by questionnaire. A total of 105 patients were analyzed for tumor invasion, methods of radiation therapy, survival, disease recurrence, and complications after treatment. The lesions were limited to the mucosal layer in 15 patients and had invaded to the submucosa in 53 patients; for 37 patients, tumor depth had not been determined. Radiation methods and doses were determined according to institutional policy; external radiation therapy alone was used to treat 58 (55%) of 105 patients, and both external and intraluminal radiation therapy were used to treat 47 patients. The overall and disease-specific 5-year survival rates were 38.7% and 71.0%, respectively. The disease-specific 5-year survival rates of the patients with mucosal and submucosal cancer were 100% and 68.5%, respectively. Thirty-one patients had recurrent disease and 22 (21%) of these patients had locoregional recurrence; 6 (6%) patients had lymph node recurrence and 2 (2%) patients developed distant metastases with local recurrence.

Table 3. Recurrence and survival with definitive radiotherapy for patients with superficial esophageal cancers

First author [Ref.]	Total number of cases	Depth of cancer invasion	Number of cases	Local recurrence (+) %	Regional lymph node recurrence (+) %	Distant metastasis (+) %	5-year survival rate (%)	
							overall	cause-specific
Okawa [6]	105	m	15	22 (21)	6 (6)	2 (2)	38.7	100
		sm	53					68.5
		undetermined	37					–*
Ishikawa [7]	68	m	18	0	0	0	59	100
		sm	50	9 (18)	3 (6)	2 (4)		75
Nishimura [8]	21	Extrabeam	8	4 (50)	0	–*	50†	67†
		Extrabeam with IBT	21	2 (10)	0	–*	85†	100†

m, mucosal; sm, submucosal; IBRT, intraluminal brachytherapy
*Not reported
†3-year survival rates

Ishikawa et al. [8] reported the efficacy and limitations of radiotherapy for stage I squamous esophageal carcinomas. Sixty-eight consecutive patients treated by definitive radiotherapy were analyzed, including 36 patients who received brachytherapy as a boost. The total radiation doses ranged from 60 to 72 Gy in 32 patients treated with external-beam radiotherapy alone and 50–64 Gy in the external beam with 9–10 Gy in intraluminal brachytherapy in the remaining 36 patients. The subjects consisted of 18 patients with mucosal cancers and 50 with submucosal cancers. They received radiotherapy alone because of inoperable conditions, refusal to undergo surgery, or presence of a positive margin following EMR. Complete response was obtained in 60 patients (88%), and no recurrences were seen in patients with mucosal cancers. However, among the patients with submucosal cancers, 14 (28%) had a recurrence after radiotherapy. Local recurrence in the esophagus occurred in 9 patients (7 in the irradiation field and 2 in regions outside the irradiation field), and 3 had regional lymph node recurrence (2 in the prophylactic field and 1 out of the field). Distant metastases appeared in 2 patients. With a median follow-up period of 51 months, the 5-year overall survival rate was 59% for all 68 patients. The cause-specific survival curves for mucosal cancer and submucosal cancer were significantly different: the 5-year cause-specific survivals for mucosal and submucosal cancers were 100% and 75%, respectively.

Nishimura et al. [9] have also reported the safety and effectiveness of external-beam radiation therapy with or without intraluminal brachytherapy for treating superficial esophageal cancers without any lymph node involvement. Twenty-one patients treated by external-beam radiotherapy were analyzed: 8 of these were treated by 60–69 Gy external beam alone, and the remaining 13 were treated with intraluminal brachytherapy (8–12 Gy) after 50–56 Gy external-beam radiotherapy. The indications for using definitive radiotherapy were refusal of surgery by 7 patients, age over 80 years for 5, being medically inoperable or in poor general condition for 5 patients, presence of a histologically positive margin after EMR for 3 patients, and a simultaneous double carcinoma for 1 patient. With a median follow-up period of 60 months, the 5-year survival rate for all 21 patients was 71%. Comparing external beam alone with intraluminal brachytherapy, all efficacy markers such as local controls, cause-specific survival, and overall survival rate showed significantly better tends in the brachytherapy group than in the external beam alone group.

Based on these reports, definitive radiotherapy could be a treatment option for patients with superficial carcinomas, particularly for those with mucosal cancers with an unresectable width by EMR (Table 3). However, these reports were retrospective series, and there were too few patients to draw definitive conclusions. Additionally, although intraluminal brachytherapy showed better trends than external beam radiation therapy alone, these were nonrandomized comparisons with a small number of patients, so the role of brachytherapy remains controversial.

Definitive chemoradiotherapy

In locoregional diseases other than superficial cancers, chemoradiotherapy has become one of the treatment options for patients who desire nonsurgical treatment. A pivotal randomized study, comparing radiotherapy alone (64 Gy) with concurrent chemoradiotherapy consisting of radiotherapy (50 Gy) plus four courses of chemotherapy with 5-fluorouracil (5-FU) and cisplatin, was reported from the Radiation Therapy Oncology Group (RTOG 85-01) [10,11]. This study revealed significantly better survival in patients assigned to the combined treatment arm than among patients with radiotherapy alone: the 5-year survival rate was 27% in the chemoradiotherapy group compared with 0% in the radiation-only group ($P < 0.001$).

For patients with superficial carcinomas, Nemoto et al. [12] reported the results of patients treated with standard radiotherapy as defined by the Japanese Society of Therapeutic Radiology and Oncology (JA90STRO) Study Group, with or without chemotherapy. Between 2000 and 2003, 141 patients with superficial esophageal cancers were treated in 24 major institutions in Japan after the publication of consensus guidelines for standard radiotherapy methods. This retrospective analysis showed a better trend in survival among 84 patients who received concurrent chemotherapy than among 57 patients who received radiotherapy alone, although the difference was not statistically significant.

Table 4. Definitive chemoradiotherapy for patients with stage I esophageal cancer

First author [Ref.]	Total number of cases	Number of CR cases (%)	Number of cases underwent salvage esophagectomy with residual/ recurrent cancers (+) %	Number of cases underwent endoscopic treatments with residual/recurrent cancers (+) %	3-year overall survival rate (%)
Ura [13]	73	68 (93)	6 (8)	12 (16)	80
Minashi [14]	41	36 (88)	3 (7)	5 (12)	79
Kato [15]	72	69 (96)	6 (8)	11 (15)	93*

CR, complete response
*Two-year survival rates

There have been two retrospective analyses of definitive chemoradiotherapy for patients with stage I esophageal cancers in Japan, although they were in abstract form (Table 4). Ura et al. reported [13] the efficacy and survival of chemoradiotherapy in patients with clinical stage I esophageal cancers. Seventy-three patients underwent definitive chemoradiotherapy in the National Cancer Center Hospital between 1997 and 2002. Of these, 68 (93%) achieved a complete response (CR). Patients who had residual tumors or locoregional recurrence after CR or who developed metachronous esophageal cancers underwent salvage surgery or EMR. With a median follow-up period of 3.0 years, the 3-year overall survival rate was 80%. We also have reported a retrospective analysis of 41 patients with stage I tumors treated with chemoradiotherapy in our institution between 1994 and 2002 [14]. Thirty-six of 41 patients (88%) achieved a CR, and the 3- and 5-year survival rates were 79% and 67%, respectively, with a median follow-up period of more than 5 years. Chemoradiotherapy consisted of two courses of 5-FU and cisplatin concurrently with external-beam radiation, with a total dose of 60 Gy in both institutions. The results in the two retrospective studies were very similar, and the survival rates were consistent with those for radical surgery in Japan.

More significant impact has been achieved recently from a multi-institutional phase II study of definitive chemoradiotherapy for stage I esophageal cancers conducted by the Japan Clinical Oncology Group (JCOG 9708) (Table 4). This study adopted two courses of chemoradiotherapy consisting of 5-FU at 700 mg/m^2 on days 1–4 and cisplatin at 70 mg/m^2 on day 1 concurrently with external-beam radiation to a total dose of 60 Gy. Seventy-two patients were registered into this study. Preliminary results were promising: the CR rate and 2-year survival rate were 96% and 93%, respectively [15]. Although the results have not yet been published, the survival results are similar to those for radical surgery in Japan, and the JCOG has decided to move on a randomized study comparing surgery with definitive chemoradiotherapy in patients with stage I esophageal cancer (JCOG 0502; Fig. 1). The inclusion criteria for this study include patients with submucosal squamous cell carcinomas of the thoracic esophagus, of which primary lesions are clinically estimated as unresectable by EMR. Because this study requires random allocation to either surgical or nonsurgical procedures, which are quite different approaches, we expect poor enrollment because of difficulties in obtaining informed consent from the patient, and the study design

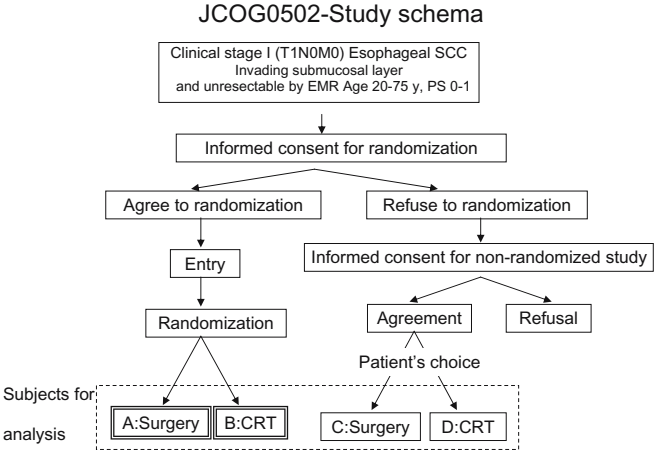

Fig. 1. Schema of JCOG 0502. *SCC*, squamous cell carcinoma; *EMR*, endoscopic mucosal resection; *PS*, performance status; *CRT*, chemoradiotherapy

has been modified as shown in Fig. 1. If a patient gives informed consent to be enrolled in the randomized study, they are randomly allocated to either surgery (group A) or chemoradiotherapy (group B) arms. If a patient refuses to be randomized, informed consent for a nonrandomized study is requested. In this case, the patient chooses either of the two treatments according to his or her own preference (surgery categorized as group C and chemoradiotherapy as group D), and the survival will be followed up for these groups separately. The primary endpoint is overall survival in the comparison of groups A and B. The secondary endpoints include a comparison of overall survival between patient groups C and D, a complete response rate of all patients treated by chemoradiotherapy, and adverse events for all. Statistically, the required sample sizes are 114 patients in the randomization part and 312 patients in the nonrandomization part. This study will constitute a key trial to determine the standard suitable treatment for patients with stage I esophageal cancers and to estimate the true impact of definitive chemoradiotherapy.

Combination of chemoradiotherapy and EMR

Although the CR rate following definitive chemoradiotherapy for patients with stage I disease was as high as 90%, approximately 25% of these patients developed local recurrence without distant metastasis [13–15] (see Table 4).

Salvage surgery would be the ideal treatment for such patients. However, this procedure is usually associated with high mortality when indicated after definitive chemoradiotherapy [16]. Because the tumors were restricted to the submucosal layer before chemoradiotherapy, any residual or locally recurrent lesions usually remained within this layer and could be treated with EMR if no involvement of lymph nodes or distant metastases was observed. In JCOG 9708, 6 (8%) patients underwent esophagectomy but 11 (15%) patients were treated with endoscopic treatments such as EMR, photodynamic therapy, and argon plasma coagulation. In the report by Ura et al., 6 (8%) patients underwent esophagectomy, and 12 (16%) patients were treated with EMR. The data from our institution showed similar results: 3 (7%) patients with residual or local recurrent lesions underwent esophagectomy, and 5 (12%) patients underwent EMR. The outcomes of these patients treated with salvage EMR were not described in these abstracts. In this regard, although the efficacy of salvage EMR for patients with baseline stage I disease has not yet been confirmed, we have already reported its efficacy in patients with baseline stage I–III diseases [17]. In this analysis, 16 patients were treated with salvage EMR among 93 consecutive patients treated with definitive chemoradiotherapy: 3 were treated for residual, 8 for local recurrent, and 5 for metachronous tumors in the esophagus. Of the 16 patients receiving EMR, 14 (88%) achieved CR. No major bleeding or perforation associated with EMR was observed. At a median follow-up of 33 months from the initiation of chemoradiotherapy, the 3-year survival rate following salvage EMR for all 16 patients was 56%. Although most patients in this analysis had had tumors that were more advanced than stage I before chemoradiotherapy, these results strongly suggest the efficacy and safety of EMR even as a salvage treatment.

Another approach in this field, reported by Shimizu et al. [18], consisted of primary EMR followed by chemoradiotherapy as a prophylactic treatment for possible lymph node metastases in patients who refused esophagotomy. The prospective study evaluated the long-term outcome of primary EMR followed by prophylactic chemoradiotherapy for patients with squamous cell carcinomas of the esophagus invading to the muscularis mucosae or upper submucosal layer, compared with the results of patients who underwent surgical resection during the same period. From 1996 to 2002, 16 patients who were diagnosed histopathologically as having cancers invading the muscularis mucosae (m3) or upper submucosal layer (sm1) in resected specimens taken following EMR were treated with prophylactic chemoradiotherapy; this consisted of two courses of 5-FU at 700 mg/m^2 and cisplatin at 15 mg/m^2 on days 1–5, given at a 3-week interval, concurrently with external-beam radiation with a total dose of 40–46 Gy. All patients completed the planned radiotherapy, but 2 of them had not received the second cycle of chemotherapy because of severe hematological toxicity seen in the first cycle. With a median follow-up period of 39 months, both 5-year overall and cause-specific survival rates were 100% in patients treated with this nonsurgical procedure, whereas these were 88% and 91%, respectively, in 39 patients treated with surgical resection during the same period. The authors concluded that the survivals of the two groups were almost equivalent and that EMR could be a primary management even for tumors clinically estimated as classes m3 to sm1, if resectable and followed by chemoradiotherapy. In our retrospective analysis of 328 patients primarily receiving EMR, 23 patients who had histologically confirmed submucosal invasion (sm1 to sm2) in endoscopically resected specimens were subsequently treated with prophylactic chemoradiotherapy [19]. Of these, only 1 patient (4%) had developed abdominal lymph node metastases by 39 months after the initial EMR. Local recurrence was found in another patient; however, this lesion was successfully removed by the second EMR. With a median follow-up of 30 months, the 3-year overall and cause-specific survival rates were 94% and 100% respectively, which seemed to be promising and similar to those reported by Shimizu et al. [18]. Based on these results, primary EMR followed by prophylactic chemoradiotherapy for clinically estimated class m3 to sm1 and sm2 cancers could be a suitable treatment approach compared with primary surgery or definitive chemoradiotherapy for the following reasons. First, this approach can avoid overtreatment. The diagnostic accuracy of either conventional endoscopy or endoscopic ultrasound in estimating the depth of tumor invasion is still insufficient [3]. EMR can easily provide information on any pathological invasion, which is the most reliable predictive marker for lymph node metastasis and helps avoid unnecessary invasive treatment such as radical surgery and definitive chemoradiotherapy in cases of pathological mucosal cancers. Second, even for pathological submucosal cancers diagnosed from endoscopically resected specimens, the risk of local recurrence after definitive chemoradiotherapy – approximately 25% [13,15] – can be reduced by obtaining complete resection based on primary EMR. Third, the dose of irradiation is reduced up to 40 Gy in prophylactic settings, whereas definitive chemoradiotherapy requires 50–60 Gy. This reduction in irradiation may decrease the risk of late toxicity, which troubles the patient and is occasionally fatal [20]. To evaluate the efficacy of this less invasive combined treatment, we have initiated a prospective multi-institutional phase II study for patients with clinically estimated stage I esophageal squamous cell carcinomas (JCOG 0508). The inclusion criteria for this study include submucosal squamous cell carcinomas of the thoracic esophagus, of which primary lesions are estimated clinically as resectable by EMR. The treatment algorithm is shown in Fig. 2. Patients with clinically estimated class sm1 to sm2 tumors are registered into this study and then receive primary EMR. If the tumors are resected completely and reveal histological invasion within the mucosal layer without vessel invasion, no additional treatments are required. If the tumors are found to have invaded to the submucosal layer or within the mucosal layer with vessel invasion, patients receive prophylactic chemoradiotherapy with two courses of chemotherapy consisting of 5-FU and cisplatin with concurrent radiotherapy at 41.4 Gy. If their tumors are resected incompletely, patients receive definitive chemoradiotherapy with a total radiation dose of 50.4 Gy.

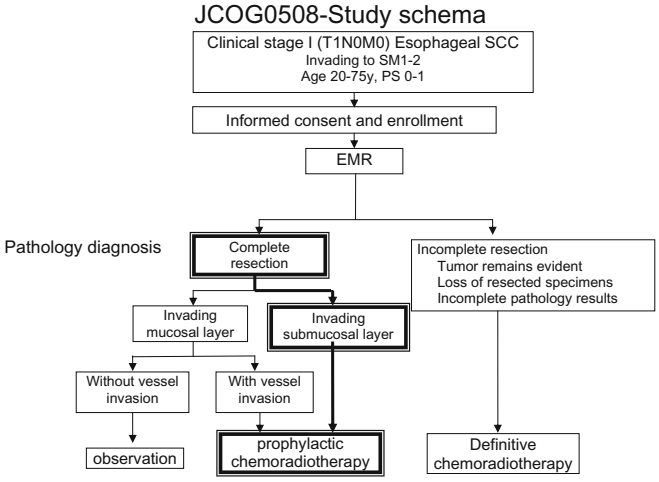

Fig. 2. Schema of JCOG 0508. *SCC*, squamous cell carcinoma; *SM*, submucosal; *PS*, performance status; *EMR*, endoscopic mucosal resection

The primary endpoint is 3-year overall survival among patients who are diagnosed with class sm1 to sm2 cancers pathologically with a completely negative cut margin by primary EMR followed by prophylactic chemoradiotherapy. Statistically, the required sample size is 82 patients in this group.

Conclusions

Recent developments in nonsurgical treatments, such as EMR and chemoradiotherapy, have yielded various treatment options, particularly for patients with stage I disease. Definitive chemoradiotherapy has shown similar survivals with those seen in radical surgery in either two retrospective studies or a multicenter prospective phase II study. The combination of primary EMR and prophylactic chemoradiotherapy has also shown promising results with less invasiveness. These nonsurgical approaches are now under evaluation in the two multi-institutional studies with large sample size in JCOG, which will clarify the treatment best fitted for this disease. Although surgery is still the standard treatment, many patients are unsuitable for radical surgery because of medical complications or advanced age, and they desire nonsurgical treatment. In such cases, an oncological team approach including surgeons and gastroenterologists is necessary to determine the best treatment for the patient.

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