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Prospective study on the value of endosonographic follow-up after surgery for esophageal carcinoma

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Background: Half of the patients who undergo surgery for cancer of the esophagus or gastric cardia present with recurrent disease within 2 years after the operation. We investigated the value of endosonography for the early detection of recurrent disease.

Methods: Forty-three patients entered a follow-up protocol in which endosonography was performed every 6 months within the first 2 years after resection.

Results: During 16 of a total of 66 examinations, suspicious abnormalities were found. In three patients free fluid was seen, but recurrence could not be confirmed during follow-up. In eight patients suspicious lymph nodes were seen; six died within 6 months, one was alive with a proven recurrence at 6 months, and one was alive without recurrence at 22 months. In five patients focal wall-thickening or a mass was seen; three died within 6 months, and two were alive with a proven recurrence at 2 and 5 months. After exclusion of free fluid, the positive predictive value of abnormalities on endoscopic ultrasonography (EUS) was 92%.

Conclusions: Endosonography, performed at 6-month intervals after resection of cancer of the esophagus or gastric cardia, is accurate in the early detection of locoregional recurrent disease. Two thirds of the patients were still without symptoms when the recurrence was found. (*Gastrointest Endosc* 1997;46:487-91.)

Carcinoma of the esophagus and gastric cardia have a poor prognosis. Although the overall 5-year survival is only 20% after resection with curative intent, no active search for tumor recurrence is usually performed.¹ Some reports, however, have suggested that recurrent tumors should be treated aggressively with a combination of chemotherapy and radiotherapy.² The aim of this aggressive therapy for recurrent disease is not only to provide palliation but to prolong survival of these patients

as well. To maximize survival benefit, it is probably of importance to detect tumor recurrence as early as possible. If we would be able to detect a recurrence at an early stage, patients will be in better condition, will have lost less weight, and could be expected to tolerate this aggressive therapy better than those in whom a recurrence is diagnosed at an advanced stage.

Tumor recurrence can be divided into locoregional recurrences and distant metastatic disease. Up to half of patients have locoregional recurrences, either alone or in combination with distant metastases.^{3, 4} Diagnosis of locoregional recurrence after surgery can be difficult because of the changed anatomy of the posterior mediastinum. With computed tomography (CT), although excellent for distant metastatic disease, it can be difficult to accurately delineate the neoesophagus and its surroundings.⁵ Endosonography has been shown to be accurate in preoperative staging of tumors of the esophagus and gastric cardia.^{6, 7} It has also been shown that EUS

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can be of assistance in the detection of anastomotic recurrences and in this respect is superior to CT.^{8,9}

The aim of the present study was to assess whether endosonography is able to detect locoregional recurrences after resection in patients without symptoms. For this purpose patients underwent EUS every 6 months during the first 2 years after surgical resection of a carcinoma of the esophagus or gastric cardia.

PATIENTS AND METHODS

Patients who underwent surgery with curative intent because of a carcinoma of the esophagus or the gastric cardia were offered an endosonographic surveillance protocol, in which endosonographic examinations were scheduled every 6 months during the first 2 years after resection. All patients had undergone resection of the esophagus and gastric cardia with reconstruction by means of a gastric pull up with a cervical anastomosis. Patients who needed endoscopic dilatation therapy because of benign postoperative anastomotic stricture were excluded from the study because of the high chance that the echoendoscope with its diameter of 13 mm could not be passed through the anastomosis. Between July 1993 and November 1995, 43 patients were included in the study. There were 31 men and 12 women, with a median age of 59 years (range 36 to 81 years). Histologic analysis had shown an adenocarcinoma in 33 patients, a squamous cell carcinoma in nine, and an undifferentiated carcinoma in one patient. Pathologic T-staging of the resected tumors had shown a T1 tumor in eight patients (one with positive lymph nodes), a T2 tumor in two patients (one with positive lymph nodes), and a T3 tumor in the remaining 33 patients (25 with positive lymph nodes). Two patients received preoperative chemotherapy, no patients received chemotherapy or radiotherapy after surgery.

Endosonography was performed after an overnight fast with the patient in left lateral position with the use of a rotating sector scanning echoendoscope (Olympus GF-UM20; Olympus Optical Co., Tokyo, Japan) and both the 7.5 and 12 MHz frequencies. The echoendoscope was introduced after 2.5 to 5 mg Midazolam intravenously and advanced in a semi-blind fashion into the antrum. A water-filled balloon was fitted around the transducer, and 100 to 200 ml of deaerated water was instilled in the gastric pull up in most patients. Instillation of water was minimized because of the increased risk of aspiration. The endosonographic part of the examination was started by localizing the splenic artery and the celiac axis. From this point the echoendoscope was slowly withdrawn. It was pulled back from the celiac axis through the mediastinum up to the aortic arch. The examination was terminated when the anastomosis had been passed and the transducer entered the short remnant of the esophagus. Only at this point was the balloon emptied and the echoendoscope removed.

The abnormalities seen during EUS were divided in three categories: (1) presence of free fluid around the gastric pull up; (2) suspicious lymph nodes, defined as

homogeneous hypoechoic, well-delineated, round-to-oval lymph nodes with a diameter of 5 mm or more; and (3) focal wall-thickening or presence of a mass adjacent to the wall of the gastric pull up.

RESULTS

First endosonography

The first endosonographic examination was performed at a median of 6 months after resection (range 3 to 14 months) and failed in 13 of the 43 patients (30%) because of the inability to pass the cervical anastomosis. No dilatation therapy was performed in these patients as they did not complain of dysphagia, and these patients left the study. In seven patients abnormalities were seen during the first endosonographic follow-up examination. Two patients had some free fluid around the gastric pull up; both were alive 16 and 22 months after the examination. In two patients one or more suspicious lymph nodes were seen, in two other patients wall thickening or an adjacent mass was present, and in one patient free fluid plus suspicious lymph nodes were seen. All five patients died of recurrent disease after a median period of 4.4 months after EUS (range 1 to 9 months).

Second endosonography

Of the 23 patients who had undergone a complete first follow-up EUS, which showed no abnormalities, two patients left the study because of the development of distant metastases, both of whom died (one at 5 months and the other at 10 months after EUS). Six other patients left the study for various reasons, all of whom were alive after a median follow-up of 10 months (range 6 to 24 months).

Fifteen patients of the study group underwent a second endosonographic follow-up examination. In three patients the EUS was performed earlier than planned because they had developed symptoms suspicious of a locoregional recurrence. The examination failed because of narrowing of the anastomosis in one patient. In seven patients no abnormalities were seen during the second endosonographic examination. In the other seven patients, five had one or more suspicious lymph nodes around the gastric pull up and two had an adjacent mass. Of these seven patients with abnormalities on the second EUS, four died of recurrent disease at a median of 3 months of follow-up (range 1 to 6 months), and three patients were still alive. Two of these three surviving patients had a histologically proven recurrence 5 and 9 months after EUS, and one was free of disease 21 months after the second EUS. Follow-up endosonographic examinations in this last patient showed regression of the lymph node.

Table 1.
Abnormalities found during the study and their positive predictive value (PPV)

Abnormality	No. of patients	PPV for recurrent disease
Free fluid	3	—
Suspicious LN	8	88%
Wall thickening or mass	5	100%

LN, Lymph nodes.

Third endosonography

Of the seven patients who had undergone a complete second follow-up EUS, which showed no abnormalities, one patient developed metastases and died after 8 months. Another patient left the study at his own request. He was alive and free of recurrent disease 8 months after the second EUS.

Five patients underwent a third endosonographic follow-up examination; in one patient this was earlier than planned because of complaints. The anastomosis could be passed in every patient. In three patients no abnormalities were seen during the third endosonographic examination. In one of the other two patients, free fluid was seen around the stomach and the other had a mass adjacent to the gastric pull up. Of these two patients, the first was alive without a proven recurrence 12 months after the third EUS and the second patient had a recurrence which was proven by biopsy 2 months later.

Fourth endosonography

All three patients who had undergone a complete third follow-up EUS, which showed no abnormalities, underwent a fourth EUS. All three examinations were complete, and no abnormalities were seen.

Overall EUS results

The total number of endosonographic examinations performed during the study in the 43 patients was 66; passage of the anastomosis was impossible in 14 examinations, 36 examinations were normal, and suspicious abnormalities were seen during 16 examinations (Fig. 1 and Table 1). Free fluid in the mediastinum around the gastric pull up was present in three patients who were alive 12, 16, and 22 months after the EUS, with a recurrence diagnosed in the last patient 12 months after the EUS. Therefore the sole finding of free fluid around the gastric pull up after an esophageal resection was not predictive of recurrent disease in this group of patients. In eight patients one or more suspicious lymph nodes were seen; one of the patients also had free

Figure 1. Flow-chart of the study. ES, Endosonography.

fluid around the gastric pull up. Six of the patients died of recurrent disease after a mean period of 4.5 months.¹⁻⁶ One was alive with a histologically proven recurrence 6 months after the EUS, and one patient was alive 22 months later without proven recurrent disease. In the last patient the endosonographic abnormalities disappeared during further follow-up and should be regarded as false positive, leading to a positive predictive value for recurrent disease of 88% when suspicious lymph nodes were found. In five patients focal wall thickening or a mass adjacent to the gastric pull up was seen; in two this was combined with free fluid around the gastric pull up. Three of them died of recurrent disease after 3.3 months (range 2 to 6 months). The other two patients were alive with biopsy-proven recurrences 2 and 5 months after the endosonographic examination. The finding of a focal wall thickening or an adjacent mass had a positive predictive value for recurrent disease of 100% in our group of patients.

Of the 12 patients with a proven recurrence, four were examined earlier than planned because of symptoms suggestive of a locoregional recurrence, which they developed 3 to 4 months after the previous EUS. All four patients were found to have abnormalities on EUS that were later proven to be tumor recurrence. The eight other patients with a proven recurrence (67%) were without symptoms when their recurrence was discovered with EUS, and a mean of 3 months elapsed (range 0 to 5 months) before their conditions became symptomatic.

DISCUSSION

The poor prognosis of carcinoma of the esophagus and gastric cardia will probably only improve when

Figure 2. Large hypoechoic tumor recurrence (arrows) adjacent to the gastric pull up and encircling the aorta (Ao).

Figure 4. Large metastatic lymph node in the area of the celiac trunk dorsally from the gastric pull up.

Figure 3. Recurrent tumor in the mediastinum on the right side of the patient, a few centimeters below a cervical esophagogastrostomy. The aortic arch (A) is seen on the opposite side.

either the diagnosis can be made at an earlier stage or when more effective treatment will become available. Presently, tumor recurrence can be expected to occur within 2 years in one of every two patients. Locoregional recurrences are usually seen in regional lymph nodes or as a mass originating in the mediastinum and infiltrating the gastric pull up from outside (Figs. 2 to 4). So-called central recur-

rences originating at the site of the anastomosis have become increasingly rare after introduction of the cervical anastomosis. We have not encountered an anastomotic recurrence in this study group.

The follow-up protocol for patients who had undergone surgical resection of a cancer of the esophagus or gastric cardia was designed with the hypothesis that it should be possible to diagnose locoregional recurrences at an early stage, before patients' conditions become symptomatic, when endosonography was performed every 6 months during the first 2 years postoperatively. The 6-month interval proved to be too long for four patients, who developed complaints suggestive of a locoregional recurrence between 3 and 4 months after their previous endosonographic examination. All of them had abnormalities on the subsequently performed examination. The other eight patients (67%) with a proven recurrence were without symptoms when their recurrence was detected, and on average 3 months elapsed before their conditions became symptomatic. If early detection is truly important, this study suggests that an interval of 6 months is too long and should be shortened to 3 or 4 months.

The patency of the cervical anastomosis was a technical problem in the present study. Approximately 30% of patients develop a benign anastomotic stricture after cervical esophagogastrostomy.¹⁰ Even after exclusion of those patients who underwent dilatation therapy for a benign anastomotic stricture, we failed to introduce the echoendoscope beyond the anastomosis during the first exam-

ination in 30% of patients. These patients did not complain of dysphagia, and therefore dilatation therapy was not indicated. The difficulty of passing the anastomosis seems also to be related to the design of the echoendoscope, which has an outer diameter of 13 mm, a rigid tip of 4.5 cm in length, and a 45-degree oblique-viewing lens system. The rigidity of the tip is probably at least partially responsible for the failures. During the performance of a forward-viewing endoscopy, some of these anastomoses were widely patent but somewhat angulated and therefore could not be passed with the echoendoscope.

We encountered three different types of abnormalities during the follow-up examinations. First, the isolated presence of free fluid around the gastric pull up was seen in three patients, one of whom only developed a clinically apparent recurrence 12 months later. It seems justified to conclude from these results that the isolated presence of free fluid is not predictive of a recurrence and is probably reactive or lymph fluid related to the major surgical procedure performed in this area. Similar data were also reported for CT.⁵ The presence of suspicious lymph nodes was the second category of abnormalities. It has been shown in earlier studies that four parameters are of importance when studying lymph nodes endosonographically. Of the four EUS features, the echo pattern (homogeneous versus heterogeneous) seems to be the most sensitive parameter for discriminating malignant from benign nodes. The next most important feature is the lymph node border, followed by shape, with lymph node size only in fourth place.¹¹ Using these criteria we diagnosed suspicious lymph nodes in eight patients, one of whom must be regarded as false positive because the patient is alive without signs of recurrent disease almost 2 years later. This results in a positive predictive value of 88%. The third category of abnormality, i.e., focal wall thickening or a mass adjacent to the gastric pull up, was seen in five patients and proved to be a poor prognostic sign as three patients died and two were alive with a biopsy-proven recurrence after 2 and 5 months. Thus, this finding had a 100% positive predictive value for recurrent disease.

From this study it can be concluded that endosonography is a sensitive and specific investigation for detecting locoregional recurrent disease after surgical resection of carcinoma of the esophagus or gastric cardia in patients with and without symptoms. We have shown that by performing EUS once every 6 months in the first 2 years after resection, we were able to detect recurrent disease in patients,

67% of whom were at that time still without symptoms. Although we found a high specificity of endosonography in these patients, a recurrence should preferably be confirmed cytologically before embarking on further aggressive therapies. In this respect endosonography-guided, fine-needle aspiration biopsy seems an ideal technique for obtaining this evidence. With this technique it has been shown to be feasible to puncture mediastinal lymph nodes with an accuracy of over 80%.¹²⁻¹⁴ Furthermore it is possible to aspirate small amounts of fluid outside the gastrointestinal tract for a cytologic evaluation.¹⁵

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