Esophagorespiratory fistulas of tumorous origin. Non-operative management of 264 cases in a 20-year period

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Abstract

Objective: Esophagorespiratory fistulas developing from malignant tumors have serious complications by maintaining continuous airway contamination. The objective was to reveal the incidence, causes and characteristics of fistula formation and to examine the possibilities and efficiency of the treatment. Methods: In a single-center study between 1984 and 2004, the data of 2113 patients with tumorous esophageal stenosis were analyzed. Esophagorespiratory fistulas were detected in 264 cases (12.5%). Successful esophageal intubation, stent correction or replacement was performed in 188 cases, while there was one lethal complication. Twenty-seven patients had an intervention for nutritional support: 25 gastrostomies, 1 jejunostomy and 1 percutaneous endoscopic gastrostomy. Results: The mean survival period of all patients was 2.8 months; patients with implanted endoprosthesis 3.4 months; with nutritional support 1.1 months and with only supportive therapy 1.3 months, respectively. The differences between the endoprosthesis implanted group and the other two groups were significant (p < 0.001). Conclusions: By sealing the fistula, a successful endoscopic esophageal intubation ends the severe respiratory contamination and the inability to swallow, improving the quality of life and survival period. After the procedure, it is the malignant tumor and not the fistula that determines the future of the patient.

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Keywords: Esophageal cancer; Esophagorespiratory fistula; Endoprosthesis; Esophageal stents

1. Introduction

Esophagorespiratory fistulas (ERF) are pathological communications between the esophagus and the respiratory tract. In clinical practice ERF is a devastating complication of some malignant diseases. The pathological basis of fistula formation is the spreading of the esophageal cancer into the airways or lungs, or the propagation of pulmonary and mediastinal tumors into the esophagus.

Presumably, it occurs more frequently than the 5—10% incidence noted in literature, especially at the end stage of the malignant disease. Its early diagnosis and treatment is extremely important, because sealing the fistula can improve the survival and the quality of life of the patient.

Since there are no relevant data about incidence, outcome or complication of ERF, our objective was to evaluate the true incidence of fistula formation, and its effects on patients’ survival. The improvement in the survival and quality of life by the termination of the pathological communication was examined. The relationship between fistula formation and the time of tumor existence, and the effects of surgical or other oncological treatment (such as irradiation therapy) were also analyzed.

2. Patients and methods

Between 1984 and 2004, 2113 patients with malignant esophageal disease were treated at our institution. Esophagorespiratory fistula was detected in 264 cases: 243 esophageal cancers, 19 pulmonary tumors and 2 mediastinal tumors, respectively.

The ratio between men and women was found to be 4.3:1. The mean age of patients with fistula was 56.7 years (range: 21—90; SD: 11.90; CI: 55.3—58.2). The clinical findings of the 264 patients included the signs of severe septic condition besides the general symptoms of a malignant disease. The average time of presentation since the first signs and symptoms was 5.3 months (range: 1—18; SD: 4.38; CI: 4.6—5.7). The degree of dysphagia was found to be: none 7 (2.7%), solid foods: 57 (21.6%), mashy foods: 93 (35.2%), fluids: 107 (40.5%). Odynophagia was present in 51 cases (19.3%), retrosternal pain in 61 cases (23.1%), and fever in 95 cases (36.9%). The mean weight loss was 10.45 kg (range: 0—25; SD: 7.35; CI: 9.6—11.4), and cachexia was diagnosed in 157 cases (59.5%). All ERF patients suffered from severe

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coughing attacks right after consuming fluid, although not all of them reported it as the leading symptom. Recurrent laryngeal nerve palsy leads to swallowing reflex disorder in 28 cases that contributed to the periodic or constant aspiration. In the background fever purulent tracheobronchitis was detected in all and pneumonia in 95% of the patients.

Weakness and fatigue were long-time symptoms described by every ERF patients. Seventeen of the 264 patients had the symptoms of the ERF as the first signs of the malignant illness. In four cases the fistula was diagnosed only at the time of the autopsy. Fistulas were detected at an average time of 7.3 months (range: 1—58; SD: 4.25; CI: 6.5—8.1) after the first symptoms of the disease. The extent and the primary (original) location of the tumor are shown in Table 1. Lower third part tumors led to fistula formation by cranial propagation (30 patients). In one patient the fistula developed as a mediastinal recurrence after the resection of the original lower esophageal tumor. The main morphological character of the tumorous lesion was stenosis (68.2%). Histological examinations revealed squamous cell carcinoma in 232 (87.9%), adenocarcinoma in 18 (6.8%), anaplastic carcinoma in 6 (2.3%), Hodgkin lymphoma in 1 (0.4%), GIST 1 (0.4 %), SCLC 3 (1.1%), and not verified in 3 (1.1%) cases. Forty-five percent of the patients had very low differentiated histological types of tumors.

At the time of fistula manifestation metastases were detected in 90.5% of the patients. Metastatic lymph nodes were detected in the collar region in 16 (6.1%) cases, in the mediastinum in 234 (88.6%) cases, in the abdomen in 33 (12.5%) cases and in the retropertitoneum in 4 (1.5%) cases, respectively. Distant organ metastases were found in the lung (36, 13.6%), pleura (3, 1.1%), pericardium (3, 1.1%), liver (29, 11%), peritoneum (4, 1.5%) and other locations (4, 1.5%). At the time of fistula manifestation, restaging of the tumor was also recorded: T4N0M0 in 22 (9.3%) patients, T4N0M1a in 3 (1.1%), T4N1M0 in 36 (13.6%), T4N1M1a in 71 (26.8%) and T4N1M1b in 132 (50%) patients were detected.

Before fistula formation, resection of the esophagus was performed in 4 cases, explorative laparotomy in 35, esophageal intubation via gastrotomy in 3, and endoscopic endoprosthesis implantation in 27 cases (Fig. 1).

Table 1

<table>
<thead>
<tr>
<th>Extent of the tumor (mean)</th>
<th>7.6 cm (2—18; SD: 4.25; CI: 7.1—8.2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary location of the tumor</td>
<td></td>
</tr>
<tr>
<td>Upper third:</td>
<td>46 (17.4%)</td>
</tr>
<tr>
<td>Middle third:</td>
<td>186 (70.5%)</td>
</tr>
<tr>
<td>Lower third:</td>
<td>31 (11.7%)</td>
</tr>
<tr>
<td>Whole esophagus involved</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>Respiratory location of the fistula</td>
<td></td>
</tr>
<tr>
<td>Trachea</td>
<td>85 (32.2%)</td>
</tr>
<tr>
<td>Bifurcation</td>
<td>35 (13.3%)</td>
</tr>
<tr>
<td>Right main bronchus</td>
<td>118 (44.7%)</td>
</tr>
<tr>
<td>Left main bronchus:</td>
<td>22 (8.3%)</td>
</tr>
<tr>
<td>Lung parenchyma</td>
<td>4 (1.5%)</td>
</tr>
<tr>
<td>Morphology</td>
<td></td>
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<tr>
<td>Stenotizing</td>
<td>180 (68.2%)</td>
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<tr>
<td>Axis deviation, angulation</td>
<td>21 (7.9%)</td>
</tr>
<tr>
<td>Necrotizing cavity</td>
<td>53 (13.3%)</td>
</tr>
<tr>
<td>Outer compression</td>
<td>28 (10.6%)</td>
</tr>
</tbody>
</table>

Prior to fistula development, 41 patients received irradiation therapy either as a preoperative procedure (1 case) or as a palliative indication (40 cases). Low dose-rate (LDR) brachytherapy with intraluminal afterloading method was carried out in 34 patients (6 cases 15 Gy; 13 cases 30 Gy; 13 cases 45 Gy; 2 cases 60 Gy doses respectively). Ten of those patients had endoscopic esophageal intubation previously. Two patients received high dose-rate (HDR) intraluminal afterloading irradiation in 12 and 24 Gy doses. One patient received irradiation by LDR method in 15 Gy doses and by external beam of 56 Gy in combination. Four patients received external irradiation therapy (40 Gy, 60 Gy, 60 Gy, 64 Gy doses respectively). Prior to irradiation therapy, bronchoscopic examination detected no sign of respiratory tract involvement in 35 cases, protuberance of the pars membranacea in 4, and hyperemic reaction in 2 patients. Fistula formation among patients, who underwent irradiation therapy, was proven after an average time of 4.4 months (range 1—13; SD: 2.98; CI: 3.5—5.4), comprising of fistula development after less than 4 weeks in four cases (LDR 15 Gy two patients, 30 Gy one patient, and 45 Gy one patient). Prior to fistula formation 18 patients received chemotherapy, one of them for neoadjuvant purpose and 4 in combination with irradiation (2 HDR and 2 LDR). After fistula manifestation none of the patients received irradiation or chemotherapy.

Registration of all the data of the patients was prospective. Statistical analysis was performed using the SPSS version 15.0 (SPSS Inc., Chicago, Illinois, USA). The differences between the therapeutic groups were analyzed with Cochran, Mantel—Haenszel log-rank test. Significance was considered when $p < 0.001$. The 95% confidence intervals (CI) and standard deviation (SD) of means were calculated.

3. Results

The therapy of patients with ERF of tumorous origin can only be a palliative solution, regarding the fact that the tumor is undoubtedly irresectable. Prior to fistula formation and diagnosis, 30 of the 264 patients had an esophageal prosthesis already implanted to restore their ability to swallow. In these cases, the fistula developed in the part of
the esophagus which was not covered by the endoprosthesis. In 13 cases the endoscopic correction of the prosthesis was able to seal off the pathological communication. The prosthesis had to be replaced with another one in six patients, while an extra stent had to be implanted over the first one in two cases. Further 167 patients were suitable for endoscopic esophageal push through intubation, which was done using Eder-Puestow bougie or Savary-Gillard dilatator and Storz endoscopes or flexible Savary-Gillard applicator, under X-ray control. The number of prostheses implanted altogether was 201. Steel wire-armored Häring endoprosthesis (Rüscher) was used in 154 cases, Wilson-Cook tubes in two cases (Wilson-Cook Med. Inc.), Ultraflex self-expanding stents (Boston Scientific Corp.) in 16 cases, and a z-stent (Wilson-Cook Med. Inc.) in one case. All of the stents were covered. The size and type of the prosthesis was selected in every individual according to the given tumor morphology in order not just to seal the fistula but also to relieve the obvious distal obstruction. In 4 cases ERF was diagnosed during autopsy, while 72 of the 264 patients were not suitable for esophageal intubation: 24 had total esophageal obstruction (the guidewire could not pass the stricture), 18 had the stricture too high in the esophagus, while in 18 cases there was a threat of a probable prosthesis migration (strictures caused by outer compression: 4 patients, mild strictures not able to keep the prosthesis in position: 5 patients, necrotizing tumorous cavity: 9 patients). Angulation or axis deviation of the esophagus prevented intubation in three patients, seven were in a very poor general state, and one patient refused to undergo the procedure. There was also one lethal complication during the intubation. In patients who were not suitable for esophageal intubation, tracheal stenting could not be carried out because of the absence of proper conditions. Catheter gastrostomy for nutrition was prepared in 25 cases, while a further 6 were carried out as a salvage solution after stent migration. Percutaneous endoscopic gastrostomy (PEG) was performed in 1 case (further 1 because of stent complication), nutritional jejunostomy in 1 case (further 1 because of stent complication), and 48 patients received only supportive conservative therapy or medical advice.

Successful esophageal intubation, stent correction or replacement was performed in 188 (71.2%) patients (Fig. 1). In 144 cases it resulted in a sudden improvement of swallowing and closure of the fistula. The early and late complications of esophageal intubation are shown in Table 2. Early complications were defined as those that occurred within 7 days of the procedure. The procedure-related mortality was 0.5%. The mean survival period of the 264 patients from the first sign of the tumorous symptoms was 10 months (range 0—58; SD: 8.0; CI: 9.1—11.0), but only 2.8 months (range 0—12; SD: 2.48; CI: 2.5—3.1) after the first signs or diagnosis of the esophagorespiratory fistula. In patients with an implanted endoprosthesis it was 3.4 months (range 0—12; SD: 2.60; CI: 3.0—3.8), with a gastrostomy, PEG or jejunostomy 1.1 months (range 0—3; SD: 0.85; CI: 0.8—1.4), and in patients who were treated only supportively 1.3 months (range 0—5; SD: 1.22; CI: 0.9—1.6), respectively (Fig. 2). The differences between the endoprothesis implanted group and the other two groups were significant (p < 0.001), while there was no significant difference in the survival of patients between the latter two groups.

4. Discussion

The incidence of fistula formation was 12.5%, corresponding to literature [1—11]. The fact that the fistula usually develops at the end stage of the malignant disease in most patients, and its severe complications make diagnosis more difficult suggests that it occurs more frequently than proven and documented [5,12]. In this study there were four cases in which the fistula was diagnosed only at autopsy. The
swallowing X-ray is an essential for diagnosis. If the contrast medium turns foamy in the esophagus, it is also a sign of a pathological communication, regardless of the size of the fistula. This phenomenon results from the mixing of air and contrast medium. To complete the diagnosis and to follow the process of the disease, standard chest X-ray, esophagoscopy, bronchoscopy, laboratory tests, ultrasonography and computed tomography are required.

According to our analysis, fistulas usually develop in the middle third part of the esophagus. Fistula formation in the lower thirds corresponds to longer tumor life and local recurrences. The histological grading suggests that fistula formation is associated with highly progressive, less differentiated tumors.

By analyzing the effect of irradiation therapy, there were only four cases hypothesized to have irradiation-induced fistula, developing within 4 weeks after the onset of the therapy. Our data suggest that irradiation therapy increases the incidence of fistula formation probably because of the longer survival period (presuming that there is no tumorous propagation in the tracheo-bronchial tract). Some authors mentioned that irradiation therapy increases the incidence of fistula formation probably because of the longer survival period (presuming that there is no tumorous propagation in the tracheo-bronchial tract). Some authors of the same opinion [2,5,7,12,13].

Theoretically, the possibilities of the treatment of esophageal fistulas are resection of the esophagus, collar esophagostomy with gastrostomy or jejunostomy for nutrition, esophageal bypass, esophageal intubation and supportive therapy (operative gastrostomy, percutaneous endoscopic gastrostomy, parenteral nutrition, intravenous rehydration, antibiotic and analgesic therapy). In the presence of a fistula it is practically impossible to carry out an esophageal resection [2—4,8,9,12—14]. Esophagostomy with the ligation of the cardia and in some instances gastroenterostomy for nutrition is known [4,8,12], but its usefulness and results are far from convincing. The different types of esophageal bypasses have high morbidity and mortality as well [2—5,9,12,14]. Endoscopy insertion of an endoprosthesis via laparotomy and gastrostomy (the pull through method) has better results, but the complications of a laparotomy are added to the complications of an esophageal intubation (perforation, bleeding, stent migration, etc.) increasing morbidity and mortality rates [4,5,12]. Endoscopic esophageal intubation (the push through method) is widely accepted and seems to be the best alternative [3,11—13,15—22]. Dua [13] called this trend in the therapy of esophageal fistulas: ‘a shifting of paradigm’. After a successful esophageal intubation, patients usually have significantly better quality of life and survival rates [13,22]. Burt and colleagues [2] demonstrated a correlation between the survival period and the beginning of the treatment (closure of the fistula); our results tend to prove the same. In our study, a completely sealed fistula was found in three of those patients, whose endoprosthesis had to be removed because of late stent migration.

A number of technical requirements have to be met in order to perform a successful endoscopic esophageal intubation. The strichure has to be able to hold the tube in place, and also has to be at a proper distance (2—2.5 cm) from the pharynx. The guidewire should be able to penetrate the obstruction, and there should be no significant morphological changes (tortuosity, angulation or axis deviation). The endoscopic intubation is relatively well tolerated by older patients as well.

The procedure is cost effective and can be performed with short-term medical attendance or on an outpatient system as well [13,22]. In our opinion the critical stage of the procedure is the dilatation of the stricture, when there is a chance for the contents of the stomach to regurgitate and for the patient to aspirate, as observed in our only case with a lethal complication. One of the biggest advantages of self-expanding stents is that they usually do not require dilatation during implantation.

In this study, endoscopic correction of the migrated prosthesis was successful in 17 cases, while we permanently had to remove the displaced tube from the stomach in 6 patients with an endoscope, and in 3 via laparotomy and gastrotomy.

The significance of gastroesophageal reflux after esophageal intubation has risen recently, since it correlates with those cases, the so-called early unexpected deaths (five cases in our study), when the patient died after leaving the hospital after a couple of days following a successful procedure [13,22]. The stenting of lesions caused by paraesophageal lymph node metastases of lung cancers is a special problem. In these cases, the morphology of the stricture caused by outer compression often does not allow the stent to remain in its position. Another frequent problem is the airway compression [13] caused by self-expanding stents, which can evolve even after the emission of the patient and can be one possible reason for early unexpected deaths. Chan and colleagues [23] compared the physical properties including the expanding force of different kinds of self-expandable metal stents.

In some of those complicated cases, when specific tumor morphology does not allow esophageal tubes to be inserted, the solutions are self-expandable metallic stents. The placement of the stents is easier, safer and causes fewer burdens to the patient [13,16,17,19,20,22,24]. The usage of the stents is exclusive in strictures located in the region of the cardia [13,18,20], in esophageal obstructions caused by pulmonary and mediastinal processes, and in soft-tissue tumors. It is important to mention that uncovered metallic stents are less likely to migrate, however they are permeable to air, thus not suitable for the closure of the fistula. Tubes combined with foam are possibilities of treatment with lower
migration rates, and are used with promising results [5,11,15], just as self-expanding metallic stents with anti-reflux mechanisms, which were designed to prevent gastro-esophageal reflux [13,18]. Other possibilities of treatment are stents used in the respiratory tract. They have an outstanding importance in those cases when fistula closure is impossible from the esophageal side, or in those cases when the esophageal prosthesis would cause tracheal compression [5,15,19].

There were also some tentative methods of direct fistula sealing, such as the application of adhesive biological agents or an endoscopic technique of slastic/nylon button implantation [2,25]. The future of patients with ERF is essentially determined by the continuous airway contamination and the inability to swallow. The main goal of short-term treatment should be the terminating of this pathological state [2,3,5,8,9,12,14,17,19,22], especially in slower progressive tumors, when a successful palliative treatment leads to better prognosis.

Nutrition support did not prolong the survival of the patients. The best result out of all the therapeutic possibilities is achieved by endoscopic esophageal intubation. The treatment of patients with malignant esophagorespiratory fistula is usually a very hard and complicated task, but if successful, the quality of life and survival of these patients can be improved significantly.

References